

Disclosure

Dr. Roth's research on vision loss is supported by National Institutes of Health Grants EY10343, EY027447, the Michael Reese Foundation Pioneers Award, and by the North American Neuro-ophthalmological Society. Dr. Roth discloses that he has provided expert witness evaluation and testimony in cases of perioperative visual loss on behalf of patients, hospitals, and healthcare providers.

Acknowledgment

This chapter is a consolidation of two chapters in the 8th edition, Chapter 41, "Patient Positioning and Associated Risks," and Chapter 100, "Postoperative Visual Loss." The editors and publisher would like to thank authors Lydia Cassorla and Jae-Woo Lee, as well as returning author Dr. Steven Roth for their contributions to the prior edition of this work. It has served as the foundation for the current chapter.

 Complete references available online at expertconsult.com.

References

1. Metzner J, et al. *Best Pract Res Clin Anaesthesiol*. 2011;25:263.
2. Cheney FW, et al. *Anesthesiology*. 1999;90:1062.
3. Warner MA. *Mayo Clin Proc*. 1998;73:567.
4. Practice advisory for the prevention of perioperative peripheral neuropathies 2018. *Anesthesiology*. 2018;128:11–26.
5. O'Brien TJ, Ebert TJ. In: Martin JT, Warner MA, eds. *Positioning in Anesthesia and Surgery*. 3rd ed. Philadelphia: Saunders; 1997.
6. Gelman S. *Anesthesiology*. 2008;108:735.
7. Luecke T, Pelosi P. *Crit Care*. 2005;9:607.
8. Froese AB. *Anesthesiology*. 2006;104:193.
9. Glenny RW. *Intensive Care Med*. 2009;35:1833.
10. Hakim TS, et al. *J Appl Physiol*. 1987;63:1114.
11. Burrowes KS, Tawhai MH. *Respir Physiol Neurobiol*. 2006;154:515.
12. Galvin I, et al. *Br J Anaesth*. 2007;98:420.
13. Petersson J, et al. *Respir Physiol Neurobiol*. 2009;166:54–60.
14. Nyren S, et al. *Anesthesiology*. 2010;112:682–687.
15. Warner MA. *Supine Positions*. 3rd ed. Philadelphia: Saunders; 1997.
16. Britt BA, Gordon RA. *Can Anaesth Soc J*. 1964;11:514.
17. Prielipp RC, et al. *Anesthesiology*. 1999;91:345.
18. Stewart JD, Shantz SH. *Can J Neurol Sci*. 2003;30:15.
19. Geerts BF, et al. *J Clin Anesth*. 2012;24:668–674.
20. Cestari A, et al. *Eur Urol*. 2010;57:530.
21. Klauschie J, et al. *J Minim Invasive Gynecol*. 2010;17:504.
22. Phong LK, Koh LK. *Anaesth Intensive Care*. 2007;35:281.
23. Coppieeters MW, et al. *Anesthesiology*. 2002;97:75.
24. Kent CD, Cheney FW. *J Clin Anesth*. 2007;19:482.
25. Coppieeters MW. *Anesthesiology*. 2006;104:1351.
26. Devarajan J, et al. *Anesth Analg*. 2012;115:867.
27. Martin JT. In: Martin JT, Warner MA, eds. *Positioning in Anesthesia and Surgery*. 3rd ed. Philadelphia: Saunders; 1997.
28. Warner ME, et al. *Anesthesiology*. 2001;94:705.
29. Wassenaar EB, et al. *Dis Colon Rectum*. 2006;49:1449.
30. Mumtaz FH, et al. *BJU Int*. 2002;90:792.
31. Simms MS, Terry TR. *Postgrad Med J*. 2005;81:534.
32. Anema JG, et al. *J Urol*. 2000;164:360–363.
33. Chase J, et al. *Dis Colon Rectum*. 2000;43:678.
34. Turnbull D, et al. *Anaesthesia*. 2002;57:905.
35. Akhavan A, et al. *Urology*. 2010;76:1309.
36. Dunn PF. *Int Anesthesiol Clin*. 2000;38:25.
37. Choi YS, et al. *J Thorac Cardiovasc Surg*. 2007;134:613.
38. Tamkus A, Rice K. *Anesth Analg*. 2012;115:663.
39. Bialis M, et al. *Br J Anaesth*. 2010;104:407.
40. Martin JT. In: Martin JT, Warner MA, eds. *Positioning in Anesthesia and Surgery*. 3rd ed. Philadelphia: Saunders; 1997.
41. Douglas, et al. *Am Rev Respir Dis*. 1977;115:559.
42. Lumb AB, Nunn JF. *Anesth Analg*. 1991;73:422.
43. Girard TD, Bernard GR. *Chest*. 2007;131:921–929.
44. Alsaghir AH, Martin CM. *Crit Care Med*. 2008;36:603–609.
45. Guerin C, et al. *N Engl J Med*. 2013;368:2159–2168.
46. Pelosi P, et al. *Anesth Analg*. 1995;80:955–960.
47. Soro M, et al. *Eur J Anaesthesiol*. 2007;24:431–437.
48. Pelosi P, et al. *Anesth Analg*. 1996;83:578–583.
49. von Ungern-Sternberg BS, et al. *Intensive Care Med*. 2007;33:1771–1777.
50. Black S, et al. *Anesthesiology*. 1988;69:49–56.
51. Peruto CM, et al. *Arthroscopy*. 2009;25:891.
52. Porter JM, et al. *Br J Anaesth*. 1999;82:117–128.
53. Himes BT, et al. *J Neurosurg*. 2017;127:182–188.
54. Newberg Milde L. In: *Positioning in Anesthesia and Surgery*. 3rd ed. Edited by Martin JT, Warner MA. Philadelphia: Saunders; 1997: 1009.
55. Hindman BJ, et al. *Anesthesiology*. 2011;114:782–795.
56. Warner MA. In: Martin JT, Warner MA, eds. *Positioning in Anesthesia and Surgery*. 3rd ed. Philadelphia: Saunders; 1997.
57. Rozet I, Vavilala MS. *Anesthesiol Clin*. 2007;25:631–53, x.
58. Mammoto T, et al. *Acta Anaesthesiol Scand*. 1998;42:643–647.
59. Klein J, et al. *World Neurosurg*. 2018;115:196–200.
60. Papadopoulos G, et al. *Acta Neurochir (Wien)*. 1994;126:140–143.
61. Mirski MA, et al. *Anesthesiology*. 2007;106:164–177.
62. Gunther F, et al. *Acta Neurochir (Wien)*. 2017;159:339–346.
63. Hanna PG, et al. *J Clin Anesth*. 1991;3:290–294.
64. Pohl A, Cullen DJ. *J Clin Anesth*. 2005;17:463.
65. Pollard V, et al. *Anesth Analg*. 1996;82:278.
66. Fischer GW. *Pain Pract*. 2009;9:304.
67. Dippman C, et al. *Arthroscopy*. 2010;26(suppl 9):S148.
68. Drummond JC, et al. *Anesth Analg*. 2012;114:1301.
69. Lam AM, Baldwin G. *Anesth Analg*. 2012;114:1156.
70. Murphy GS, et al. *Anesth Analg*. 2010;111:496.
71. Ghosh A, et al. *Anesth Analg*. 2012;115:1373.
72. Rains DD, et al. *Arthroscopy*. 2011;27:532–541.
73. Hu JC, et al. *JAMA*. 2009;302:1557–1564.
74. Wright JD, et al. *JAMA*. 2013;309:689–698.
75. Gainsburg DM. *Minerva Anestesiol*. 2012;78:596–604.
76. Kalmar AF, De Wolf A, Hendrickx JF. *Adv Anesth*. 2012;20:75–96.
77. Lester M, et al. *Anesth Analg*. 2011;113:1069–1075.
78. Mills JT, et al. *J Urol*. 2013;190:580–584.
79. Ulm MA, et al. *Gynecol Oncol*. 2014;135:534–538.
80. Wen T, et al. *J Endourol*. 2014;28:660–667.
81. Souki FG, et al. *BMC Anesthesiol*. 2018;18:117.
82. Cheney FW. *Anesthesiology*. 1999;91:552–556.
83. Kroll DA, et al. *Anesthesiology*. 1990;73:202–207.
84. Lee LA, et al. *Anesthesiology*. 2004;101:143–152.
85. Fitzgibbon DR, et al. *Anesthesiology*. 2004;100:98–105.
86. Kamel IR, et al. *Anesth Analg*. 2006;102:1538–1542.
87. Chui J, et al. *Anesth Analg*. 2018;127:134–143.
88. Goubier J, Teboul F. Nerves and Nerve Injuries. In: Tubbs R, Shojaku M, Barbaro N, Rizk E, Loukas M, Spinner R, eds. *Amsterdam*. Elsevier; 2015.
89. Winfree CJ, Kline DG. *Surg Neurol*. 2005;63:5.
90. Welch MB, et al. *Anesthesiology*. 2009;111:490.
91. Warner MA, et al. *Anesthesiology*. 1999;90:54.
92. Cooper DE, et al. *Clin Orthop Relat Res*. 1988;228:33.
93. Kang SW, et al. *Surgery*. 2009;146:1048–1055.
94. Luginbuhl A, et al. *Laryngoscope*. 2012;122:110.
95. Davis SF, et al. *Am J Electroneurodiagnostic Technol*. 2011;51:274.
96. Hanson MR, et al. *Ann Thorac Surg*. 1983;36:675.
97. Jellish WS, et al. *J Cardiothorac Vasc Anesth*. 1994;8:398.
98. Liao DW. *ASA Newsletter*. 2006;70:11–13, 16.
99. Warner MA, et al. *Anesthesiology*. 1994;81:6–12.
100. Morell RC, et al. *Anesth Analg*. 2003;97:1183.
101. Cooper DE, et al. *Clin Orthop Relat Res*. 1988;228:33.
102. Aminoff MJ. *Anesthesiology*. 2004;100:1298.
103. Dylewsky W, McAlpine FS. In: Martin JT, Warner MA, eds. *Positioning in Anesthesia and Surgery*. 3rd ed. Philadelphia: Saunders; 1997.

107. Borsook D, et al. *Ann Surg*. 2013;257:403.
108. Primiano M, et al. *AORN J*. 2011;94:555–566.
109. Edsberg LE, et al. *J Wound Ostomy Continence Nurs*. 2016;43:585–597.
110. Cushing CA, Phillips LG. *Plast Reconstr Surg*. 2013;132:1720–1732.
111. Aronovitch SA. *J Wound Ostomy Continence Nurs*. 1999;26:130–136.
112. Hayes RM, et al. *Am J Med Qual*. 2015;30:591–597.
113. Campbell C, Parish LC. *Clin Dermatol*. 2010;28:527–532.
114. Kayser SA, et al. *Adv Skin Wound Care*. 2018;31:276–285.
115. Schwartz DM, et al. *Spine (Phila Pa 1976)*. 2011;36:1046–1049.
116. Brockerville M, et al. *J Neuroanesthet Crit Care*. 2017;4:78–84.
117. Lalwani K. *Curr Opin Anaesthesiol*. 2006;19:430.
118. Biouss V, et al. *Ophthalmology*. 2018;125:1597–1607.
119. Biouss V, Newman NJ. *N Engl J Med*. 2015;373:1677.
120. De la Garza-Ramos R, et al. *Spine J*. 2016;16:516–522.
121. Gayat E, et al. *Anesth Analg*. 2011;112:126–128.
122. Frenkel RE, Shin DH. *Arch Ophthalmol*. 1986;104:1459–1463.
123. Hart RH, et al. *Am J Ophthalmol*. 2002;134:761–763.
124. Roth S, et al. *Anesthesiology*. 1996;85:1020–1027.
125. Warner ME, et al. *Anesth Analg*. 2001;93:1417.
126. Roth S, et al. *Anesthesiology*. 1996;85:1020.
127. Shen Y, et al. *Anesth Analg*. 2009;109:1534.
128. Patil CG, et al. *Spine*. 2008;33:1491.
129. Stevens WR, et al. *Spine*. 1997;22:1319.
130. Chang SH, et al. *Spine*. 2005;30:1299.
131. Shapira OM, et al. *Ann Thorac Surg*. 1996;61:660.
132. Nuttall GA, et al. *Anesth Analg*. 2001;93:1410.
133. Kalyani SD, et al. *Ann Thorac Surg*. 2004;78:34.
134. Rubin DS, et al. *Anesthesiology*. 2017;126:810–821.
135. Myers MA, et al. *Spine*. 1997;22:1325.
136. Lee LA, et al. *Anesthesiology*. 2006;105:652.
137. Postoperative visual loss study group. *Anesthesiology*. 2012;116:15.
138. Dattilo M, et al. *Neuro Clin*. 2017;35:83–100.
139. Goldsmith MO. *Ophthalmologica*. 1967;153:191–196.
140. Katz DA, et al. *Spine*. 2005;30:E83.
141. Marks SC, et al. *Head Neck*. 1990;12:342–345.
142. Blauth CI, et al. *J Thoracic Cardiovasc Surg*. 1988;95:668.
143. Wray SH. *J Neurol Neurosurg Psychiatry*. 1993;56:234–240.
144. Tobalem S, et al. *BMC Ophthalmol*. 2018;18:101.
145. Alm A, et al. In: Moses A, Hart C, eds. *Adler's Physiology of the Eye*. 8th ed. St. Louis: CV Mosby; 1987:183.
146. Hayreh SS, et al. *Exp Eye Res*. 2004;78:723.
147. Hayreh SS, et al. *Br J Ophthalmol*. 1980;64:818.
148. Roth S, et al. *Invest Ophthalmol Vis Sci*. 1994;35:3209.
149. Lin J, et al. *Invest Ophthalmol Vis Sci*. 1999;40:2925.
150. Chen X, et al. *Invest Ophthalmol Vis Sci*. 2005;46:2611.
151. Ettaiache M, et al. *Brain Res*. 2001;890:118.
152. Roth S, et al. *Invest Ophthalmol Vis Sci*. 1998;39:775.
153. Calway T, et al. *Ophthalmology*. 2017;124:189–196.
154. Calway T, et al. *J Neuroophthalmol*. 2018;38:36–41.
155. Van Dijk FS, Sillence DO. *Am J Med Genet A*. 2014;164a:1470–1481.
156. Cole DE, Carpenter TO. *J Pediatr*. 1987;110:76–80.
157. Sys J, et al. *Eur Spine J*. 1996;5:74.
158. Grossman W, et al. *Spine*. 1993;18:1226.
159. Kumar N, et al. *Am J Ophthalmol*. 2004;138:889.
160. Carr RE, et al. *Arch Ophthalmol*. 1973;90:21.
161. Jampol LM, et al. *Arch Ophthalmol*. 1975;93:1311.
162. Jayam AV, et al. *J Neurol Sci*. 1974;22:413.
163. Hollenhorst RW, et al. *Arch Ophthalmol*. 1954;52:819.
164. Bui BV, et al. *Invest Ophthalmol Vis Sci*. 2005;46:202.
165. Zhang C, et al. *Invest Ophthalmol Vis Sci*. 2002;43:3059–3066.
166. Zhu Y, et al. *Invest Ophthalmol Vis Sci*. 2002;43:1903–1911.
167. Grant GP, et al. *Anesth Analg*. 2006;103:499–500.
168. Roth S, et al. *Anesth Analg*. 2007;104:1185.
169. Rubinstein A, et al. *Arch Ophthalmol*. 2005;123:1452.
170. Amorim Correa JL, Acioly MA. *World Neurosurg*. 2018;110:309–314.
171. Habets JGV, et al. *World Neurosurg*. 2018;114:72–75.
172. Pahl FH, et al. *World Neurosurg*. 2018;109:218–221.
173. Rimpilainen R, et al. *Perfusion*. 2011;26:479–486.
174. Blauth CI, et al. *J Thorac Cardiovasc Surg*. 1990;99:61.
175. Slaughter MS, et al. *Artif Organs*. 2008;32:880–884.
176. Herren JI, et al. *Stroke*. 1998;29:2396.
177. Bhatti MT, et al. *Surv Ophthalmol*. 2003;48:389.
178. Haller D, et al. *Rhinology*. 2006;44:216.
179. Savino PJ, et al. *J Clin Neuroophthalmol*. 1990;10:140–144.
180. Jacobs SM, et al. *Ophthalmology*. 2018;125:1100–1108.
181. Christie B, et al. *J Plast Reconstr Aesthet Surg*. 2018;71:155–161.
182. Moss WJ, et al. *Laryngoscope*. 2015;125:796–800.
183. Byers B. *Arch Ophthalmol*. 1979;97:79.
184. Watanabe W, et al. *Graefes Arch Clin Exp Ophthalmol*. 2002;240:1033.
185. Anderson Jr B. *Trans Am Ophthalmol Soc*. 1968;66:423–474.
186. Ahn SJ, et al. *Invest Ophthalmol Vis Sci*. 2013;54:7746–7755.
187. Nedelmann M, et al. *Stroke*. 2015;46:2322–2324.
188. Schrag M, et al. *JAMA Neurol*. 2015;72:1148–1154.
189. Page PS, et al. *Front Neurol*. 2018;9:76.
190. Tamai K, et al. *Br J Ophthalmol*. 1997;81:789–794.
191. Schultheiss M, et al. *PLOS One*. 2016;11:e0148616.
192. Reinhard K, et al. *Invest Ophthalmol Vis Sci*. 2016;57:658–663.
193. Johnson LJ, et al. *J Clin Neuroophthalmol*. 1994;14:38.
194. Arnold AC. *J Neuroophthalmol*. 2003;23:157.
195. Tice DA. *Am Thorac Surg*. 1987;44:677.
196. Schobel GA, et al. *Int J Oral Maxillofac Surg*. 1995;24:283.
197. Fenton S, et al. *J Laryngol Otol*. 2001;115:158–160.
198. Kaeser PF, Borrutat FX. *J Arthroplasty*. 2011;26:338.e17–9.
199. Huang TW, et al. *Otolaryngol Head Neck Surg*. 2003;129:448–450.
200. Buono LM, Foroozan R, et al. *Surv Ophthalmol*. 2005;50:15–26.
201. Roth S, et al. *Eur J Anaesthesiol*. 2018;35:840–847.
202. Arnold AC, et al. *Am J Ophthalmol*. 1994;117:222.
203. Subramanian PS, et al. *Br J Ophthalmol*. 2017;101:671–675.
204. Grieshaber MC, et al. *Surv Ophthalmol*. 2007;52:S115.
205. Guy J. *Curr Opin Ophthalmol*. 2000;11:421.
206. Bernstein SL, et al. *Invest Ophthalmol Vis Sci*. 2003;44:4153–4162.
207. Tesser RA, et al. *Ophthalmology*. 2003;110:2031.
208. Patel HR, Margo CE. *Arch Pathol Lab Med*. 2017;141:162–166.
209. Hayreh SS. In: Pillunat LE, Harris A, Anderson DR, et al., eds. *Current Concepts in Ocular Blood Flow in Glaucoma*. The Hague, Netherlands: Kugler; 1999:3.
210. Olver JM, et al. *Eye*. 1990;4:7.
211. Knox DL, et al. *Trans Am Ophthalmol Soc*. 2000;98:203.
212. Hayreh SS, Zimmerman MB. *Ophthalmology*. 2008;115:2275–2281.
213. Saito H, et al. *Ophthalmology*. 2008;115:1585–1590.
214. Beck RW, et al. *Ophthalmology*. 1987;94:1503.
215. Hayreh SS, Jonas JB. *Ophthalmology*. 2001;108:1586–1594.
216. Isayama Y, et al. *Ophthalmologica*. 1983;186:197–203.
217. Hayreh SS, et al. *Graefes Arch Clin Exp Ophthalmol*. 1994;232:745–752.
218. Weinstein JM, et al. *Invest Ophthalmol Vis Sci*. 1983;24:1559–1565.
219. Movaffagh A, et al. *Exp Eye Res*. 1998;67:561–568.
220. Riva CE, et al. *Graefes Arch Clin Exp Ophthalmol*. 1997;235:618–626.
221. Pillunat LE, et al. *Exp Eye Res*. 1997;64:737–744.
222. Vaphiades MS. *J Neuroophthalmol*. 2004;24:235.
223. Bolacchi F, et al. *Invest Ophthalmol Vis Sci*. 2012;53:4191.
224. Parisi V, et al. *Eur J Neurol*. 2008;15:839–845.
225. Ho VTG, et al. *J Neurosurg Anesthesiol*. 2005;17:38.
226. Golinvaux NS, et al. *Spine (Phila Pa 1976)*. 2014;39:2019–2023.
227. Holy SE, et al. *Anesthesiology*. 2009;110:246.
228. Practice advisory for perioperative visual loss associated with spine surgery. *Anesthesiology*. 2006;104:1319–1328.
229. Practice advisory for perioperative visual loss associated with spine surgery. *Anesthesiology*. 2012;116:274–285.
230. Practice advisory for perioperative visual loss associated with spine surgery 2019. *Anesthesiology*. 2019;130:12–30.
231. Farshad M, et al. *Spine J*. 2018;18:1625–1631.
232. Brown RH, et al. *Anesthesiology*. 1994;80:222.
233. Katz DM, et al. *Arch Ophthalmol*. 1994;112:925.
234. Shen Y, et al. *J Neurosurg Anesthesiol*. 2009;21:21–30.
235. Murphy GS, et al. *Anesth Analg*. 2009;108:1394–1417.
236. Practice guidelines for perioperative blood management. *Anesthesiology*. 2015;122:241–275.
237. Ferraris VA, et al. *Ann Thorac Surg*. 2007;83:S27–86.
238. Williams EL, et al. *Anesth Analg*. 1995;80:1018–1029.
239. Hayreh SS. *Ophthalmology*. 1987;94:1488–1502.
240. Chamot SR. *Klin Monbl Augenheilkd*. 2002;219:292–295.
241. Lee LA, et al. *Anesthesiology*. 2008;108:864–872.
242. Grant GP, et al. *Anesthesiology*. 2010;112:57–65.
243. Cheng MA, et al. *Anesthesiology*. 2001;95:1351–1355.
244. Murphy MA. *Ophthalmology*. 2003;110:1454–1457.
245. Roth S, et al. *J Neurosurg Anesthesiol*. 1997;9:346–348.
246. Geijer C, Bill A. *Invest Ophthalmol Vis Sci*. 1979;18:1030–1042.
247. He Z, et al. *Invest Ophthalmol Vis Sci*. 2006;47:4872–4880.

248. Bui BV, Fortune B. *J Physiol*. 2004;555:153–173.
249. Cullinane DC, et al. *J Trauma*. 2000;48:381.
250. Sullivan SR, et al. *J Trauma*. 2006;60:72–76.
251. Alian AA, et al. *Anesth Analg*. 2016;123:346–356.
252. Hayreh SS, et al. *Am J Ophthalmol*. 1994;118:766–780.
253. Lee LA, et al. *Anesthesiology*. 2001;95:793.
254. Corda DM, et al. *Mayo Clin Proc*. 2011;86:865–868.
255. Bae J, Lee SH. *Neurospine*. 2018;15:18–24.
256. Hussain NS, Perez-Cruet MJ. *Neurosurg Focus*. 2011;31:E2.
257. Edwards 2nd CC, et al. *Spine Deform*. 2018;6:141–147.
258. Hassanzadeh H, et al. *Spine J*. 2013;13:1717–1722.
259. Maddox JJ, et al. *Spine J*. 2014;14:1159–1165.
260. Passias PG, et al. *Spine J*. 2017;17:1091–1099.
261. Siemionow K, et al. *Neurol Neurochir Pol*. 2014;48:403–409.
262. Hayreh SS. *Br J Ophthalmol*. 1974;58:981.
264. Wolf GL, et al. *Anesthesiology*. 1983;59:547.
265. Vote BJ, et al. *Anesthesiology*. 2002;97:1305.
266. Seaberg RR, et al. *Anesthesiology*. 2002;97:1309.

References

1. Metzner J, Posner KL, Lam MS, Domino KB. Closed claims' analysis. *Best Pract Res Clin Anaesthesiol*. 2011;25:263–276.
2. Cheney FW, Domino KB, Caplan RA, Posner KL. Nerve injury associated with anesthesia: a closed claims analysis. *Anesthesiology*. 1999;90:1062–1069.
3. Warner MA. Perioperative neuropathies. *Mayo Clin Proc*. 1998;73:567–574.
4. Practice advisory for the prevention of perioperative peripheral neuropathies 2018: an updated report by the American Society of Anesthesiologists Task Force on Prevention of Perioperative Peripheral Neuropathies. *Anesthesiology*. 2018;128:11–26.
5. O'Brien T, Ebert T. In: Martin J, Warner M, eds. *Physiologic Changes Associated With the Supine Position, Positioning in Anesthesia and Surgery*. 3rd ed. Philadelphia: Saunders; 1997.
6. Gelman S. Venous function and central venous pressure: a physiologic story. *Anesthesiology*. 2008;108:735–748.
7. Luecke T, Pelosi P. Clinical review: positive end-expiratory pressure and cardiac output. *Crit Care*. 2005;9:607–621.
8. Glenny RW. Determinants of regional ventilation and blood flow in the lung. *Intensive Care Med*. 2009;35:1833–1842.
9. Froese AB. Gravity, the belly, and the diaphragm: you can't ignore physics. *Anesthesiology*. 2006;104:193–196.
10. Hakim TS, Lisbona R, Dean GW. Gravity-independent inequality in pulmonary blood flow in humans. *J Appl Physiol* (1985). 1987;63:1114–1121.
11. Burrowes KS, Tawhai MH. Computational predictions of pulmonary blood flow gradients: gravity versus structure. *Respir Physiol Neurobiol*. 2006;154:515–523.
12. Galvin I, Drummond GB, Nirmalan M. Distribution of blood flow and ventilation in the lung: gravity is not the only factor. *Br J Anaesth*. 2007;98:420–428.
13. Petersson J, Rohdin M, Sanchez-Crespo A, et al. Regional lung blood flow and ventilation in upright humans studied with quantitative SPECT. *Respir Physiol Neurobiol*. 2009;166:54–60.
14. Nyren S, Radell P, Lindahl SG, et al. Lung ventilation and perfusion in prone and supine postures with reference to anesthetized and mechanically ventilated healthy volunteers. *Anesthesiology*. 2010;112:682–687.
15. Warner MA. *Supine Positions*. 3rd ed. Philadelphia: Saunders; 1997.
16. Britt BA, Gordon RA. Peripheral nerve injuries associated with anaesthesia. *Can Anaesth Soc J*. 1964;11:514–536.
17. Prielipp RC, Morell RC, Walker FO, Santos CC, Bennett J, Butterworth J. Ulnar nerve pressure: influence of arm position and relationship to somatosensory evoked potentials. *Anesthesiology*. 1999;91:345–354.
18. Stewart JD, Shantz SH. Perioperative ulnar neuropathies: a medico-legal review. *Can J Neurol Sci*. 2003;30:15–19.
19. Geerts BF, van den Bergh L, Stijnen T, Aarts LP, Jansen JR. Comprehensive review: is it better to use the Trendelenburg position or passive leg raising for the initial treatment of hypovolemia? *J Clin Anesth*. 2012;24:668–674.
20. Cestari A, Buffi NM, Scapaticci E, et al. Simplifying patient positioning and port placement during robotic-assisted laparoscopic prostatectomy. *Eur Urol*. 2010;57:530–533.
21. Klauschie J, Wechter ME, Jacob K, et al. Use of anti-skid material and patient-positioning to prevent patient shifting during robotic-assisted gynecologic procedures. *J Minim Invasive Gynecol*. 2010;17:504–507.
22. Phong SV, Koh LK. Anaesthesia for robotic-assisted radical prostatectomy: considerations for laparoscopy in the Trendelenburg position. *Anaesth Intensive Care*. 2007;35:281–285.
23. Coppiepers MW, Van de Velde M, Stappaerts KH. Positioning in anaesthesia: toward a better understanding of stretch-induced perioperative neuropathies. *Anesthesiology*. 2002;97:75–81.
24. Kent CD, Cheney FW. A case of bilateral brachial plexus palsy due to shoulder braces. *J Clin Anesth*. 2007;19:482–484.
25. Coppiepers MW. Shoulder restraints as a potential cause for stretch neuropathies: biomechanical support for the impact of shoulder girdle depression and arm abduction on nerve strain. *Anesthesiology*. 2006;104:1351–1352.
26. Devarajan J, Byrd JB, Gong MC, et al. Upper and middle trunk brachial plexopathy after robotic prostatectomy. *Anesth Analg*. 2012;115:867–870.
27. Martin JT. In: Martin JT, Warner MA, eds. *Lithotomy, Positioning in Anesthesia and Surgery*. 3rd ed. Philadelphia: Saunders; 1997.
28. Warner ME, LaMaster LM, Thoeming AK, Marienau ME, Warner MA. Compartment syndrome in surgical patients. *Anesthesiology*. 2001;94:705–708.
29. Wassenaar EB, van den Brand JG, van der Werken C. Compartment syndrome of the lower leg after surgery in the modified lithotomy position: report of seven cases. *Dis Colon Rectum*. 2006;49:1449–1453.
30. Mumtaz FH, Chew H, Gelister JS. Lower limb compartment syndrome associated with the lithotomy position: concepts and perspectives for the urologist. *BJU Int*. 2002;90:792–799.
31. Simms MS, Terry TR. Well leg compartment syndrome after pelvic and perineal surgery in the lithotomy position. *Postgrad Med J*. 2005;81:534–536.
32. Anema JG, Morey AF, McAninch JW, Mario LA, Wessells H. Complications related to the high lithotomy position during urethral reconstruction. *J Urol*. 2000;164:360–363.
33. Chase J, Harford F, Pinzur MS, Zussman M. Intraoperative lower extremity compartment pressures in lithotomy-positioned patients. *Dis Colon Rectum*. 2000;43:678–680.
34. Turnbull D, Farid A, Hutchinson S, Shorthouse A, Mills GH. Calf compartment pressures in the Lloyd-Davies position: a cause for concern? *Anaesthesia*. 2002;57:905–908.
35. Akhavan A, Gainsburg DM, Stock JA. Complications associated with patient positioning in urologic surgery. *Urology*. 2010;76:1309–1316.
36. Dunn PF. Physiology of the lateral decubitus position and one-lung ventilation. *Int Anesthesiol Clin*. 2000;38:25–53.
37. Choi YS, Bang SO, Shim JK, Chung KY, Kwak YL, Hong YW. Effects of head-down tilt on intrapulmonary shunt fraction and oxygenation during one-lung ventilation in the lateral decubitus position. *J Thorac Cardiovasc Surg*. 2007;134:613–618.
38. Tamkus A, Rice K. The incidence of bite injuries associated with transcranial motor-evoked potential monitoring. *Anesth Analg*. 2012;115:663–667.
39. Biaia M, Bernard O, Ha JC, Degryse C, Sztark F. Abilities of pulse pressure variations and stroke volume variations to predict fluid responsiveness in prone position during scoliosis surgery. *Br J Anaesth*. 2010;104:407–413.
40. Martin JT. In: Martin JT, Warner MA, eds. *The Ventral Decubitus (Prone) Positions, Positioning in Anesthesia and Surgery*. 3rd ed. Philadelphia: Saunders; 1997.
41. Douglas WW, Rehder K, Beynen FM, Sessler AD, Marsh HM. Improved oxygenation in patients with acute respiratory failure: the prone position. *Am Rev Respir Dis*. 1977;115:559–566.
42. Lumb AB, Nunn JF. Respiratory function and ribcage contribution to ventilation in body positions commonly used during anaesthesia. *Anesth Analg*. 1991;73:422–426.
43. Girard TD, Bernard GR. Mechanical ventilation in ARDS: a state-of-the-art review. *Chest*. 2007;131:921–929.
44. Alsaghir AH, Martin CM. Effect of prone positioning in patients with acute respiratory distress syndrome: a meta-analysis. *Crit Care Med*. 2008;36:603–609.
45. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med*. 2013;368:2159–2168.
46. Pelosi P, Croci M, Calappi E, et al. The prone positioning during general anaesthesia minimally affects respiratory mechanics while improving functional residual capacity and increasing oxygen tension. *Anesth Analg*. 1995;80:955–960.
47. Soro M, Garcia-Perez ML, Belda FJ, et al. Effects of prone position on alveolar dead space and gas exchange during general anaesthesia in surgery of long duration. *Eur J Anaesthesiol*. 2007;24:431–437.
48. Pelosi P, Croci M, Calappi E, et al. Prone positioning improves pulmonary function in obese patients during general anaesthesia. *Anesth Analg*. 1996;83:578–583.
49. von Ungern-Sternberg BS, Hammer J, Frei FJ, Jordi Ritz EM, Schibler A, Erb TO. Prone equals prone? Impact of positioning techniques on respiratory function in anesthetized and paralyzed healthy children. *Intensive Care Med*. 2007;33:1771–1777.
50. Black S, Ockert DB, Oliver Jr WC, Cucchiara RF. Outcome following posterior fossa craniectomy in patients in the sitting or horizontal positions. *Anesthesiology*. 1988;69:49–56.

51. Peruto CM, Ciccotti MG, Cohen SB. Shoulder arthroscopy positioning: lateral decubitus versus beach chair. *Arthroscopy*. 2009;25:891–896.
52. Porter JM, Pidgeon C, Cunningham AJ. The sitting position in neurosurgery: a critical appraisal. *Br J Anaesth*. 1999;82:117–128.
53. Himes BT, Mallory GW, Abcejo AS, et al. Contemporary analysis of the intraoperative and perioperative complications of neurosurgical procedures performed in the sitting position. *J Neurosurg*. 2017;127:182–188.
54. Newberg Milde L: *The Head-Elevated Positions, Positioning in Anesthesia and Surgery*. 3rd ed. Martin JT, Warner MA, eds. Philadelphia: Saunders; 1997: 1009.
55. Hindman BJ, Palecek JP, Posner KL, et al. Cervical spinal cord, root, and bony spine injuries: a closed claims analysis. *Anesthesiology*. 2011;114:782–795.
56. Warner MA. In: Martin JT, Warner MA, eds. *Positioning of the Head and Neck, Positioning in Anesthesia and Surgery*. 3rd ed. Philadelphia: Saunders; 1997.
57. Rozet I, Vavilala MS. Risks and benefits of patient positioning during neurosurgical care. *Anesthesiol Clin*. 2007;25:631–653, x.
58. Mammo T, Hayashi Y, Ohnishi Y, Kuro M. Incidence of venous and paradoxical air embolism in neurosurgical patients in the sitting position: detection by transesophageal echocardiography. *Acta Anaesthesiol Scand*. 1998;42:643–647.
59. Klein J, Juratli TA, Weise M, Schackert G. A systematic review of the semi-sitting position in neurosurgical patients with patent foramen ovale: how frequent is paradoxical embolism? *World Neurosurg*. 2018;115:196–200.
60. Papadopoulos G, Kuhly P, Brock M, Rudolph KH, Link J, Eyrich K. Venous and paradoxical air embolism in the sitting position. A prospective study with transoesophageal echocardiography. *Acta Neurochir (Wien)*. 1994;126:140–143.
61. Mirski MA, Lele AV, Fitzsimmons L, Toung TJ. Diagnosis and treatment of vascular air embolism. *Anesthesiology*. 2007;106:164–177.
62. Gunther F, Frank P, Nakamura M, Hermann EJ, Palmaers T. Venous air embolism in the sitting position in cranial neurosurgery: incidence and severity according to the used monitoring. *Acta Neurochir (Wien)*. 2017;159:339–346.
63. Hanna PG, Gravenstein N, Pashayan AG. In vitro comparison of central venous catheters for aspiration of venous air embolism: effect of catheter type, catheter tip position, and cardiac inclination. *J Clin Anesth*. 1991;3:290–294.
64. Pohl A, Cullen DJ. Cerebral ischemia during shoulder surgery in the upright position: a case series. *J Clin Anesth*. 2005;17:463–469.
65. Pollard V, Prough DS, DeMelo AE, Deyo DJ, Uchida T, Widman R. The influence of carbon dioxide and body position on near-infrared spectroscopic assessment of cerebral hemoglobin oxygen saturation. *Anesth Analg*. 1996;82:278–287.
66. Fischer GW, Torrillo TM, Weiner MM, Rosenblatt MA. The use of cerebral oximetry as a monitor of the adequacy of cerebral perfusion in a patient undergoing shoulder surgery in the beach chair position. *Pain Pract*. 2009;9:304–307.
67. Lam AM, Baldwin G. Blood pressure and adverse perioperative neurologic outcomes: an uncomfortable position. *Anesth Analg*. 2012;114:1156–1159.
68. Murphy GS, Szokol JW, Marymont JH, et al. Cerebral oxygen desaturation events assessed by near-infrared spectroscopy during shoulder arthroscopy in the beach chair and lateral decubitus positions. *Anesth Analg*. 2010;111:496–505.
69. Ghosh A, Elwell C, Smith M. Review article: cerebral near-infrared spectroscopy in adults: a work in progress. *Anesth Analg*. 2012;115:1373–1383.
70. Rains DD, Rooke GA, Wahl CJ. Pathomechanisms and complications related to patient positioning and anesthesia during shoulder arthroscopy. *Arthroscopy*. 2011;27:532–541.
71. Hu JC, Gu X, Lipsitz SR, et al. Comparative effectiveness of minimally invasive vs open radical prostatectomy. *JAMA*. 2009;302:1557–1564.
72. Wright JD, Ananth CV, Lewin SN, et al. Robotically assisted vs laparoscopic hysterectomy among women with benign gynecologic disease. *JAMA*. 2013;309:689–698.
73. Gainsburg DM. Anesthetic concerns for robotic-assisted laparoscopic radical prostatectomy. *Minerva Anestesiol*. 2012;78:596–604.
74. Hsu RL, Kaye AD, Urman RD. Anesthetic challenges in robotic-assisted urologic surgery. *Rev Urol*. 2013;15:178–184.
75. Kalmar AF, De Wolf A, Hendrickx JF. Anesthetic considerations for robotic surgery in the steep Trendelenburg position. *Adv Anesth*. 2012;20:75–96.
76. Lester M, Gunnarsson L, Lagerstrand L, Wiklund P, Odeberg-Wernerman S. Hemodynamic perturbations during robot-assisted laparoscopic radical prostatectomy in 45 degrees Trendelenburg position. *Anesth Analg*. 2011;113:1069–1075.
77. Mills JT, Burris MB, Warburton DJ, Conaway MR, Schenkman NS, Krupski TL. Positioning injuries associated with robotic assisted urological surgery. *J Urol*. 2013;190:580–584.
78. Ulm MA, Fleming ND, Rallapali V, et al. Position-related injury is uncommon in robotic gynecologic surgery. *Gynecol Oncol*. 2014;135:534–538.
79. Wen T, Deibert CM, Siringo FS, Spencer BA. Positioning-related complications of minimally invasive radical prostatectomies. *J Endourol*. 2014;28:660–667.
80. Souki FG, Rodriguez-Blanco YF, Polu SR, Eber S, Candiotti KA. Survey of anesthesiologists' practices related to steep Trendelenburg positioning in the USA. *BMC Anesthesiol*. 2018;18:117.
81. Cheney FW. The American Society of Anesthesiologists Closed Claims Project: what have we learned, how has it affected practice, and how will it affect practice in the future? *Anesthesiology*. 1999;91:552–556.
82. Kroll DA, Caplan RA, Posner K, Ward RJ, Cheney FW. Nerve injury associated with anesthesia. *Anesthesiology*. 1990;73:202–207.
83. Lee LA, Posner KL, Domino KB, Caplan RA, Cheney FW. Injuries associated with regional anesthesia in the 1980s and 1990s: a closed claims analysis. *Anesthesiology*. 2004;101:143–152.
84. Fitzgibbon DR, Posner KL, Domino KB, Caplan RA, Lee LA, Cheney FW. Chronic pain management: American Society of Anesthesiologists Closed Claims Project. *Anesthesiology*. 2004;100:98–105.
85. Kamel IR, Drum ET, Koch SA, et al. The use of somatosensory evoked potentials to determine the relationship between patient positioning and impending upper extremity nerve injury during spine surgery: a retrospective analysis. *Anesth Analg*. 2006;102:1538–1542.
86. Chui J, Murkin JM, Posner KL, Domino KB. Perioperative peripheral nerve injury after general anesthesia: a qualitative systematic review. *Anesth Analg*. 2018;127:134–143.
87. Goubier J, Teboul F. In: Tubbs R, Shoja M, Barbaro N, Rizk E, Loukas M, Spinner R, eds. *Grading of Nerve Injuries, Nerves and Nerve Injuries*. Amsterdam: Elsevier; 2015.
88. Winfree CJ, Kline DG. Intraoperative positioning nerve injuries. *Surg Neurol*. 2005;63:5–18; discussion 18.
89. Welch MB, Brummett CM, Welch TD, et al. Perioperative peripheral nerve injuries: a retrospective study of 380,680 cases during a 10-year period at a single institution. *Anesthesiology*. 2009;111:490–497.
90. Warner MA, Warner DO, Matsumoto JY, Harper CM, Schroeder DR, Maxson PM. Ulnar neuropathy in surgical patients. *Anesthesiology*. 1999;90:54–59.
91. Prielipp RC, Morell RC, Butterworth J. Ulnar nerve injury and perioperative arm positioning. *Anesthesiol Clin North America*. 2002;20:589–603.
92. Cheney FW. Perioperative ulnar nerve injury: a continuing medical and liability problem. *ASA Newsletter*. 1998;62:10–11.
93. Warner MA, Warner ME, Martin JT. Ulnar neuropathy. Incidence, outcome, and risk factors in sedated or anesthetized patients. *Anesthesiology*. 1994;81:1332–1340.
94. Contreras MG, Warner MA, Charboneau WJ, Cahill DR. Anatomy of the ulnar nerve at the elbow: potential relationship of acute ulnar neuropathy to gender differences. *Clin Anat*. 1998;11:372–378.
95. Morell RC, Prielipp RC, Harwood TN, James RL, Butterworth JF. Men are more susceptible than women to direct pressure on unmyelinated ulnar nerve fibers. *Anesth Analg*. 2003;97:1183–1188, table of contents.
96. Cooper DE, Jenkins RS, Bready L, Rockwood Jr CA. The prevention of injuries of the brachial plexus secondary to malposition of the patient during surgery. *Clin Orthop Relat Res*. 1988;33–41.
97. Kang SW, Lee SC, Lee SH, et al. Robotic thyroid surgery using a gasless, transaxillary approach and the da Vinci S system: the operative outcomes of 338 consecutive patients. *Surgery*. 2009;146:1048–1055.
98. Luginbuhl A, Schwartz DM, Sestokas AK, Cognetti D, Pribitkin E. Detection of evolving injury to the brachial plexus during transaxillary robotic thyroidectomy. *Laryngoscope*. 2012;122:110–115.

99. Davis SF, Abdel Khalek M, Giles J, Fox C, Lurette L, Kandil E. Detection and prevention of impending brachial plexus injury secondary to arm positioning using ulnar nerve somatosensory evoked potentials during transaxillary approach for thyroid lobectomy. *Am J Electroneurodiagnostic Technol.* 2011;51:274–279.
100. Hanson MR, Breuer AC, Furlan AJ, et al. Mechanism and frequency of brachial plexus injury in open-heart surgery: a prospective analysis. *Ann Thorac Surg.* 1983;36:675–679.
101. Jellish WS, Martucci J, Blakeman B, Hudson E. Somatosensory evoked potential monitoring of the brachial plexus to predict nerve injury during internal mammary artery harvest: intraoperative comparisons of the Rultract and Pittman sternal retractors. *J Cardiothorac Vasc Anesth.* 1994;8:398–403.
102. Liau DW. Injuries and liability related to peripheral catheters: a closed claim analysis. *ASA Newsletter.* 2006;70(6):11–13, 16.
103. Warner MA, Martin JT, Schroeder DR, Offord KP, Chute CG. Lower-extremity motor neuropathy associated with surgery performed on patients in a lithotomy position. *Anesthesiology.* 1994;81:6–12.
104. Warner MA, Warner DO, Harper CM, Schroeder DR, Maxson PM. Lower extremity neuropathies associated with lithotomy positions. *Anesthesiology.* 2000;93:938–942.
105. Aminoff MJ. Electrophysiologic testing for the diagnosis of peripheral nerve injuries. *Anesthesiology.* 2004;100:1298–1303.
106. Dwlewsy W. In: Martin JT, Warner MA, eds. *Peripheral Nervous System, Positioning in Anesthesia and Surgery.* 3rd ed. Philadelphia: Saunders; 1997.
107. Borsook D, Kussman BD, George E, Becerra LR, Burke DW. Surgically induced neuropathic pain: understanding the perioperative process. *Ann Surg.* 2013;257:403–412.
108. Primiano M, Friend M, McClure C, et al. Pressure ulcer prevalence and risk factors during prolonged surgical procedures. *AORN J.* 2011;94:555–566.
109. Edsberg LE, Black JM, Goldberg M, McNichol L, Moore L, Sieggreen M. Revised national pressure ulcer advisory panel pressure injury staging system: revised pressure injury staging system. *J Wound Ostomy Continence Nurs.* 2016;43:585–597.
110. Cushing CA, Phillips LG. Evidence-based medicine: pressure sores. *Plast Reconstr Surg.* 2013;132:1720–1732.
111. Aronovitch SA. Intraoperatively acquired pressure ulcer prevalence: a national study. *J Wound Ostomy Continence Nurs.* 1999;26:130–136.
112. Hayes RM, Spear ME, Lee SI, et al. Relationship between time in the operating room and incident pressure ulcers: a matched case-control study. *Am J Med Qual.* 2015;30:591–597.
113. Campbell C, Parish LC. The decubitus ulcer: facts and controversies. *Clin Dermatol.* 2010;28:527–532.
114. Kayser SA, VanGilder CA, Ayello EA, Lachenbruch C. Prevalence and analysis of medical device-related pressure injuries: results from the international pressure ulcer prevalence survey. *Adv Skin Wound Care.* 2018;31:276–285.
115. Schwartz DM, Sestokas AK, Dormans JP, et al. Transcranial electric motor evoked potential monitoring during spine surgery: is it safe? *Spine (Phila Pa 1976).* 2011;36:1046–1049.
116. Brockerville M, Lakshmikumar V, Manninen P. Macroglossia in neurosurgery. *J Neuroanesthet Crit Care.* 2017;4:78–84.
117. Lalwani K. Demographics and trends in nonoperating-room anesthesia. *Curr Opin Anaesthesiol.* 2006;19:430–435.
118. Biouss V, Nahab F, Newman NJ. Management of acute retinal ischemia: follow the guidelines!. *Ophthalmology.* 2018;125:1597–1607.
119. Biouss V, Newman NJ. Ischemic optic neuropathies. *N Engl J Med.* 2015;373:1677.
120. De la Garza-Ramos R, Samdani AF, Sponseller PD, et al. Visual loss after corrective surgery for pediatric scoliosis: incidence and risk factors from a nationwide database. *Spine J.* 2016;16:516–522.
121. Gayat E, Gabison E, Devys JM. Case report: bilateral angle closure glaucoma after general anesthesia. *Anesth Analg.* 2011;112:126–128.
122. Frenkel RE, Shin DH. Prevention and management of delayed suprachoroidal hemorrhage after filtration surgery. *Arch Ophthalmol.* 1986;104:1459–1463.
123. Hart RH, Vote BJ, Borthwick JH, McGeorge AJ, Worsley DR. Loss of vision caused by expansion of intraocular perfluoropropane (C(3)F(8)) gas during nitrous oxide anesthesia. *Am J Ophthalmol.* 2002;134:761–763.
124. Roth S, Thisted RA, Erickson JP, Black S, Schreider BD. Eye injuries after nonocular surgery. A study of 60,965 anesthetics from 1988 to 1992. *Anesthesiology.* 1996;85:1020–1027.
125. Warner ME, Warner MA, Garrity JA, MacKenzie RA, Warner DO. The frequency of perioperative vision loss. *Anesth Analg.* 2001;93:1417–1421. table of contents.
126. Shen Y, Drum M, Roth S. The prevalence of perioperative visual loss in the United States: a 10-year study from 1996 to 2005 of spinal, orthopedic, cardiac, and general surgery. *Anesth Analg.* 2009;109:1534–1545.
127. Rubin DS, Parakati I, Lee LA, Moss HE, Joslin CE, Roth S. Perioperative visual loss in spine fusion surgery: ischemic optic neuropathy in the United States from 1998 to 2012 in the Nationwide Inpatient Sample. *Anesthesiology.* 2016;125:457–464.
128. Patil CG, Lad EM, Lad SP, Ho C, Boakye M. Visual loss after spine surgery: a population-based study. *Spine (Phila Pa 1976).* 2008;33:1491–1496.
129. Stevens WR, Glazer PA, Kelley SD, Lietman TM, Bradford DS. Ophthalmic complications after spinal surgery. *Spine (Phila Pa 1976).* 1997;22:1319–1324.
130. Chang SH, Miller NR. The incidence of vision loss due to perioperative ischemic optic neuropathy associated with spine surgery: the Johns Hopkins Hospital Experience. *Spine (Phila Pa 1976).* 2005;30:1299–1302.
131. Shapira OM, Kimmel WA, Lindsey PS, Shahian DM. Anterior ischemic optic neuropathy after open heart operations. *Ann Thorac Surg.* 1996;61:660–666.
132. Nuttall GA, Garrity JA, Dearani JA, Abel MD, Schroeder DR, Mullany CJ. Risk factors for ischemic optic neuropathy after cardiopulmonary bypass: a matched case/control study. *Anesth Analg.* 2001;93:1410–1416. table of contents.
133. Kalyani SD, Miller NR, Dong LM, Baumgartner WA, Alejo DE, Gilbert TB. Incidence of and risk factors for perioperative optic neuropathy after cardiac surgery. *Ann Thorac Surg.* 2004;78:34–37.
134. Deleted in proofs.
135. Myers MA, Hamilton SR, Bogosian AJ, Smith CH, Wagner TA. Visual loss as a complication of spine surgery. A review of 37 cases. *Spine (Phila Pa 1976).* 1997;22:1325–1329.
136. Lee LA, Roth S, Posner KL, et al. The American Society of Anesthesiologists Postoperative Visual Loss Registry: analysis of 93 spine surgery cases with postoperative visual loss. *Anesthesiology.* 2006;105:652–659. quiz 867–8.
137. Postoperative Visual Loss Study Group. Risk factors associated with ischemic optic neuropathy after spinal fusion surgery. *Anesthesiology.* 2012;116:15–24.
138. Dattilo M, Biouss V, Newman NJ. Update on the management of central retinal artery occlusion. *Neurol Clin.* 2017;35:83–100.
139. Goldsmith MO. Occlusion of the central retinal artery following retrolbulbar hemorrhage. *Ophthalmologica.* 1967;153:191–196.
140. Katz DA, Karlin LI. Visual field defect after posterior spine fusion. *Spine (Phila Pa 1976).* 2005;30:E83–E85.
141. Marks SC, Jaques DA, Hirata RM, Saunders Jr JR. Blindness following bilateral radical neck dissection. *Head Neck.* 1990;12:342–345.
142. Blauth C, Arnold J, Kohner EM, Taylor KM. Retinal microembolism during cardiopulmonary bypass demonstrated by fluorescein angiography. *Lancet.* 1986;2:837–839.
143. Wray SH. The management of acute visual failure. *J Neurol Neurosurg Psychiatry.* 1993;56:234–240.
144. Tobalem S, Schutz JS, Chronopoulos A. Central retinal artery occlusion—rethinking retinal survival time. *BMC Ophthalmol.* 2018;18:101.
145. Alm A, Bill A. In: Moses A, Hart C, eds. *Ocular Circulation, Adler's Physiology of the Eye.* 8th ed. St Louis: CV Mosby; 1987.
146. Hayreh SS, Zimmerman MB, Kimura A, Sanon A. Central retinal artery occlusion. Retinal survival time. *Exp Eye Res.* 2004;78:723–736.
147. Hayreh SS, Kolder HE, Weingeist TA. Central retinal artery occlusion and retinal tolerance time. *Ophthalmology.* 1980;87:75–78.
148. Roth S, Pietrzky Z. Blood flow after retinal ischemia in cats. *Invest Ophthalmol Vis Sci.* 1994;35:3209–3217.
149. Lin J, Roth S. Ischemic preconditioning attenuates hypoperfusion after retinal ischemia in rats. *Invest Ophthalmol Vis Sci.* 1999;40:2925–2931.
150. Chen X, Liang Z, Shen W, Shou T. Differential behavior of simple and complex cells in visual cortex during a brief IOP elevation. *Invest Ophthalmol Vis Sci.* 2005;46:2611–2619.

151. Ettaiche M, Heurteaux C, Blondeau N, Borsotto M, Tinel N, Lazdunski M. ATP-sensitive potassium channels (K_{ATP}) in retina: a key role for delayed ischemic tolerance. *Brain Res.* 2001;890:118–129.
152. Roth S, Li B, Rosenbaum PS, et al. Preconditioning provides complete protection against retinal ischemic injury in rats. *Invest Ophthalmol Vis Sci.* 1998;39:777–785.
153. Calway T, Rubin DS, Moss HE, Joslin CE, Beckmann K, Roth S. Perioperative retinal artery occlusion: risk factors in cardiac surgery from the United States National Inpatient Sample 1998–2013. *Ophthalmology.* 2017;124:189–196.
154. Calway T, Rubin DS, Moss HE, Joslin CE, Mehta AI, Roth S. Perioperative retinal artery occlusion: incidence and risk factors in spinal fusion surgery from the US National Inpatient Sample 1998–2013. *J Neuroophthalmol.* 2018;38:36–41.
155. Van Dijk FS, Sillence DO. Osteogenesis imperfecta: clinical diagnosis, nomenclature and severity assessment. *Am J Med Genet A.* 2014;164a:1470–1481.
156. Cole DE, Carpenter TO. Bone fragility, craniosynostosis, ocular proptosis, hydrocephalus, and distinctive facial features: a newly recognized type of osteogenesis imperfecta. *J Pediatr.* 1987;110:76–80.
157. Sys J, Michielsen J, Mertens E, Verstreken J, Tassignon MJ. Central retinal artery occlusion after spinal surgery. *Eur Spine J.* 1996;5:74–75.
158. Grossman W, Ward WT. Central retinal artery occlusion after scoliosis surgery with a horseshoe headrest. Case report and literature review. *Spine (Phila Pa 1976).* 1993;18:1226–1228.
159. Kumar N, Jivan S, Topping N, Morrell AJ. Blindness and rectus muscle damage following spinal surgery. *Am J Ophthalmol.* 2004;138:889–891.
160. Carr RE, Siegel IM. Unilateral retinitis pigmentosa. *Arch Ophthalmol.* 1973;90:21–26.
161. Jampol LM, Goldbaum M, Rosenberg M, Bahr R. Ischemia of ciliary arterial circulation from ocular compression. *Arch Ophthalmol.* 1975;93:1311–1317.
162. Malihu M, Turbin RE, Frohman LP. Saturday night retinopathy with ophthalmoplegia: a case series. *Neuroophthalmology.* 2015;39:77–82.
163. Hollenhorst RW, Sviens HJ, Benoit CF. Unilateral blindness occurring during anesthesia for neurosurgical operations. *AMA Arch Ophthalmol.* 1954;52:819–830.
164. Bui BV, Edmunds B, Cioffi GA, Fortune B. The gradient of retinal functional changes during acute intraocular pressure elevation. *Invest Ophthalmol Vis Sci.* 2005;46:202–213.
165. Zhang C, Rosenberg DM, Shaikh AR, et al. Ischemic preconditioning attenuates apoptotic cell death in the rat retina. *Invest Ophthalmol Vis Sci.* 2002;43:3059–3066.
166. Zhu Y, Ohlemiller KK, McMahan BK, Gidday JM. Mouse models of retinal ischemic tolerance. *Invest Ophthalmol Vis Sci.* 2002;43:1903–1911.
167. Grant GP, Turbin RE, Bennett HL, Szirth BC, Heary RF. Use of the Proneview Helmet System with a modified table platform for open access to the eyes during prone spine surgery. *Anesth Analg.* 2006;103:499–500.
168. Roth S, Tung A, Ksiazek S. Visual loss in a prone-positioned spine surgery patient with the head on a foam headrest and goggles covering the eyes: an old complication with a new mechanism. *Anesth Analg.* 2007;104:1185–1187; tables of contents.
169. Rubinstein A, Riddell CE, Akram I, Ahmad A, Benjamin L. Orbital emphysema leading to blindness following routine functional endoscopic sinus surgery. *Arch Ophthalmol.* 2005;123:1452.
170. Amorim Correa JL, Acioly MA. The enigma of orbital compartment syndrome after lumbar spine surgery in the prone position: case report and literature review. *World Neurosurg.* 2018;110:309–314.
171. Habets JGV, Haeren RHL, Lie SAN, Bauer NJC, Dings JTA. Acute monocular blindness due to orbital compartment syndrome following pterional craniotomy. *World Neurosurg.* 2018;114:72–75.
172. Pahl FH, de Oliveira MF, Dal Col Lucio JE, Souza ECEF. Orbital compartment syndrome after frontotemporal craniotomy: case report and review of literature. *World Neurosurg.* 2018;109:218–221.
173. Rimpilainen R, Hautala N, Koskenkari J, et al. Comparison of the use of minimized cardiopulmonary bypass with conventional techniques on the incidence of retinal microemboli during aortic valve replacement surgery. *Perfusion.* 2011;26:479–486.
174. Blauth CI, Smith PL, Arnold JV, Jagoe JR, Wootton R, Taylor KM. Influence of oxygenator type on the prevalence and extent of microembolic retinal ischemia during cardiopulmonary bypass. Assessment by digital image analysis. *J Thorac Cardiovasc Surg.* 1990;99:61–69.
175. Slaughter MS, Sobieski MA, Tatooles AJ, Pappas PS. Reducing emboli in cardiac surgery: does it make a difference? *Artif Organs.* 2008;32:880–884.
176. Herren JI, Kunzelman KS, Vocolka C, Cochran RP, Spiess BD. Angiographic and histological evaluation of porcine retinal vascular damage and protection with perfluorocarbons after massive air embolism. *Stroke.* 1998;29:2396–2403.
177. Bhatti MT, Stankiewicz JA. Ophthalmic complications of endoscopic sinus surgery. *Surv Ophthalmol.* 2003;48:389–402.
178. Haller D, Gosepath J, Mann WJ. The management of acute visual loss after sinus surgery—two cases of rhinogenic optic neuropathy. *Rhinology.* 2006;44:216–218.
179. Savino PJ, Burde RM, Mills RP. Visual loss following intranasal anesthetic injection. *J Clin Neuroophthalmol.* 1990;10:140–144.
180. Jacobs SM, McInnis CP, Kapelis M, Chang SH. Incidence, risk factors, and management of blindness after orbital surgery. *Ophthalmology.* 2018;125:1100–1108.
181. Christie B, Block L, Ma Y, Wick A, Afifi A. Retrobulbar hematoma: a systematic review of factors related to outcomes. *J Plast Reconstr Aesthet Surg.* 2018;71:155–161.
182. Moss WJ, Kjos KB, Karnezis TT, Lebovits MJ. Intranasal steroid injections and blindness: our personal experience and a review of the past 60 years. *Laryngoscope.* 2015;125:796–800.
183. Byers B. Blindness secondary to steroid injections into the nasal turbinates. *Arch Ophthalmol.* 1979;97:79–80.
184. Watanabe W, Kuwabara R, Nakahara T, et al. Severe ocular and orbital toxicity after intracarotid injection of carboplatin for recurrent glioblastomas. *Graefes Arch Clin Exp Ophthalmol.* 2002;240:1033–1035.
185. Anderson Jr B. Ocular effects of changes in oxygen and carbon dioxide tension. *Trans Am Ophthalmol Soc.* 1968;66:423–474.
186. Ahn SJ, Kim JM, Hong JH, et al. Efficacy and safety of intra-arterial thrombolysis in central retinal artery occlusion. *Invest Ophthalmol Vis Sci.* 2013;54:7746–7755.
187. Nedelmann M, Graef M, Weinand F, et al. Retrobulbar spot sign predicts thrombolytic treatment effects and etiology in central retinal artery occlusion. *Stroke.* 2015;46:2322–2324.
188. Schrag M, Youn T, Schindler J, Kirshner H, Greer D. Intravenous fibrinolytic therapy in central retinal artery occlusion: a patient-level meta-analysis. *JAMA Neurol.* 2015;72:1148–1154.
189. Page PS, Khattar NK, White AC, et al. Intra-arterial thrombolysis for acute central retinal artery occlusion: a systematic review and meta-analysis. *Front Neurol.* 2018;9:76.
190. Tamai K, Toumoto E, Majima A. Local hypothermia protects the retina from ischaemic injury in vitrectomy. *Br J Ophthalmol.* 1997;81:789–794.
191. Deleted in proofs.
192. Deleted in proofs.
193. Johnson LN, Arnold AC. Incidence of nonarteritic and arteritic anterior ischemic optic neuropathy. Population-based study in the state of Missouri and Los Angeles County, California. *J Neuroophthalmol.* 1994;14:38–44.
194. Arnold AC. Pathogenesis of nonarteritic anterior ischemic optic neuropathy. *J Neuroophthalmol.* 2003;23:157–163.
195. Tice DA. Ischemic optic neuropathy and cardiac surgery. *Ann Thorac Surg.* 1987;44:677.
196. Schobel GA, Schmidbauer M, Millesi W, Undt G. Posterior ischemic optic neuropathy following bilateral radical neck dissection. *Int J Oral Maxillofac Surg.* 1995;24:283–287.
197. Fenton S, Fenton JE, Browne M, Hughes JP, Connor MO, Timon CI. Ischaemic optic neuropathy following bilateral neck dissection. *J Laryngol Otol.* 2001;115:158–160.
198. Kaeser PF, Borrut FX. Visual loss after orthopedic procedures. *J Arthroplasty.* 2011;26: 338.e17–9.
199. Huang TW, Liu CM, Cheng PW, Yang CH. Posterior ischemic optic neuropathy following endoscopic sinus surgery. *Otolaryngol Head Neck Surg.* 2003;129:448–450.
200. Buono LM, Foroozan R. Perioperative posterior ischemic optic neuropathy: review of the literature. *Surv Ophthalmol.* 2005;50:15–26.
201. Roth S, Dreixler J, Newman NJ. Haemodilution and head-down tilting induce functional injury in the rat optic nerve: a model for peri-operative ischemic optic neuropathy. *Eur J Anaesthesiol.* 2018;35:840–847.

202. Arnold AC, Hepler RS. Fluorescein angiography in acute non-arteritic anterior ischemic optic neuropathy. *Am J Ophthalmol*. 1994;117:222–230.
203. Subramanian PS, Gordon LK, Bonelli L, Arnold AC. Progression of asymptomatic optic disc swelling to non-arteritic anterior ischaemic optic neuropathy. *Br J Ophthalmol*. 2017;101:671–675.
204. Grieshaber MC, Flammer J. Does the blood-brain barrier play a role in glaucoma? *Surv Ophthalmol*. 2007;52(suppl 2):S115–S121.
205. Guy J. New therapies for optic neuropathies: development in experimental models. *Curr Opin Ophthalmol*. 2000;11:421–429.
206. Bernstein SL, Guo Y, Kelman SE, Flower RW, Johnson MA. Functional and cellular responses in a novel rodent model of anterior ischemic optic neuropathy. *Invest Ophthalmol Vis Sci*. 2003;44:4153–4162.
207. Tesser RA, Niendorf ER, Levin LA. The morphology of an infarct in nonarteritic anterior ischemic optic neuropathy. *Ophthalmology*. 2003;110:2031–2035.
208. Patel HR, Margo CE. Pathology of ischemic optic neuropathy. *Arch Pathol Lab Med*. 2017;141:162–166.
209. Hayreh S, In: Pillunat L, Harris A, Anderson D, Greve E, eds. *Blood Supply of the Optic Nerve Head: A “Reality Check”*. Current Concepts in Ocular Blood Flow In Glaucoma. The Hague: Kugler; 1999.
210. Olver JM, Spalton DJ, McCartney AC. Microvascular study of the retrobulbar optic nerve in man: the possible significance in anterior ischaemic optic neuropathy. *Eye (Lond)*. 1990;4(Pt 1):7–24.
211. Knox DL, Kerrison JB, Green WR. Histopathologic studies of ischemic optic neuropathy. *Trans Am Ophthalmol Soc*. 2000;98:203–220; discussion 221–2.
212. Hayreh SS, Zimmerman MB. Nonarteritic anterior ischemic optic neuropathy: refractive error and its relationship to cup/disc ratio. *Ophthalmology*. 2008;115:2275–2281.
213. Saito H, Tomidokoro A, Tomita G, Araie M, Wakakura M. Optic disc and peripapillary morphology in unilateral nonarteritic anterior ischemic optic neuropathy and age- and refraction-matched normals. *Ophthalmology*. 2008;115:1585–1590.
214. Beck RW, Servais GE, Hayreh SS. Anterior ischemic optic neuropathy. IX. Cup-to-disc ratio and its role in pathogenesis. *Ophthalmology*. 1987;94:1503–1508.
215. Hayreh SS, Jonas JB. Optic disc morphology after arteritic anterior ischemic optic neuropathy. *Ophthalmology*. 2001;108:1586–1594.
216. Isayama Y, Hiramatsu K, Asakura S, Takahashi T. Posterior ischemic optic neuropathy. I. Blood supply of the optic nerve. *Ophthalmologica*. 1983;186:197–203.
217. Hayreh SS, Bill A, Sperber GO. Effects of high intraocular pressure on the glucose metabolism in the retina and optic nerve in old atherosclerotic monkeys. *Graefes Arch Clin Exp Ophthalmol*. 1994;232:745–752.
218. Weinstein JM, Duckrow RB, Beard D, Brennan RW. Regional optic nerve blood flow and its autoregulation. *Invest Ophthalmol Vis Sci*. 1983;24:1559–1565.
219. Movaffagh A, Chamot SR, Petrig BL, Riva CE. Blood flow in the human optic nerve head during isometric exercise. *Exp Eye Res*. 1998;67:561–568.
220. Riva CE, Hero M, Titze P, Petrig B. Autoregulation of human optic nerve head blood flow in response to acute changes in ocular perfusion pressure. *Graefes Arch Clin Exp Ophthalmol*. 1997;235:618–626.
221. Pillunat LE, Anderson DR, Knighton RW, Joos KM, Feuer WJ. Autoregulation of human optic nerve head circulation in response to increased intraocular pressure. *Exp Eye Res*. 1997;64:737–744.
222. Vaphiades MS. Optic nerve enhancement in hypotensive ischemic optic neuropathy. *J Neuroophthalmol*. 2004;24:235–236.
223. Bolacchi F, Garaci FG, Martucci A, et al. Differences between proximal versus distal intraorbital optic nerve diffusion tensor magnetic resonance imaging properties in glaucoma patients. *Invest Ophthalmol Vis Sci*. 2012;53:4191–4196.
224. Parisi V, Gallinaro G, Ziccardi L, Coppola G. Electrophysiological assessment of visual function in patients with non-arteritic ischaemic optic neuropathy. *Eur J Neurol*. 2008;15:839–845.
225. Ho VT, Newman NJ, Song S, Ksiazek S, Roth S. Ischemic optic neuropathy following spine surgery. *J Neurosurg Anesthesiol*. 2005;17:38–44.
226. Golinvaux NS, Bohl DD, Basques BA, Grauer JN. Administrative database concerns: accuracy of International Classification of Diseases, Ninth Revision coding is poor for preoperative anemia in patients undergoing spinal fusion. *Spine (Phila Pa 1976)*. 2014;39:2019–2023.
227. Holy SE, Tsai JH, McAllister RK, Smith KH. Perioperative ischemic optic neuropathy: a case control analysis of 126,666 surgical procedures at a single institution. *Anesthesiology*. 2009;110:246–253.
228. Practice advisory for perioperative visual loss associated with spine surgery: a report by the American Society of Anesthesiologists Task Force on Perioperative Blindness. *Anesthesiology*. 2006;104:1319–1328.
229. Practice advisory for perioperative visual loss associated with spine surgery: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Visual Loss. *Anesthesiology*. 2012;116:274–285.
230. Practice advisory for perioperative visual loss associated with spine surgery 2019: an Updated Report by the American Society of Anesthesiologists Task Force on Perioperative Visual Loss, the North American Neuro-Ophthalmology Society, and the Society for Neuroscience in Anesthesiology and Critical Care. *Anesthesiology*. 2019;130:12–30.
231. Farshad M, Bauer DE, Wechsler C, Gerber C, Aichmair A. Risk factors for perioperative morbidity in spine surgeries of different complexities: a multivariate analysis of 1,009 consecutive patients. *Spine J*. 2018;18:1625–1631.
232. Brown RH, Schauble JF, Miller NR. Anemia and hypotension as contributors to perioperative loss of vision. *Anesthesiology*. 1994;80:222–226.
233. Katz DM, Trobe JD, Cornblath WT, Kline LB. Ischemic optic neuropathy after lumbar spine surgery. *Arch Ophthalmol*. 1994;112:925–931.
234. Shen Y, Silverstein JC, Roth S. In-hospital complications and mortality after elective spinal fusion surgery in the United States: a study of the Nationwide Inpatient Sample from 2001 to 2005. *J Neurosurg Anesthesiol*. 2009;21:21–30.
235. Murphy GS, Hessel 2nd EA, Groom RC. Optimal perfusion during cardiopulmonary bypass: an evidence-based approach. *Anesth Analg*. 2009;108:1394–1417.
236. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management*. *Anesthesiology*. 2015;122:241–275.
237. Ferraris VA, Ferraris SP, Saha SP, et al. Perioperative blood transfusion and blood conservation in cardiac surgery: the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists clinical practice guideline. *Ann Thorac Surg*. 2007;83:S27–86.
238. Williams EL, Hart Jr WM, Tempelhoff R. Postoperative ischemic optic neuropathy. *Anesth Analg*. 1995;80:1018–1029.
239. Hayreh SS. Anterior ischemic optic neuropathy. 8th. Clinical features and pathogenesis of post-hemorrhagic amaurosis. *Ophthalmology*. 1987;94:1488–1502.
240. Chamot SR, Petrig BL, Pournaras CJ, Riva CE. Effect of isovolumic hemodilution on oxygen delivery to the optic nerve head. *Klin Monbl Augenheilkd*. 2002;219:292–295.
241. Lee LA, Deem S, Glenny RW, et al. Effects of anemia and hypotension on porcine optic nerve blood flow and oxygen delivery. *Anesthesiology*. 2008;108:864–872.
242. Grant GP, Szirth BC, Bennett HL, et al. Effects of prone and reverse Trendelenburg positioning on ocular parameters. *Anesthesiology*. 2010;112:57–65.
243. Cheng MA, Todorov A, Tempelhoff R, McHugh T, Crowder CM, Lau-ryssen C. The effect of prone positioning on intraocular pressure in anesthetized patients. *Anesthesiology*. 2001;95:1351–1355.
244. Murphy MA. Bilateral posterior ischemic optic neuropathy after lumbar spine surgery. *Ophthalmology*. 2003;110:1454–1457.
245. Roth S, Nunez R, Schreider BD. Unexplained visual loss after lumbar spinal fusion. *J Neurosurg Anesthesiol*. 1997;9:346–348.
246. Geijer C, Bill A. Effects of raised intraocular pressure on retinal, pre-laminar, laminar, and retrobulbar optic nerve blood flow in monkeys. *Invest Ophthalmol Vis Sci*. 1979;18:1030–1042.
247. He Z, Bui BV, Vingrys AJ. The rate of functional recovery from acute IOP elevation. *Invest Ophthalmol Vis Sci*. 2006;47:4872–4880.
248. Bui BV, Fortune B. Ganglion cell contributions to the rat full-field electroretinogram. *J Physiol*. 2004;555:153–173.
249. Cullinane DC, Jenkins JM, Reddy S, et al. Anterior ischemic optic neuropathy: a complication after systemic inflammatory response syndrome. *J Trauma*. 2000;48:381–386; discussion 386–7.
250. Sullivan SR, Ahmadi AJ, Singh CN, et al. Elevated orbital pressure: another untoward effect of massive resuscitation after burn injury. *J Trauma*. 2006;60:72–76.

251. Alian AA, Atteya G, Gaal D, et al. Ventilation-induced modulation of pulse oximeter waveforms: a method for the assessment of early changes in intravascular volume during spinal fusion surgery in pediatric patients. *Anesth Analg*. 2016;123:346–356.
252. Hayreh SS, Joos KM, Podhajsky PA, Long CR. Systemic diseases associated with nonarteritic anterior ischemic optic neuropathy. *Am J Ophthalmol*. 1994;118:766–780.
253. Lee LA, Lam AM. Unilateral blindness after prone lumbar spine surgery. *Anesthesiology*. 2001;95:793–795.
254. Corda DM, Dexter F, Pasternak JJ, Trentman TL, Nottmeier EW, Brull SJ. Patients' perspective on full disclosure and informed consent regarding postoperative visual loss associated with spinal surgery in the prone position. *Mayo Clin Proc*. 2011;86:865–868.
255. Bae J, Lee SH. Minimally invasive spinal surgery for adult spinal deformity. *Neurospine*. 2018;15:18–24.
256. Hussain NS, Perez-Cruet MJ. Complication management with minimally invasive spine procedures. *Neurosurg Focus*. 2011;31:E2.
257. Edwards 2nd CC, Lessing NL, Ford L, Edwards CC. Deep vein thrombosis after complex posterior spine surgery: does staged surgery make a difference? *Spine Deform*. 2018;6:141–147.
258. Hassanzadeh H, Gjolaj JP, El Dafrawy MH, et al. The timing of surgical staging has a significant impact on the complications and functional outcomes of adult spinal deformity surgery. *Spine J*. 2013;13:1717–1722.
259. Maddox JJ, Pruitt DR, Agel J, Bransford RJ. Unstaged versus staged posterior-only thoracolumbar fusions in deformity: a retrospective comparison of perioperative complications. *Spine J*. 2014;14:1159–1165.
260. Passias PG, Poorman GW, Jalai CM, et al. Outcomes of open staged corrective surgery in the setting of adult spinal deformity. *Spine J*. 2017;17:1091–1099.
261. Siemionow K, Tyrakowski M, Patel K, Neckrysh S. Comparison of perioperative complications following staged versus one-day anterior and posterior cervical decompression and fusion crossing the cervico-thoracic junction. *Neurol Neurochir Pol*. 2014;48:403–409.
262. Hayreh SS. Anterior ischaemic optic neuropathy. 3rd. Treatment, prophylaxis, and differential diagnosis. *Br J Ophthalmol*. 1974;58:981–989.
263. Saxena R, Singh D, Sharma M, James M, Sharma P, Menon V. Steroids versus no steroids in nonarteritic anterior ischemic optic neuropathy: a randomized controlled trial. *Ophthalmology*. 2018;125:1623–1627.
264. Wolf GL, Capuano C, Hartung J. Nitrous oxide increases intraocular pressure after intravitreal sulfur hexafluoride injection. *Anesthesiology*. 1983;59:547–548.
265. Vote BJ, Hart RH, Worsley DR, Borthwick JH, Laurent S, McGeorge AJ. Visual loss after use of nitrous oxide gas with general anesthetic in patients with intraocular gas still persistent up to 30 days after vitrectomy. *Anesthesiology*. 2002;97:1305–1308.
266. Seaberg RR, Freeman WR, Goldbaum MH, Manecke Jr GR. Permanent postoperative vision loss associated with expansion of intraocular gas in the presence of a nitrous oxide-containing anesthetic. *Anesthesiology*. 2002;97:1309–1310.

JIE ZHOU, ALA NOZARI, BRIAN BATEMAN, PAUL DENNEY ALLEN, and ISAAC NESS PESSAH

KEY POINTS

- Malignant hyperthermia (MH) is a pharmacogenetic disorder inherited primarily in an autosomal dominant pattern.
- MH susceptibility is linked to 230 mutations in the skeletal muscle ryanodine receptor (RyR1) and four mutations in the calcium voltage-gated channel subunit alpha1 S (CACNA1S) genes that encode two Ca^{2+} channels necessary for skeletal muscle excitation-contraction coupling.
- Physical interactions between L-type Ca^{2+} channel ($\text{Ca}_v1.1$) and RyR1 tightly regulate initiation and termination of skeletal muscle excitation-contraction coupling.
- Skeletal muscle accounts for approximately 40% of body weight and inherent changes in its metabolism have profound impacts on whole-body metabolism and physiology.
- Carriers of MH mutations can exhibit mild to moderate muscle impairments in the absence of triggering agents but are rarely diagnosed.
- Carriers of MH mutations are susceptible to anesthetic-triggered runaway skeletal muscle metabolism, which if not promptly treated is lethal.
- Signs of MH, including increased end-tidal CO_2 , increased core temperature, muscle rigidity, tachycardia, and more, are consequences of the fulminant hypermetabolic crisis.
- Exposure to triggering agents or heat stress leads to acute loss of RyR1/ $\text{Ca}_v1.1$ channel regulation, rapid accumulation of Ca^{2+} within the sarcoplasm, and a hypermetabolic crisis that stimulates adenosine triphosphate (ATP) utilization by pumps attempting to restore resting Ca^{2+} balance among sarcoplasmic reticulum, mitochondrial, and extracellular compartments.
- Dantrolene markedly attenuates myoplasmic calcium (Ca^{2+}) concentrations and thereby restores resting Ca^{2+} balance and metabolism, with reversal of clinical signs.
- Evaluation of persons susceptible to MH includes an *in vitro* contracture test (IVCT) and caffeine/halothane contracture test (CHCT), and evaluation of DNA to identify mutations.
- Currently DNA testing alone can be used to evaluate 42 human mutations and all swine, equine, and canine MH.
- Future MH goals include advancement of genetic evaluations in North American and European medical programs and stronger finances to support genetic studies, the identification of the mode of action of dantrolene, a determination of the immediate cause of triggering MH, and the development of effective, noninvasive tests for MH susceptibility.
- The absence of mutations in dystrophin, along with dystrophin-associated glycoproteins, is involved in sarcolemmal stability. Its defects are responsible for Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD).
- Whereas the risk for an MH mutation in DMD and BMD patients is similar to that in the general population, the incidence of MH-like anesthetic events has been reported to be 0.002 with DMD and 0.00036 with BMD.
- Succinylcholine is contraindicated in DMD and BMD patients because of the risk of rhabdomyolysis and hyperkalemia as a result of their unstable sarcolemmal membrane.
- Reversal of neuromuscular blockade with sugammadex is a practical alternative to the management of many of these disorders, if rocuronium or vecuronium is used. The combination of rocuronium and sugammadex has improved the anesthetic management for some of these challenging disorders.

Malignant Hyperthermia

Malignant hyperthermia (MH) is one of the most devastating anesthesia-related complications. The fulminant MH syndrome is elicited by the administration of triggering anesthetic agents, such as volatile halogenated anesthetics or depolarizing neuromuscular blocking agents (NMBAs). MH has been and continues to be a life-threatening complication of anesthesia if the diagnosis is not made promptly and treatment is not begun in a timely fashion. Unlike other disorders described in this chapter, MH has virtually no characteristic phenotype before exposure to the triggering agent and is truly an example of the interaction of genes and the environment. Also covered in this chapter are some of the neuromuscular disorders, although rarely encountered in a routine anesthetic practice. This group of disorders challenges both perioperative management and intensive care. They affect the normal function of peripheral nerves, the neuromuscular junction, and/or muscles. Although such diseases are thought to be rare, the number of patients that a clinician may encounter is increasing because of better medical care, increasing longevity, and other possible unidentified factors. Neuromuscular disorders have significant potential to interact with an improper anesthetic plan, and all affected patients require special perioperative attention for anesthetic management. In this area, the armamentarium of invasive and noninvasive diagnostic tools is being developed, especially in genetics.

MH is a pharmacogenetic clinical syndrome that, in its classic form, occurs during anesthesia with volatile halogenated alkanes such as halothane, isoflurane/sevoflurane, /desflurane, and/or administration of the depolarizing muscle relaxant succinylcholine. The fulminant MH episode observed clinically produces muscle hypermetabolism with rapidly increasing body temperature, by as much as 1°C in 5 minutes, and extreme acidosis as a result of acute loss of control of intracellular ionized calcium (Ca^{2+}). It is the sustained high levels of sarcoplasmic Ca^{2+} that rapidly drives skeletal muscle into a hypermetabolic state that may proceed to severe rhabdomyolysis. Although MH was initially associated with a mortality rate of 60%, earlier diagnosis and the use of dantrolene have reduced the mortality to less than 1.4%.¹ Current cases of MH are restricted in severity because of diagnostic awareness, early detection through end-expired carbon dioxide (CO_2), the use of less potent anesthetic triggers, and prior administration of drugs that attenuate the progression of the fulminant episode. Estimates of the incidence of fulminant MH vary widely from one case per 10,000 to 1:250,000 anesthetics administered.² The prevalence of MH events in Japan was calculated to be between 1:60,000 and 1:73,000.^{3,4} However, the prevalence of MH mutations within kindred known to transmit MH-susceptibility (MHS) mutations may be as high as 1:2000.⁵ Males appear to be more susceptible to developing a clinical MH episode than females.^{3,6} A gender difference in MHS has also been demonstrated in knock-in mice expressing human MH mutation RyR1-T4825I.⁷ The pediatric population accounts for 52.1% of all MH reactions.^{8,9}

Between 50% and 80% of genotyped patients who have had a clinical MH syndrome and a positive muscle biopsy

have had their disease linked to one of more than 230 mutations in the type 1 ryanodine receptor (RyR1; sarcoplasmic reticulum [SR] Ca^{2+} release channel) gene and four mutations in L-type Ca^{2+} channel ($\text{Ca}_V1.1$), the pore subunit of the slowly inactivating L-type Ca^{2+} channel encoded by Calcium Voltage-Gated Channel Subunit Alpha1 S (CACNA1S) (also referred to as the dihydropyridine receptor [DHPR]).¹⁰ The genetics of MHS and the related abnormal function of RyR1, the DHPR, and associated proteins are being investigated at the molecular biologic level, with a porcine model and several new mouse models providing intricate details about the etiology of the disorder. Parallel studies in humans are limited by scarce material for scientific study and are complicated by the fact that phenotypes within a single genotype vary as a result of sex, age, genetic, epigenetic, and environmental modifiers.

Public education and communication in the United States are provided by Malignant Hyperthermia Association of the United States (MHAUS, 11 E. State Street, P.O. Box 1069, Sherburne, NY 13460, U.S.A.; telephone: (+1) 607-674-7901; fax: (+1) 607-674-7910; e-mail: info@mhaus.org; website: <http://www.mhaus.org>), and by emergency consultation with the MH Hotline (1-800-MHHYPER, or 1-800-644-9737). The North American Malignant Hyperthermia Registry (NAMHR), a professional subsidiary of MHAUS, collates findings from muscle biopsy centers in Canada and the United States (NAMHR, 1345 SW Center Drive, P.O. Box 100254, Gainesville, FL 32610, U.S.A.); telephone: (+1) 888-274-7899; fax: (+1) 352-392-7029.; website <http://anest.ufl.edu/namhr/>).

HISTORY

Between 1915 and 1925, one family experienced three anesthetic-induced MH deaths with rigidity and hyperthermia and was puzzled for decades regarding the cause of these deaths.^{11,12} MHS was eventually confirmed in three descendants by *in vitro* muscle biopsy tests.¹¹ In 1929, Ombrédanne described anesthesia-induced post-operative hyperthermia and pallor in children accompanied by significant mortality but did not detect any familial relationships.¹³ Critical worldwide attention to MH began in 1960 when Denborough and associates reported a 21-year-old Australian with an open leg fracture who was more anxious about anesthesia than about surgery because 10 of his relatives died during or after anesthesia.¹⁴ Denborough and colleagues initially anesthetized him with the then-new agent halothane, halted it when signs of MH appeared, successfully treated the symptoms, aborted the syndrome, and subsequently used spinal anesthesia. Further evaluations by George Locher in Wausau, Wisconsin, and Beverly Britt in Toronto, Canada, led to the discovery that MH risk was indeed familial.¹⁵ It was also found that the cause of the syndrome was the result of skeletal muscle involvement rather than central loss of temperature control by the recognition of increased muscle metabolism or muscle rigidity early in the syndrome, low-threshold contracture responses, and elevated creatine kinase (CK) values.¹⁶

Interestingly, a similar syndrome was discovered in swine inbred with breeding patterns designed to produce

a rapid growth rate and superior muscle development (e.g., Landrace, Piétrain, Duroc, and Poland China). *Porcine stress syndrome*,¹⁷ which is associated with increased metabolism, acidosis, rigidity, fever, and death from rapid deterioration of muscle and results in pale, soft, exudative pork,¹⁸ can be triggered by any stress, such as separation, shipping conditions, weaning, fighting, coitus, or preparation for slaughter, and had become a significant problem for meat production. In 1966, Hall and coworkers reported that a syndrome that appeared to be identical to MH could be induced in stress-susceptible swine by the administration of halothane and succinylcholine.¹⁹ The cause of this syndrome in pigs was discovered to be a single missense mutation in RyR1, and all susceptible swine have the same Arg615Cys mutation in the SR calcium release channel RyR1.²⁰

In 1975, Harrison described the efficacy of dantrolene in preventing and treating porcine MH,²¹ which was rapidly confirmed in humans by a multihospital evaluation of dantrolene used to treat anesthetic-induced MH episodes.²² Today, dantrolene still remains the primary pharmacologic approach for successful MH therapy.

PHYSIOLOGY AND PATHOPHYSIOLOGY OF EXCITATION-CONTRACTION COUPLING AND MALIGNANT HYPERTHERMIA

MH is a syndrome caused by dysregulation of excitation-contraction (EC) coupling in skeletal muscle. Normal muscle contraction is initiated by nerve impulses arriving at the neuromuscular junction (i.e., the motor end plate) that trigger the release of acetylcholine from the nerve terminal. Acetylcholine activates nicotinic cholinergic receptors (nAChR), nonselective cation channels located at the postsynaptic neuromuscular junction, that are essential for local depolarization of the surface muscle membrane (sarcolemma) and initiating action potentials that propagate

rapidly along the sarcolemma of muscle cells. Invaginations of the sarcolemma (termed transverse or T tubules) act as conduits to rapidly and uniformly direct-action potentials deep within the myofibrils where they transduce a conformational change in the "voltage sensor" protein $\text{Ca}_V1.1$. A central T-tubule is flanked on both sides by a terminal cisternae element from the SR that contains the Ca^{2+} release channels (RyR1). Conformational changes in $\text{Ca}_V1.1$ residing within the T-tubule are mechanically transmitted to RyR1 residing in the junctional face of the SR. More specifically, physical coupling of four $\text{Ca}_V1.1$ (dihydropyridine receptor) units to every second RyR1 channel form linear arrays at specialized junctions (*triadic junctions*) that are essential for linking electrical signals at the T tubules with the release of Ca^{2+} stored within the SR. Release of SR Ca^{2+} causes the free, cytoplasmic (sarcoplasmic) Ca^{2+} concentration to increase from 10^{-7} M to about 10^{-5} M. This released Ca^{2+} binds to contractile proteins (troponin C and tropomyosin) in the thin filament to expose myosin's actin binding sites which allow shortening and force development by the muscle fibers (i.e., muscle contraction). The entire process is termed excitation-contraction coupling (EC coupling). Intracellular Ca^{2+} pumps (i.e., sarcoplasmic/endoplasmic reticulum Ca^{2+} -adenosine triphosphatase [ATPase], or SERCA) rapidly sequester Ca^{2+} back into the SR lumen, and muscle relaxation begins when the Ca^{2+} concentration falls below 10^{-6} M and ends when the resting sarcoplasmic Ca^{2+} concentration is restored to 10^{-7} M. Because both contraction and relaxation are energy-related processes that consume adenosine triphosphate (ATP), knowing the molecular events contributing to EC coupling and the subsequent relaxation phase is essential to understanding the cause of MH (Fig. 35.1). Clinical and laboratory data from humans, swine, and mice with knock-in mutations indicate that the fulminant MH syndrome is associated with a persistent increase in the concentration of sarcoplasmic Ca^{2+} .²³⁻²⁶ The increased activity of pumps and exchangers trying

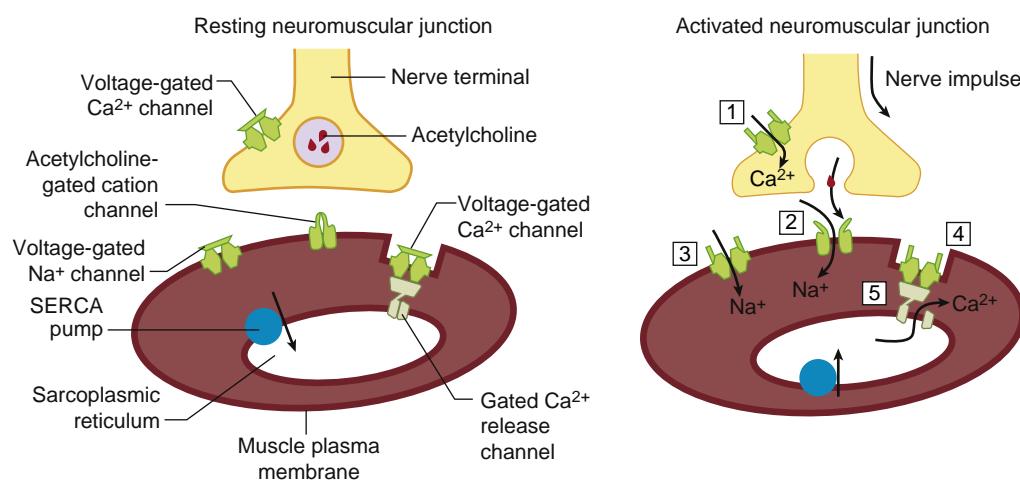


Fig. 35.1 Key ion channels involved in neuromuscular transmission and excitation-contraction coupling. Nerve impulses arriving at the nerve terminal activate voltage-gated Ca^{2+} channels (1). The resulting increase in cytosolic Ca^{2+} concentration is essential for the exocytosis of acetylcholine. Binding of acetylcholine to postsynaptic nicotinic cholinergic receptors (nAChR) activates an integral nonselective cation channel that depolarizes the sarcolemma (2). Depolarizing the sarcolemma to threshold activates voltage-gated Na^+ channels (3), which initiates action potential impulses that propagate deep into the muscle through the transverse tubule system. Within the transverse tubule system, L-type voltage-gated Ca^{2+} channels sense membrane depolarization and undergo a conformational change (4). A physical link between these voltage sensors and the ryanodine receptor (RyR1) sarcoplasmic reticulum Ca^{2+} channel is the means by which the electrical signal is transferred from the T tubule to Ca^{2+} release from the sarcoplasmic reticulum (5). (Modified from Alberts B, Bray D, Lewis J, et al. *Molecular Biology of the Cell*. 3rd ed. New York: Garland Press; 1994.)

correct the increase in sarcoplasmic Ca^{2+} associated with triggered MH increases the need for ATP, which in turn produces heat. Thus the common etiological feature of the disorder is hyperthermia. The rigidity that is frequently seen during a fulminant MH episode is the result of the inability of the Ca^{2+} pumps and transporters to reduce the unbound sarcoplasmic Ca^{2+} below the contractile threshold (10^{-6} M). Dantrolene is an effective therapeutic for treatment of fulminant MH because it reduces the concentration of sarcoplasmic Ca^{2+} to below contractile threshold. However, the pathway by which dantrolene lowers sarcoplasmic Ca^{2+} is complex and still not fully understood. Dantrolene's ability to suppress Ca^{2+} release from SR appears to depend on elevated sarcoplasmic Mg^{2+} concentration²⁷; however the drug also attenuates depolarized-triggered Ca^{2+} entry mediated by $\text{Ca}_V1.1$, which is exacerbated in MHS muscle cells and MH normal muscle cells exposed to ryanodine.²⁸ Thus whether dantrolene directly inhibits RyR1 or requires additional intermediates within the triad junctions remains to be clarified.

Malignant Hyperthermia Is the Result of Abnormal Function of Muscle Calcium Release Units

RYANODINE RECEPTORS

Ryanodine receptors (RyRs) within the muscle are synonymous with the junctional foot protein/SR calcium release channel, and are so named because they specifically bind the toxic plant alkaloid ryanodine, which can activate or inhibit the channel depending on its concentration.^{29,30} In all mammals there are three RyR isoforms. In humans, they are encoded by three genes located on chromosomes 19q13.1,³¹ 1q42.1-q43,³² and 15q14-q15,³³ for the "skeletal" (RyR1), "cardiac" (RyR2), and "brain" (RyR3) isoforms, respectively. Each functional RyR is a homotetramer consisting of four identical subunits (~5000 amino acids each), and an accessory protein, calstabin 1 (FK506 12-kd binding protein [FKBP12]).³⁴⁻³⁷ The total mass of the tetramer exceeds 2 mega-Daltons. Thus it is one of the largest known proteins and the largest known channel in mammalian species. Evidence of direct coupling of $\text{Ca}_V1.1$ and RyR1 has been demonstrated both by expressing chimeric $\text{Ca}_V1.1/\text{Ca}_V1.2$ cDNA in dysgenic myotubes that lack constitutive expression of $\text{Ca}_V1.1$ ^{38,39} and chimeric RyR1/RyR2/3 cDNA in dyspedic myotubes that lack constitutive expression of RyR1, 2, and 3. Such studies have provided compelling evidence that the cytoplasmic region between repeats II and III (i.e., cytosolic II-III loop) of $\text{Ca}_V1.1$ contains a stretch of 46 amino acids (L720 to Q765) and multiple regions of RyR1 that are essential for engaging bidirectional signaling between $\text{Ca}_V1.1$ and RyR1.⁴⁰⁻⁴²

In the last two decades, our understanding of EC coupling has increased significantly by identifying protein-protein interactions that regulate both the release and sequestration of Ca^{2+} within skeletal muscle. The elemental unit of function has been named the Ca^{2+} release unit (CRU), and it is localized within junctional regions of T-tubule and SR membranes.⁴³ The CRU is a macromolecular assembly of interacting proteins that participate in regulating EC

coupling. RyR1 is a high-conductance channel that regulates release of SR Ca^{2+} and is the central component of the CRU. The functional RyR1 tetramer anchored within the SR membrane physically spans the junctional space to interact with tetrads composed of four voltage-activated $\text{Ca}_V1.1$ subunits within the T-tubule membrane. This physical interaction engages a form of bidirectional signaling that tightly regulates the function of both proteins. Moreover, interaction of $\text{Ca}_V1.1$ and RyR1 does not occur in isolation, but are further subject to regulation by a number of proteins localized within the triad junction, including Homer 1, which physically binds and functionally couples target proteins, calstabin 1, triadin, junctin, Mg29, junctophilin 1 and 2, calsequestrin, calmodulin, STAC 3, the catalytic and regulatory subunits of protein kinase A, and protein phosphatase 1.⁴⁴⁻⁵⁰ It is likely that this list is not complete and that there are other critical components which make up this tightly regulated macromolecular complex. More importantly, there is increasing experimental evidence that mutations found in RyR1 (_{MH}RyR) or $\text{Ca}_V1.1$ (_{MH} $\text{Ca}_V1.1$) can alter protein-protein interactions in the CRU,⁵¹⁻⁵³ as well as alter the functional fidelity of bidirectional signals.⁵⁴⁻⁵⁸

In the presence of certain chemical substances, MH mutations in RyR1 or DHPR cause severe dysregulation of RyR1 channel function. This can be seen in vitro as a heightened sensitivity to volatile anesthetics, 4-chloro-*m*-cresol, caffeine, ryanodine, and potassium depolarization.⁵⁹⁻⁶¹ Chemically induced dysfunction of the RyR1 complex appears to be the principal cause of triggering uncontrolled skeletal muscle metabolic acidosis (aerobic and glycolytic), rigidity, and hyperkalemia, but the mechanisms governing the syndrome are unclear. Also unclear is the relationship among exertional heat illness, exertional rhabdomyolysis, and MHS, an area that requires more investigation and, if possible, controlled clinical studies.⁶²

Two essential cations greatly shape the kinetics and magnitude of Ca^{2+} release in response to depolarizing triggers: Ca^{2+} itself and Mg^{2+} . The normal RyR1 complex responds to Ca^{2+} in a biphasic manner. First, Ca^{2+} activates the channel in a graded manner between 100 nM and 100 μM , whereas higher concentrations inhibit channel activity.^{63,64} This biphasic action is thought to occur via binding of Ca^{2+} to two classes of regulatory sites on RyR1, a high-affinity stimulatory site and a low-affinity inhibitory site.⁴⁶ Mg^{2+} -induced inhibition is the second important physiologic regulator of RyR1 activity in skeletal muscle.^{65,66} Mg^{2+} inhibits RyR1 in a cooperative manner ($n_H \approx 2$; 50% inhibitory concentration [IC_{50}] $\approx 650 \mu\text{M}$). It is likely that Mg^{2+} acts by competing with Ca^{2+} at its activator sites and by binding to yet unidentified low-affinity inhibitory sites.^{67,68} It is possible that MH mutations introduce allosteric instability into the RyR1 complex which leads to a reduction of inhibition rather than directly altering the binding properties of Ca^{2+} or Mg^{2+} , or both, at the activator or inhibitor sites. Therefore hypersensitivity to pharmacologic agents is likely to be closely tied to altered responses to physiologic ligands. However, whether MHS channels are primarily hyporesponsive to inhibition by Mg^{2+} or Ca^{2+} (or both),^{69,70} are hypersensitive to activation by Ca^{2+} , or exhibit altered sensitivities in both directions to both ions seems to be highly dependent on the location of the MH mutation.^{71,72} Studies have also pursued the "leaky channel" hypothesis by examining

SR preparations from homozygous R615C MHS pigs and heterozygous R163C and C512S mice. They observed a significantly lower Ca^{2+} loading capacity (38%, 23%, and 22% lower than matched wild type mice, respectively) primarily mediated by the presence of leaky channels that remain active even with 100 nM extravesicular Ca^{2+} .^{73,74} Recent studies indicated that expression of $\text{Ca}_v1.1$ represses the basal activity of the ryanodine-insensitive RyR1 leaky state.⁵⁶ It is important that MHS mutations appear to not only alter bidirectional signaling during EC coupling^{57,58} and inherent regulation of RyR1 channel functions,^{71,72} but also weaken negative regulation conferred by $\text{Ca}_v1.1$ on RyR1 Ca^{2+} leak under nontriggering conditions.⁵⁴ These findings at the molecular and cellular level using knock-in MHS mice confirm earlier measurements made in porcine and human MHS muscles, myotubes, and myoball preparations and in dyspedic myotubes expressing $_{\text{MH}}\text{RyR1}$ cDNAs, all of which have been shown to have chronically elevated resting cytoplasmic $[\text{Ca}^{2+}]_i$.^{53,60,75}

Results from both functional and structural evidence suggests that long-range interdomain interactions between regions of RyR1 are involved in channel regulation by stabilizing protein conformations critical for normal channel transitions.⁷⁶ A three-dimensional reconstruction of RyR1 by Samso and coworkers shows that the RyR1 architecture is designed to support long-range allosteric pathways such as coupling with $\text{Ca}_v1.1$ and binding to ligands such as calmodulin and FKBP12.⁷⁷ This structural model for gating has been recently confirmed at molecular scale resolution by several laboratories.⁷⁸

VOLTAGE-GATED CALCIUM CHANNELS: ROLE OF $\text{Ca}_v1.1$

Although the majority of mutations that confer MHS reside in the RyR1 gene, three mutations in the *CACNA1S* gene encoding for the $\text{Ca}_v1.1$ subunit of skeletal muscle have been linked to human MHS.^{5,79-81} The Arg1086His mutation in the intracellular loop connecting homologous repeats III and IV of $\text{Ca}_v1.1$ represented the first MHS-causing mutation so far identified in a protein other than RyR1. Physiological characterization of the R1086H mutation further demonstrated that sensitivity of RyR1 activity was significantly enhanced by membrane depolarization or by pharmacologic activators of RyR1 (e.g., caffeine).⁸² In addition, Pirone and associates have identified an MHS-causing Thr1354Ser mutation in the S5-S6 extracellular pore-loop region of the homologous repeat IV of $\text{Ca}_v1.1$. Expression of the T1354S mutation also accelerated L-type Ca^{2+} current kinetics and also contributed to an increase in RyR1-mediated Ca^{2+} release.⁸¹ The Arg174Trp $\text{Ca}_v1.1$ MHS mutation occurs at the innermost basic residue of the IS4 voltage-sensing helix, a residue conserved among all Ca_v channels. Unlike the other $\text{Ca}_v1.1$ MHS mutations, homozygous expression of R174W completely ablates the L-type current, but despite this, has no influence on normal EC coupling. In murine studies, muscle fibers from Het R174W animals verify the increased sensitivity of Ca^{2+} release to caffeine and halothane compared with myotubes expressing wild type $\text{Ca}_v1.1$,^{54,83} but whether this mutation is sufficient to confer anesthetic- or heat-triggered fulminant MHS remains to be tested.

FACTORS OTHER THAN RYANODINE RECEPTOR ABNORMALITIES

Other cellular processes can affect MHS episodes. It has been demonstrated that concurrent administration of nondepolarizing neuromuscular blocking drugs at the same time as triggering agents can delay or prevent the onset of clinical MHS syndrome. Pretreatment of MHS pigs with sufficient nondepolarizing neuromuscular blocking agent, which is used to completely abolish muscle twitch elicited by electrical stimulation of the nerve, prevented halothane from triggering the clinical syndrome for 90 minutes, the longest time point tested.⁸⁴ However, in the continued presence of halothane, when function of the neuromuscular junction was restored by administration of the cholinesterase inhibitor neostigmine, clinical MHS was triggered immediately. This suggested a close relationship between functional neuromuscular junctions or depolarization of the sarcolemma (or both) and the clinical syndrome.

In myotubes, sarcolemmal excitation-coupled Ca^{2+} entry (ECCE) is sensitive to the conformation of the RyR1 and is enhanced by several mutations in RyR1, including MHS mutations.^{44,52,85} ECCE appears to be an inherent property of $\text{Ca}_v1.1$ during long or repetitive depolarization of myotubes,⁸⁶ possibly mediated by shifting $\text{Ca}_v1.1$ to the mode 2 gating conformation. Nevertheless, enhanced ECCE in MHS muscle may contribute to an increased sensitivity to depolarization and appears to be one target for dantrolene's abrogation of responses to both electrical and potassium chloride depolarization.⁵¹ Although *CACNA1S* expression undergoes developmental switching to a splice variant that downregulates Ca^{2+} current density of $\text{Ca}_v1.1$ channels in adult fibers, mutations that maintain Ca^{2+} current density more similar to those measured with embryonic myotubes has recently been shown to promote muscle pathology.⁸⁷

In addition to ECCE, classic store-operated capacitive Ca^{2+} entry pathways similar to the store-operated Ca^{2+} entry (SOCE) seen in nonexcitable cells⁸⁸ have been shown to be present in skeletal muscle⁸⁹⁻⁹¹ and appear to be more active in MHS muscles both at rest as a response to chronic store depletion and during an MHS crisis. These SOCE channels have also been suggested to be a target for dantrolene, but this has not been validated by other studies.⁹² Together, these data suggest that $_{\text{MH}}\text{RyRs}$ or $_{\text{MH}}\text{Ca}_v1.1$ assume a conformation that enhances Ca^{2+} entry via ECCE or SOCE (or both). This enhanced entry, when combined with decreased sensitivity of $_{\text{MH}}\text{RyRs}$ to Ca^{2+} and Mg^{2+} inhibition, could provide cellular conditions that heighten sensitivity to triggering agents and perpetuate the fulminant clinical MHS syndrome.

DANTROLENE

Dantrolene is the only medication that has been shown to be effective in reversing the symptoms of MHS. Preadministration of dantrolene will also prevent the development of fulminant MHS in homozygous pigs or MHS mice when exposed to a triggering stimulus. Dantrolene sodium is a hydantoin derivative (1-[5-(4-nitrophenyl)-2-furanyl]methylene] imino]-2,4-imidazolidinedione) that does not block neuromuscular transmission, but causes muscle weakness by direct muscular action. The properties of dantrolene have been closely correlated with its ability to reduce efflux of Ca^{2+} from the SR in vitro.⁹³ Dantrolene (20 μM) counteracts the

effect of reduced Mg^{2+} inhibition in MH-affected muscle.⁹⁴ Dantrolene (20 μ M) can inhibit the enhanced sensitivity to caffeine seen in MH muscles, and both dantrolene and its more water-soluble analog azumolene (150 μ M) have been shown to reduce depolarization-induced release of Ca^{2+} , both in muscle and in triadic vesicles.⁹⁵ The idea that dantrolene suppresses SR Ca^{2+} release as a result of direct interactions with RyR1 is somewhat controversial. Paul-Pletzer and associates demonstrated that [3 H]azidodantrolene specifically labels the amino terminus of RyR1 defined by the 1400-amino acid residue N-terminal calpain digestion fragment of RyR1.⁹⁶ More detailed analysis further localized the [3 H]azidodantrolene binding site to a single domain containing the core sequence corresponding to amino acid residues 590 through 609 of RyR1.⁹⁶ However, to date, we lack evidence of a direct action of dantrolene on single RyR1 channels studied in lipid bilayers, even though they are reconstituted with calstabin 1, ATP, and activating concentrations of Ca^{2+} , which suggests that dantrolene's main action is to alter key protein-protein interactions. The recent discovery that inhibition of SR Ca^{2+} release by dantrolene requires Mg^{2+} may help resolve the controversy of the conflicting observations on dantrolene inhibition of RyR1 channel activity in Mg^{2+} -free bilayer experiments.²⁷

Genetics

RyR1 mutations have been found in 50% to 80% of patients and relatives who are labeled MHS by positive contracture tests and in almost all families with central core disease (CCD) and King-Denborough syndrome (KDS). More than 210 missense mutations and 8 deletions associated with MH have thus far been detected. Another 29 missense

mutations are associated with CCD and multimimicore disease (MMD) in patients with unknown MH testing status.¹⁰ Interestingly, 40% of missense *RyR1* mutations occur at CpG dinucleotide sequences. Five other loci (17q21-24, 1q32, 3q13, 7q21-24, and 5p) have been linked to families with both positive contracture tests and an unusual response to anesthesia, and have been designated MHS loci 2 through 6, respectively. However, of these five, the only gene that has been shown to be associated with MH is *CACNA1S*,⁹⁷ which codes for $Ca_V1.1$ (the α_{1S} -subunit of DHPR) in the MHS3 locus. Two causative mutations in this gene are linked to less than 1% of MHS families worldwide. In some of the other loci, all genes within the locus have been ruled out as causing susceptibility to MH. Hence for practical reasons, the *RyR1* gene remains the primary target for current clinical genetic analysis.

DISTRIBUTION OF *RyR1* MUTATIONS

The missense mutations associated with MHS, CCD, or, in some cases, both, are dispersed throughout the coding region of the *RyR1* gene, and all allow transcription of a protein that is putatively functional.^{10,98} Until recently, it was thought that most *RyR1* mutations were clustered in three "hot spots:" between amino acid residues 35 and 614 (MH/CCD region 1), between amino acid residues 2163 and 2458 (MH/CCD region 2) in the sarcoplasmic foot region of the protein, and between amino acids 4643 and 4898 in the carboxyl-terminal transmembrane loop or pore region (MHS/CCD region 3) (Fig. 35.2).⁹⁹ It appears that the supposition that there were "hot spots" was simply due to bias in sample analysis inasmuch as the missense mutations associated with MH or CCD (or both) are scattered over 54 of the 107 exons of *RyR1*. Approximately 41% of reported MH

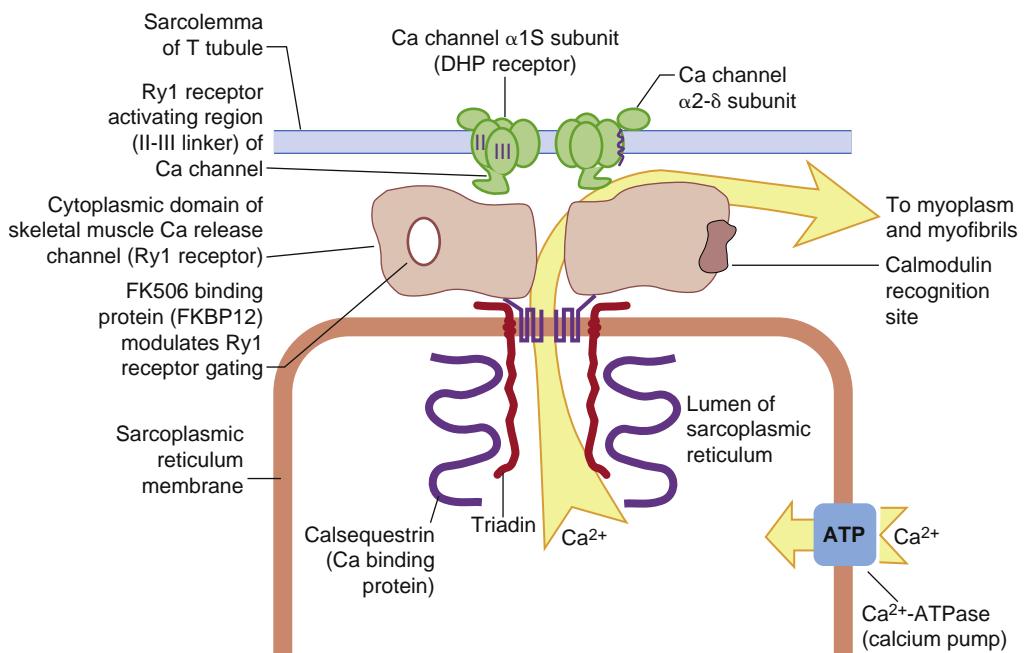


Fig. 35.2 Schematic representation of the triad junction of skeletal muscle shows the junctional foot protein (ryanodine [RyR1] receptor) and its associated proteins. In skeletal muscle, the α_{1S} -subunit of the dihydropyridine receptor (DHPR) participates in excitation-contraction coupling. These physical links transmit essential signals across the narrow gap of the triadic junction that activate the RyR1 and release Ca^{2+} from the sarcoplasmic reticulum. (Modified from Pessah IN, Lynch C III, Gronert GA: Complex pharmacology of malignant hyperthermia. *Anesthesiology* 1996;84:1275.)

mutations are found in multiple families. CCD mutations are predominantly found in the C-terminal region of the gene (exons 85–103), and only 10 mutations (17%) have been described in more than one family: R4861H ($n = 14$), V4849I ($n = 9$), I4898T ($n = 7$), L4824P ($n = 4$), A4940T ($n = 4$), G4638D ($n = 3$), R4893W ($n = 3$), R4861C ($n = 2$), R4893Q ($n = 2$), and G4899E ($n = 2$).

The true ethnic distribution of MH and CCD is difficult to ascertain. MH and CCD have been reported in Western populations predominantly, but this is likely the result of the manner and frequency in which cases are reported. It does appear that some mutations are clustered in a given region of the world, but the distribution and frequency appear to be somewhat population specific. In the United Kingdom, 69 *RyR1* mutations have been discovered, 25 of which are found only in a single family. G2434R is found in approximately 40% of the 434 mutation-positive MH families investigated in the United Kingdom, with the next most common mutations being T2206M (10%) and G341R (8%). In Switzerland, V2168M and I2336H are the predominant mutations,¹⁰⁰ and in Germany, R163C (MH and CCD), R614C (MH), T2206M (MH), G2434R (MH), and R2454H (MH) have each been detected in five or more independent cases.^{101,102} G341R and R614C are common in France,¹⁰³ and R614C has also been found in several MH families from Italy¹⁰³ and Canada.¹⁰⁴ G341R has been found frequently in Belgium.¹⁰³ The mutation common to Europe and North America is G2434R, which occurs in 4% to 7% of European and 5.5% of North American families.¹⁰⁵ Single-family mutations are the most common mutations reported in Japanese, Chinese, Taiwanese, Australian, and New Zealand MH families with the exception of the R163C mutation reported in a large population in rural New South Wales in Australia and the T4826I mutation which is found in numerous families in the Maori population of New Zealand.^{106–108} However, despite these two exceptions, it is likely that the reason for unique family mutations in Asia and Australasia may reflect the small number of cases investigated there. Because genetic screening in European and North American studies has predominantly targeted only regions 1 and 2 of the original hot spots in the gene, the absence of *RyR1* mutations in some of the screened population could be explained by *RyR1* mutations located outside these two regions or by involvement of other genes.

INHERITANCE AND PENETRANCE OF MALIGNANT HYPERTERMIA

Inheritance of human MH can no longer be considered to be solely autosomal dominant with variable penetrance because more than one MH-linked mutation has been identified in some probands and families. Six non-consanguineous families harbor at least two *RyR1* mutations that have both been linked to MHS, and in two of those families, one is an *RyR1* mutation and the second is a *Cav1.1* mutation.⁵ Although MHS homozygotes are common in affected pigs, they are rare in humans and only found in 50% of currently available transgenic mouse populations. The known MHS homozygous humans also appear clinically normal, but exhibit stronger responses to *in vitro* contracture test (IVCT) and caffeine/halothane contracture tests (CHCTs) than heterozygous individuals do.^{109–112} Homozygosity of

two MH mutations in “hot spot” 1 leads to perinatal lethality in mice.^{73,74} Double heterozygous individuals do not appear to show any additive effect of the second mutation on IVCT.⁵

IN VITRO CONTRACTURE TEST AND CAFFEINE HALOTHANE CONTRACTURE TEST

The gold standard for diagnosis of MH is the halothane and caffeine muscle contracture test, also known as the IVCT or the CHCT. There are two protocols developed by the European Malignant Hyperthermia Group (EMHG) and the North American Malignant Hyperthermia Group (NAMHG), respectively.⁹ The two protocols are similar, but not identical. For the purpose of differentiation, we designate IVCT to the EMHG protocol and CHCT to the NAMHG protocol.

For IVCT, the muscle biopsy will be performed on the quadriceps (either vastus medialis or vastus lateralis)^{113,114} and consists of three parts: a static caffeine test, a static halothane test, and a dynamic halothane test.¹¹⁴ For the static caffeine test, a stepwise increased concentration (0.5, 1, 1.5, 2, 3, 4, and 32 mmol/L) is applied. The lowest concentration of caffeine which produces a sustained increase of at least 0.2 g in baseline tension is reported as the caffeine threshold. Then, the halothane threshold is obtained using the same method by exposing the muscle to halothane concentrations of 0.5%, 1%, 2%, and 3% v/v. The dynamic halothane test is performed with the muscle stretched at a constant rate of 4 mm/min to achieve a force of approximately 3 g and held at the new length for 1 min for a 3 min exposure to halothane. For each cycle, halothane concentration will be increased from 0.5%, 1%, 2%, to 3% v/v: volume (solute) per volume (solvent). The concentration of halothane which produces a sustained increase of at least 0.2 g in the muscle tension compared to the pre-halothane control is defined as the dynamic halothane threshold.¹¹⁴ The IVCT protocol classifies the patients into three groups: MH Susceptible (MHS_{HC}) group with a caffeine threshold at the caffeine concentration of 2 mmol or less and a halothane threshold of 2% v/v halothane or less; MH Normal (MHN) group with a caffeine threshold at the caffeine concentration of 3 mmol or more without a halothane response at 2% v/v; MHS_H and MHS_C groups which describe individuals that used to be classified as MHE (equivocal) who are only responsive to either halothane or caffeine alone.^{113,114} The MHE descriptor was dropped because use of the ‘equivocal’ label outside of its laboratory context has the potential to confuse patients and clinicians unfamiliar with its derivation.¹¹⁵

For CHCT, a muscle biopsy can be taken from the following sites in the order of preference: (1) the vastus group, (2) the rectus abdominis, and (3) other muscle groups under special circumstances.¹¹⁶ Required tests include exposure of muscle to 3% v/v halothane alone and to incremental caffeine concentrations (0.5, 1, 2, 4 mmol, and 8.0 mmol if the response at 4 mmol is <1 g, and 32 mmol) alone. Optional tests include exposure of muscle to a combination of both 1% halothane and incremental caffeine concentrations, and to 2% v/v halothane alone.¹¹⁶ According to CHCT protocol, an individual is MHS when either of the halothane or the caffeine test is positive, and MHN when both tests are negative.¹¹⁶

The sensitivity of IVCT was reported to be 99.0% (95% confidence interval [CI] 94.8%-100%) if the MHE group is considered susceptible and the specificity of IVCT was 93.6% (95% CI 89.2%-96.5%).¹¹⁴ While the sensitivity and specificity of CHCT was 97% (95% CI 84%-100%) and 78% (95% CI 69%-85%), respectively.¹¹⁷ Recently, fluoroquinolones and statins, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, were found to induce significant contractures in MHS muscle bundles, but not in MHN.^{118,119} Ondansetron and 3,4-methylenedioxymethamphetamine (MDMA) may also dose-dependently induce contracture or increase the sensitivity of the contractile apparatus to calcium in both MHS and MHN fibers.^{120,121} Modifications to the IVCT protocol by adding ryanodine¹²² or 4-chloro-*m*-cresol,^{114,123} a RyR-specific agonist, has been reported, but has not been included in the standard protocol. Furthermore, Metterlein and associates studied the possibility of replacing halothane with newer volatile agents in IVCT. At increasing concentration, except for sevoflurane, all newer volatile agents, including enflurane, isoflurane, and desflurane, induced significantly greater contractures in MHS muscle compared to MHN bundles. However, within the MHS muscle bundles, halothane produced significantly higher contractures, and was considered the strongest discriminator for MH using the IVCT protocol.¹²⁴ A direct application of high sevoflurane concentration of 8%, instead of the stepwise application, has been shown to induce significantly stronger contractures in MHS subjects.¹²⁵ Nevertheless, from the retrospective analysis of the Japanese MH database, there was no evidence between the severity of MH triggered by sevoflurane and isoflurane, or other agents, suggesting sevoflurane is a weak or weaker MH triggering agent.¹²⁶

DISCORDANCE BETWEEN GENETIC AND IN VITRO CONTRACTURE TEST/CAFFEINE/ HALOTHANE CONTRACTURE TESTS MALIGNANT HYPERHERMIA TESTING

Discordance has confounded linkage analysis worldwide. Examples include MHN patients carrying an *RyR1* mutation associated with MH and MHS patients who do not carry the familial *RyR1* mutation. Several explanations are possible, the most likely being that IVCT/CHCT is not clinically precise and that the thresholds for IVCT or CHCT are inexact. This would lead to errors in determining whether a patient was MHN or MHS. A second possibility is variable penetrance with possible allelic silencing,¹²⁷ and a third is that individuals with discordance have mutations in other unknown genes or modifier genes that affect the function of *RyR1* and its phenotypic penetrance. The discrepancy between the incidence estimates of MH events and the prevalence estimates also points to possible epigenetic factors at work. Carpenter and associates have suggested that the severity of MHS may be related to the *RyR1* variant and mutation found within the highly conserved regions of *RyR1* gene.⁷⁹ The rarity of large kindreds with MH makes linkage analysis and understanding variability in clinical manifestations difficult. Robinson and associates demonstrated by the transmission disequilibrium test that loci on chromosomes 5 and 7 and, to a lesser extent, loci on chromosomes 1 and 7 influence susceptibility to MH.¹⁰³

GUIDELINES FOR GENETIC SCREENING

In 2000, the European MH group (EMHG) formulated guidelines for *RyR1* mutation screening with linkage data to other loci for some MH families, but all MH investigators emphasized the vital role of IVCT in the diagnosis of MH.¹²⁸ These guidelines for screening have reduced the number of relatives requiring contracture testing without increasing the risk of misdiagnosis.^{129,130} In 2015, the EMHG published a revision of the guidelines for the investigation of MHS. This updated guideline provided a detailed patient referral criteria and clinical interpretation of IVCT results (<https://www.emhg.org/testing-for-mh-1>).

Only a small number of MHS families have been investigated extensively in North America by phenotyping, linkage analysis, and screening of specific genes. Collaborative protocols over the past several years between MH biopsy centers and molecular biologists have screened 209 unrelated MHS subjects for mutations in the *RyR1* gene (see Distribution of *RyR1* Mutations).

Larach and coworkers reported a 34.8% morbidity rate in 181 MH cases reported to the NAMHR between January 1987 and December 2006. They also reported that the occurrence was more frequent in young males (75%) (median age of 22.0) and 75% of these patients had undergone at least one general anesthetic with no observed signs of MHS.¹³¹ This underscores the complication of determining the prevalence of MHS in the absence of an inexpensive MH diagnostic test.

Fulminant Malignant Hyperthermia

Fulminant MH is rare. Acute episodes of MH depend on four variables: a genetic (perhaps rarely acquired) predisposition, the absence of inhibiting factors, the presence of an anesthetic or nonanesthetic trigger, and the presence of environmental factors that could potentiate the action of one or more of the other three variables.

ANESTHETIC TRIGGERING

Anesthetic drugs that trigger MH include ether, halothane, enflurane, isoflurane, desflurane, sevoflurane, and depolarizing muscle relaxants, the only currently used of which is succinylcholine. Desflurane and sevoflurane appear to be less potent triggers than halothane and produce a more gradual onset of MH.^{132,133} The onset may be explosive if succinylcholine is used. MHS swine were traditionally screened by induction with a volatile anesthetic, which led to pronounced hind limb rigidity within 5 minutes, frequently sooner.¹³⁴ Prior exercise even an hour before induction of anesthesia increased the severity and hastened the onset of rigidity in swine.¹³⁴ Similarly, in the new knock-in mouse models, the onset of limb rigidity after commencing exposure to volatile anesthetics is very rapid. There are also several modifying factors that are more likely to be present in humans than in pigs or mice and can alter (or even prevent) the onset of clinical MH. Mild hypothermia and preadministration of barbiturates, tranquilizers, propofol, or nondepolarizing neuromuscular blockers delay or prevent the onset of MH^{25,134-136} in MHS humans, thus

making them respond less predictably than swine or MH knock-in mice. There have been many instances in which fulminant MH has been reported in patients who have previously tolerated potent triggers without difficulty.¹³⁷ The reason behind why this occurs is unknown, but it is likely to be related to prior or concurrent administration of drugs that prevent or delay onset of the syndrome, as described earlier, or unknown environmental influences that help provoke the positive incident. Thus onset of the syndrome in humans is extremely variable both in initial symptoms and in the time of onset of the syndrome. Its onset is so variable that making the diagnosis in the setting of a clinical anesthetic can be quite difficult. Although not perfect, the clinical grading scale developed by Larach and colleagues¹³⁸ is a useful way for clinicians to retrospectively determine whether a patient who responded abnormally to anesthesia is in any way likely to actually have had a clinical MH episode. However, MH is most easily diagnosed prospectively by vigilance, recognizing its signs and symptoms, and knowing how to treat the syndrome.

The two classic clinical manifestations of fulminant MH syndrome may start in one of the following two scenarios.

1. Rigidity after induction with thiopental and succinylcholine, but successful intubation, followed rapidly by the symptoms listed after scenario 2.
2. Normal response to induction of anesthesia and uneventful anesthetic course until onset of the following symptoms:
 - Unexplained sinus tachycardia or ventricular arrhythmias, or both
 - Tachypnea if spontaneous ventilation is present
 - Unexplained decrease in O₂ saturation (because of a decrease in venous O₂ saturation)
 - Increased end-tidal PCO₂ with adequate ventilation (and in most cases unchanged ventilation)
 - Unexpected metabolic and respiratory acidosis
 - Central venous desaturation
 - Increase in body temperature above 38.8°C with no obvious cause

The usually muted onset of MH (scenario 2) is in most cases detected quickly by the development of tachycardia, increased levels of expired CO₂, and muscle rigidity. It can be delayed for several reasons and may not be overt until the patient is in the recovery room. Once initiated, the course of MH can be rapid. When clinical signs such as increased expired CO₂, muscle rigidity, tachycardia, and fever suggest MH, more than one abnormal sign must be observed before making the diagnosis because according to a metaanalysis of many reported cases, a single adverse sign does not usually indicate MH.¹³⁸ The mechanism by which anesthetics and depolarizing muscle relaxants trigger MH is unsolved, but it cannot be ignored that they are etiologic agents and that early diagnosis is critical for successful treatment.

NONANESTHETIC MALIGNANT HYPERTHERMIA

MH can be triggered by stress such as exercise and overheating, known as “awake” MH. Numerous anecdotal reports of MH-like episodes in humans after stressful situations were reported.¹³⁹⁻¹⁴⁴ Measurement of plasma catecholamine

levels during exercise showed no differences between MHS and normal individuals.^{145,146} Therefore it is unlikely that these responses were provoked by sympathetic overdrive or catecholamine surge.¹⁴⁷

Wappler and associates reported *RyR1* mutations in three of twelve unrelated patients with exercise-induced rhabdomyolysis (ER); and 10 of those same 12 patients produced abnormal contracture response with IVCT.¹⁴⁸ One had an equivocal response. In susceptible swine, environmental stress such as exercise, heat, anoxia, apprehension, and excitement triggers fulminant MH (see History).^{9,134} These responses are related to muscle movement or to increased temperature. Increased ambient temperature triggers fulminant MH in four strains of heterozygous MH mice and in two homozygous strains.^{74,75} Epidemiologic studies have shown that exercise-induced symptoms, including rhabdomyolysis, may occur more frequently in MHS patients¹⁴⁸; and an Arg401Cys *RyR1* mutation was present in three cases of exercise-induced rhabdomyolysis.¹⁰⁶ Other reports are largely anecdotal and relate heat stroke, sudden and unexpected death, unusual stress and fatigue, or myalgias to possible “awake” MH episodes. Stresses associated with these episodes include exercise and environmental exposure to volatile nonanesthetic vapors.^{141,149,150} In the United States, MHAUS provided recommendations of adverse effects of heat and exercise in relation to MHS.¹⁵¹

Malignant Hyperthermia-Associated Syndromes

MASSETER SPASM (“THIOPENTAL-SUCCINYLCHOLINE OR HALOTHANE-SUCCINYLCHOLINE RIGIDITY”)

A masseter spasm or trismus is defined as jaw muscle rigidity in association with limb muscle flaccidity after the administration of succinylcholine. The masseter and lateral pterygoid muscles contain slow tonic fibers that can respond to depolarizing neuromuscular blockers with a contracture.^{152,153} This is manifested clinically on exposure to succinylcholine as an increase in jaw muscle tone, and was well defined by van der Spek and associates.¹⁵⁴ There is a spectrum of responses, for example, a tight jaw that becomes a rigid jaw and then a very rigid jaw (Fig. 35.3). This jaw rigidity may occur even after pretreatment with a “defasciculating” dose of a nondepolarizing relaxant. If there is rigidity of other muscles in addition to trismus, the association with MH is absolute; anesthesia should be halted as soon as possible and treatment of MH begun.

However, in more than 80% of patients with trismus but no rigidity of other muscles, it is a variant found in normal patients. If trismus occurs, proper monitoring should include end-expired CO₂, examination for pigmenturia, and arterial or venous blood sampling for CK, acid-base status, and electrolyte levels, particularly potassium. Although scientifically unproven, it is thought that the initial tightness of the jaw and its duration may predict the gravity of the response. MHAUS recommends following CK and urine myoglobin for 36 hours with 6-hour intervals. Patients with masseter spasm should be observed closely for at least 12 hours.

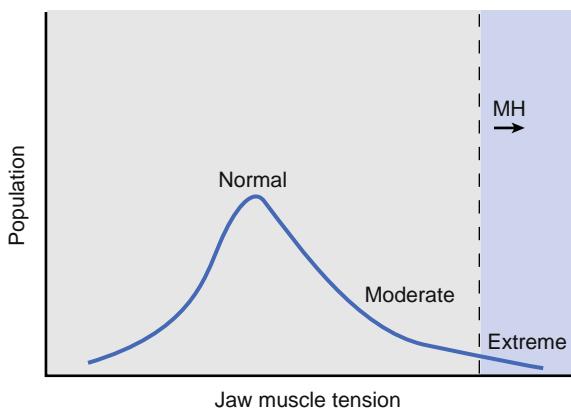


Fig. 35.3 Succinylcholine usually increases jaw muscle tone slightly. In some patients this increase is moderate, and in very few, the effect is extreme (i.e., "jaws of steel"). As many as 50% of this latter group may be susceptible to malignant hyperthermia (MH). Somewhere in the area of the declining curve is the boundary for the MH population.

CORE MYOPATHIES

CCD is a rare hereditary disease. It was first reported in 1956 by Magee and Shy.¹⁵⁵ A recent population study in northern England revealed a prevalence of 1:250,000.¹⁵⁶ In 1971, Engel and colleagues reported a related congenital myopathy, multicore disease.^{157,158} Subsequently, various designations of the terms were reported for the variations of the disease, including minicore myopathy and multiminicore myopathy.¹⁵⁷ MmD is now the most official term for these variations sponsored by the European Neuromuscular Centre.¹⁵⁷

As mentioned, most CCD cases are due to dominant missense mutations in the *RyR1* gene. Clinically, CCD patients present with muscle weakness of variable degree and histologically with central cores in the skeletal muscle type I fibers.¹⁵⁹ MmD is considered a recessively inherited myopathy with severe axial weakness, while respiratory, bulbar, and extraocular muscles are commonly affected.¹⁵⁹ MmD has a heterogenous genetic association with a recessive mutation in the *SEPN1* gene on chromosome 1p36 and in the *RyR1* gene.¹⁵⁹ Both type 1 and type 2 fibers may be affected.¹⁵⁷

Serum CK levels in CCD patients are often normal but may be elevated up to 6 to 14 times in rare cases. Muscle ultrasound often demonstrates increased echogenicity in the quadriceps muscle with relative sparing of the rectus muscle. This characteristic pattern of selective involvement can also be seen on the muscle MRI and has been reported in the patients with typical CCD,¹⁵⁷ which seems to be distinctive to conditions linked to *RyR1* locus.

The relationship between CCD and MHS is complex. A positive IVCT test has been confirmed in many patients with CCD, whereas MHS has been excluded in some. In consideration of the strong link and potential risk, it is advisable to consider all patients with CCD at risk for MH unless the patient has a negative IVCT. Although MHS has not been reported in *SEPN1*-related myopathies, it is prudent to apply a nontriggering approach to MmD patients, given the potential risk in *RyR1*-related MmD. Clinical MH reactions have been reported in MmD patients.^{160,161}

KING-DENBOROUGH SYNDROME

To address the KDS, we first introduce Noonan syndrome, an autosomal dominant condition involving the face, cardiovascular, hematological, and skeletal systems. Named after Dr. Jacqueline Anne Noonan, a pediatric cardiologist, typical Noonan syndrome features delayed puberty, down-slanting or wide-set eyes, hearing loss, low-set or abnormal shaped ears, mild mental retardation (in about 25% of the cases), ptosis, short stature, small penis and undescended testicles in males, pectus excavatum, and a webbed and short neck. The incidence is 1:1000-1:2500 live births.¹⁶² Fifty percent of the patients have protein-tyrosine phosphatase, nonreceptor-type II (*PTPN2*) mutations.¹⁶³ Other genes involved are *SOS1*, *KRAS*, *RAF1*, *BRAF*, *MEK1*, and *NRAS*, and they encode proteins that are part of the Ras (a GTPase)-mitogen activated protein kinase (RAS-MAPK) signaling pathway.¹⁶⁴ Noonan syndrome was recently defined as part of the neuro-cardio-facial-cutaneous syndrome family.¹⁶⁵ An earlier study with a series of 27 patients demonstrated one case of mildly elevated CK despite multiple uneventful cases of general anesthesia with halothane and succinylcholine.¹⁶⁶ Although there is weak evidence for MHS for patients with Noonan syndrome, its resemblances to KDS should raise the concern for the confirmation of the diagnosis. Prevalence of bleeding disorders in Noonan syndrome was reported to be from 20% to 89%,¹⁶⁴ ranging from thrombocytopenia to platelet dysfunction to von Willebrand disease to factor deficiencies. Routine screening including, but not limited to, bleeding history, platelet count, coagulation panel, and factor XI level, was recommended.^{165,167} Hematological consultation becomes appropriate if any of these tests are abnormal. The high palatal arch, dental malocclusion, and the webbed neck of Noonan syndrome make tracheal intubation potentially risky.¹⁶⁸ Nevertheless, odontoid hypoplasia and atlanto-axial instability may result in cervical cord compression. Preoperative cervical spine evaluation is advisable.¹⁶⁹ Right ventricular function needs to be monitored closely because 30% to 50% of the patients with Noonan syndrome have pulmonary stenosis.¹⁷⁰ Regional anesthesia in Noonan patients may be technically challenging due to the prevalence of scoliosis. The spread of local anesthetic can be unpredictable.^{169,171}

KDS features the dysmorphic facial and skeletal abnormalities similar to Noonan syndrome and congenital myopathy with proximal muscle weakness.¹⁶³ Sporadic cases have been reported in the literature.¹⁷²⁻¹⁸¹ The inheritance pattern of the disease is not clear. Elevated baseline CK appears in approximately one half of the KDS patients. A heterozygous A97G point mutation in exon 2 of the *RyR1*, causing a substitution of lysine for glutamine at amino acid residue 33 (Lys33Glu), was reported.¹⁸² This substitution creates a major polarity change, from positive to negative, in a known hot spot for an MH causative mutation. Dowling and associates recently identified *RyR1* mutation in three out of the four patients with KDS, which supports the hypothesis of its genetic heterogeneity.¹⁸³ Given the strong evidence for MHS in KDS patients, MH triggering agents should be avoided for anesthesia on KDS patients.

BOX 35.1 Clinical Signs of Malignant Hyperthermia

Early Signs

Elevated end-tidal CO₂
Tachypnea and/or tachycardia
Masseter spasm if succinylcholine has been used
Generalized muscle rigidity
Mixed metabolic and respiratory acidosis
Profuse sweating
Mottling of skin
Cardiac arrhythmias
Unstable blood pressure

Late Signs

Hyperkalemia
Rapid increase of core body temperature
Elevated creatine phosphokinase levels
Gross myoglobinemia and myoglobinuria
Cardiac arrest
Disseminated intravascular coagulation

BOX 35.2 Conditions and Disorders that May Mimic Malignant Hyperthermia

Anaphylactic reaction
Alcohol therapy for limb arteriovenous malformation
Contrast dye injection
Cystinosis
Diabetic coma
Drug toxicity or abuse
Elevated end-tidal CO₂ due to laparoscopic operation
Environmental heat gain more than loss
Equipment malfunction with increased carbon dioxide
Exercise hyperthermia
Freeman-Sheldon syndrome
Generalized muscle rigidity
Heat stroke
Hyperthyroidism
Hyperkalemia
Hypokalemic periodic paralysis
Hypoventilation or low fresh gas flow
Increased ETCO₂ from laparoscopic surgery
Insufficient anesthesia and/or analgesia
Malignant neuroleptic syndrome
Muscular dystrophies (Duchenne and Becker)
Myoglobinuria
Myotonias
Osteogenesis imperfecta
Pheochromocytoma
Prader-Willi syndrome
Recreational drugs
Rhabdomyolysis
Sepsis
Serotonin syndrome
Stroke
Thyroid crisis
Ventilation problems
Wolf-Hirschhorn syndrome

Diagnosis in the Operating Room and Postanesthesia Care Unit

As stated earlier, fulminant MH is rare, and early signs of clinical MH may be subtle (Box 35.1). These signs must be distinguished from other disorders with similar signs (Box 35.2).

When the diagnosis is obvious (i.e., fulminant MH or succinylcholine-induced rigidity with rapid metabolic changes), marked hypermetabolism and heat production occur, and there may be little time left for specific therapy to prevent death or irreversible morbidity. If the syndrome begins with slowly increasing end-tidal CO₂ (defined earlier), specific therapy can await a complete clinical workup before treatment. In general, MH is not expected to occur when no triggers are administered (see “Anesthesia for Susceptible Patients”). However, several confirmed fulminant nonanesthetic cases of MH that resulted in death have been reported (see “Nonanesthetic Malignant Hyperthermia”).¹⁴⁸

When volatile anesthetics or succinylcholine are used, MH should be suspected whenever there is an unexpected increase in end-tidal CO₂ (ETCO₂), undue tachycardia, tachypnea, arrhythmias, mottling of the skin, cyanosis, muscle rigidity, sweating, increased body temperature, or unstable blood pressure. If any of these occur, signs of increased metabolism, acidosis, or hyperkalemia must be sought. The most common cause for sudden ETCO₂ during general anesthesia and sedation is hypoventilation. Increased minute ventilation should be able to correct such a problem.

The diagnosis of MH can be supported by the analysis of arterial or venous blood gases which demonstrates a mixed respiratory and metabolic acidosis;¹⁸⁴ however, the respiratory component of acidosis may be predominate in the very early stage of the onset of fulminant MH. O₂ and CO₂ change more markedly in the central venous compartment than in arterial blood; therefore end-expired or venous CO₂ levels more accurately reflect whole-body stores. Venous CO₂, unless the blood drains an area of increased metabolic activity, should have PCO₂ levels of only about 5 mm Hg

greater than that of expected or measured PaCO₂. In small children, particularly those without oral food or fluid for a prolonged period, the base deficit may be 5 mEq/L because of their smaller energy stores.

Any patient suspected of having an MH episode should be reported to the North American MH Registry via the adverse metabolic/muscular reaction to anesthesia (AMRA) report available from the website at <http://anest.ufl.edu/namhr/namhr-report-forms/>.

TREATMENT

Acute management for MH can be summarized as follows:

1. Discontinue all triggering anesthetics, maintain intravenous agents, such as sedatives, opioids, and nondepolarizing muscular blockers as needed, and hyperventilate with 100% oxygen with a fresh flow to at least 10 L/min. With increased aerobic metabolism, normal ventilation must increase. However, CO₂ production is also increased because of neutralization of fixed acid by bicarbonate; hyperventilation removes this additional CO₂.
2. Administer dantrolene rapidly (2.5 mg/kg intravenously [IV] to a total dose of 10 mg/kg IV) every 5 to 10 minutes until the initial symptoms subside.

3. Administer bicarbonate (1-4 mEq/kg IV) to correct the metabolic acidosis with frequent monitoring of blood gases and pH.
4. Control fever by administering iced fluids, cooling the body surface, cooling body cavities with sterile iced fluids, and if necessary, using a heat exchanger with a pump oxygenator. Cooling should be halted at 38°C to prevent inadvertent hypothermia.
5. Monitor and treat arrhythmia. Advanced cardiac life support protocol may be applied.
6. Monitor and maintain urinary output to greater than 1 to 2 mL/kg/h and establish diuresis if urine output is inadequate. Administer bicarbonate to alkalinize urine to protect the kidney from myoglobinuria-induced renal failure.
7. Further therapy is guided by blood gases, electrolytes, CK, temperature, muscle tone, and urinary output. Hyperkalemia should be treated with bicarbonate, glucose, and insulin, typically 10 units of regular insulin and 50 mL of 50% dextrose for adult patients. The most effective way to lower serum potassium is reversal of MH by effective doses (ED) of dantrolene. In severe cases, calcium chloride or calcium gluconate may be used.
8. Recent data demonstrated that magnesium level could be a prerequisite for dantrolene efficacy in managing MH crisis.
9. Analyze coagulation studies (e.g., international normalized ratio [INR], platelet count, prothrombin time, fibrinogen, fibrin split, or degradation products).
10. Once the initial reaction is controlled, continued monitoring in the intensive care unit for 24 to 48 hours is usually recommended.

Adequate personnel support is critical to the successful management of such a crisis. Discontinuation of the trigger may be adequate therapy for acute MH if the onset is slow or if exposure was brief. Changing the breathing circuit and CO₂ absorbent can be time-consuming. However, application of activated charcoal filters may rapidly reduce the volatile anesthetic concentration to an acceptable level in less than 2 minutes, if they are readily available.¹⁸⁵

Dantrolene used to be packaged in 20-mg bottles with sodium hydroxide for a pH of 9.5 (otherwise it will not dissolve) and with 3 g of mannitol (converts the hypotonic solution to isotonic). The initial dose should be 2.5 mg/kg dantrolene reconstituted in sterile water and administered intravenously. Dantrolene *must* be reconstituted in sterile water rather than salt solutions or it will precipitate. It has been shown that prewarming of sterile water may expedite the solubilization of dantrolene compared to water in ambient temperature.¹⁸⁶ In 2009, a newer, rapid soluble lyophilized powder form of dantrolene became available for intravenous use. It reconstitutes in less than a minute which is much faster than the older version.¹⁸⁷ The higher dosing capacity, 250 mg per vial, of the newer version of dantrolene also reduces the storage space with a similar recommended shelf life as the older versions.

In awake, healthy volunteers, the maximum twitch depression occurs at a dantrolene dose of 2.4 mg/kg.¹⁸⁸ Therefore it is not surprising that at therapeutic concentrations, dantrolene may prolong the need for intubation and assisted ventilation. Brandom and associates reviewed

the complications associated with the administration of dantrolene from 1987 to 2006 using the dataset in the NAMHR via the AMRA reports and found that the most frequent complications of dantrolene were muscle weakness (21.7%), phlebitis (9%), gastrointestinal upset (4.1%), respiratory failure (3.8%), hyperkalemia (3.3%), and excessive secretions (8.2%).¹⁸⁹ Given its high pH, it is advisable to administer dantrolene through a large bore IV line. It has been demonstrated that dantrolene interferes with EC coupling of murine intestinal smooth muscle cells,¹⁹⁰ rat gastric fundus, and colon,¹⁹¹ which in part explains its gastrointestinal side effect. Caution should be used when ondansetron is to be used in this setting. As a serotonin antagonist, ondansetron may increase serotonin at the 5-HT_{2A} receptor in the presynaptic space. In MHS individuals, agonism of 5-HT_{2A} receptor may produce a deranged response, precipitating MH.¹⁹²

The clinical course will determine further therapy and studies. Dantrolene should probably be repeated at least every 10 to 15 hours, since it has a half-life of at least 10 hours in children and adults.^{188,193} The total dose of dantrolene that can be used is up to 30 mg/kg in some cases. Recrudescence of MH can approach 50%, usually within 6.5 hours.^{194,195} When indicated, calcium and cardiac glycosides may be used safely. They can be lifesaving during persistent hyperkalemia. Slow voltage-gated calcium channel blockers do not increase porcine survival.^{196,197} Instead, a recent study by Migita demonstrated that calcium channel blockers, including dihydropyridine (i.e., nifedipine), phenylalkylamine (i.e., verapamil), and benzothiazepine (i.e., diltiazem), led to increased [Ca²⁺]_i in human skeletal muscle cells. Interestingly, the potency of such calcium release is correlated with the number of binding sites on DHPR (i.e., nifedipine > verapamil > diltiazem).¹⁹⁸ Clinical doses of dantrolene were only able to attenuate 20% of the nifedipine-induced [Ca²⁺]_i surge.¹⁹⁸ Current recommendations of MHAUS discourage the use of calcium channel blockers in the presence of dantrolene because they can worsen the hyperkalemia resulting in cardiac arrest. Although administration of magnesium sulfate could not prevent the development of MH and did not influence the clinical course in succinylcholine-induced MH,¹⁹⁹ recent data suggested that dantrolene might require magnesium to arrest the course of MH triggered by halothane.²⁰⁰ Permanent neurologic sequelae, such as coma or paralysis, may occur in advanced cases, probably because of inadequate cerebral oxygenation and perfusion for the increased metabolism and because of the fever, acidosis, hypo-osmolality with fluid shifts, and potassium release.

For MH cases diagnosed in the ambulatory surgical centers, guidelines have been recently proposed for the transferring of care to receiving hospital facilities.²⁰¹ Although it is preferable that immediate treatment and stabilization of the patient be achieved onsite, several factors need to be considered before implementation of a transfer plan, which include capabilities of the available professionals at the initial treatment and receiving facilities, clinical best interests of patients, and capabilities of the transfer team.²⁰² The validity of stocking dantrolene in ambulatory surgery centers was confirmed with a cost-effectiveness analysis.²⁰³

Anesthesia for Susceptible Patients

Safe anesthetics consist of nitrous oxide, barbiturates, etomidate, propofol, opiates, tranquilizers, and nondepolarizing muscle relaxants. Potent volatile anesthetics and succinylcholine must be avoided, even in the presence of dantrolene. There are anecdotal reports that some human patients have experienced a hypermetabolic state despite these precautions, but they have always responded favorably to the administration of intravenous dantrolene. Preoperative dantrolene is never needed because the use of nontriggering agents is almost always associated with uneventful anesthesia. Regional anesthesia is safe and may be preferred. Amide anesthetics such as lidocaine were once considered dangerous in susceptible patients because they were thought to induce or worsen muscle contractures *in vitro* as a result of their effect of increasing calcium efflux from the SR. Porcine and human studies have consistently demonstrated the lack of danger of amide anesthetics.

Before being used for MHS patients, anesthetic machines may be “cleansed” of potent volatile agents by disconnecting or removing the vaporizers from the anesthesia workstation, renewing the CO₂ absorbent, using a new, disposable breathing circuit, and, if possible, a fresh gas hose. If there is no dedicated machine for MHS patients, flushing the anesthesia workstation to less than 5 parts per million (ppm) of the volatile anesthetic agents concentration is generally accepted.²⁰⁴ It may take 10 to 104 min with different machines.^{185,205-214} This preparation process also should be directed based on the halogenated volatile agents that have been used. Jones and colleagues demonstrated that desflurane required longer purge time than sevoflurane on both the Datex-Ohmeda Aestiva and Aisys machines.²¹³ Application of activated charcoal filters have been shown to successfully accelerate the process of cleansing.^{185,215-217} Such filters should be placed on both the inspiratory and expiratory limbs of the anesthesia machine with replacement of a new set every 60 minutes on patients who are exhaling volatile anesthetics.¹⁸⁵ MHAUS recommends flushing and preparing the anesthesia workstation according to the manufacturer’s recommendations or published studies.²¹⁸ During the case, lowering the fresh gas rate after the washout period may allow the concentration of volatile anesthetic agents to reaccumulate.²⁰⁹ Fresh gas flow should be kept to at least 10 L/min to avoid this rebound.

It is important to be aware that the National Institute for Occupational Safety and Health issued “Criteria for a Recommended Standard- Occupational Exposure to Waste Anesthetic Gases (WAGs) and Vapors.”²¹⁹ No worker is exposed to halogenated anesthetic agents at concentrations greater than 2 ppm when used alone or greater than 0.5 ppm when used in combination with nitrous oxide over a sampling period not to exceed 1 hour. Anesthetic gas machines, non-rebreathing systems, and T-tube devices shall have an effective scavenging device that collects all WAGs. Occupational Safety and Health Administration also has guidelines for workplace exposures.²²⁰

The anesthesiologist should confidently discuss anesthetic care with MHS patients and assure them that all will

be done to avoid difficulties with MH and that the appropriate drugs, knowledge, and skills are immediately at hand if any problems occur. Many of these patients have undergone procedures uneventfully, such as dental analgesia and obstetric anesthesia, before the diagnosis of susceptibility was made. The patient can enter the therapeutic environment in a reassured, relaxed, and comfortable state. Outpatient procedures are feasible in most environments; the time of discharge depends on the usual outpatient criteria.

Any facility using MH triggers on an inpatient or outpatient basis should have dantrolene available immediately. The current recommendation by MHAUS to stock 36 vials of 20 mg dantrolene Dantrium/Revonto is based on dantrolene needed to treat an MH crisis on a 70-kg patient.¹⁸⁷ FDA approved the Ryanodex in 2014. Administration of three vials of 250 mg Ryanodex injectable suspension is the alternative preparation plan.

EVALUATION OF SUSCEPTIBILITY

Evaluation of susceptibility includes a history and physical examination to detect any subclinical abnormality. A genealogy with specific information about anesthetic exposure and agents can estimate the likelihood of exposure to triggering agents. Blood CK values, when determined in a resting, fasting state without recent trauma, reflect muscle membrane stability. When the CK level is elevated in a close relative of a person with known MHS, the relative may be considered to have MHS without contracture testing. If the CK level is normal on several occasions, there is no predictive value, and contracture studies are necessary. The patient must travel to the test center for a surgical biopsy to ensure viability and accurate results. Muscle biopsy contracture studies, performed at about 30 centers around the world, involve exposure of the muscle biopsy sample to halothane, caffeine, and, in the North American test, to halothane plus caffeine.¹²⁸ Sensitivity to 4-chloro-*m*-cresol or ryanodine have also been used by some centers.⁵² It is also important to note that contracture responses are sometimes positive in patients with myopathies that bear no direct relationship to MH and therefore may not indicate susceptibility. Dantrolene must be avoided before biopsy because it masks the response to contracture-producing drugs. After a patient is diagnosed as being MHS, DNA testing for mutations should follow. When a mutation is detected, other relatives with that mutation should be considered to be MHS without the need for an invasive contracture test, and they need not travel to a testing center (see Genetics).

MHS patients and all patients who are not biopsy tested, but who present with a clinical picture that suggests a high probability for MHS, should be given advice. Precautions are necessary in regard to general anesthesia, and triggers include all potent volatile agents and succinylcholine. Awake episodes are uncommon, and if not experienced before diagnosis, they are an unlikely problem. The true predictive value (i.e., percentage of positive results that are true positives) or efficiency (i.e., percentage of all results that are true, whether positive or negative) of contracture testing in determining susceptibility in the general population cannot be estimated because of the selection process that has been used to date for testing (i.e., limited to those with anesthesia

reactions who do not have any other muscle disease pathology). False-positive results from cautious interpretation or decreased specificity are masked because the patient will never be exposed to triggering agents. A promising innovative *in vivo* human application involves physiologically based microdialysis infusion of caffeine or halothane into muscle of MHS patients to trigger exaggerated localized changes in acid-base balance.²²¹⁻²²⁵ White blood cells express RyR1-MHS and provide a substrate for a less invasive analysis for susceptibility but have the limitation that not all causative mutations are expressed in the white blood cells.²²⁶⁻²³⁰ Nuclear magnetic resonance has promise,^{231,232} but to date it has been difficult to standardize a stress, such as forearm ischemia, that can differentiate susceptibles from normals.

For anesthesia assessment of the non-MHS pregnant patient carrying a potential MHS fetus, the parturient should be treated as MHS until the fetus is delivered.²³³⁻²³⁵ For emergencies in such patients, the use of succinylcholine, although little of the drug crosses the placenta, is controversial.²³⁶

Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune disorder characterized by T-cell-mediated autoantibodies against myelin and a subsequent inflammatory response within the central nervous system (CNS: brain and spinal cord), where it primarily affects the optic nerve, the corticospinal tract, or posterior columns. Thus MS is a disorder of the myelinated part of the axon that leads to secondary nerve conduction failure. It is characterized by sensitization of the peripheral leukocytes to the myelin antigen and a subsequent inflammatory response, monocytic and lymphocytic perivascular cuffing, and glial scars with plaque formation within the central nervous system, especially in the periventricular white matter. The disease affects mainly women, primarily between 20 and 40 or 45 and 60 years of age. Although the etiology is unknown, it has been speculated that MS is caused by environmental factors combined with a genetic predisposition. Naturally, researchers have focused on identifying key events and the genetic origin of the disorder to provide diagnostic and possibly also therapeutic tools for the management of MS patients.

Its clinical course is characterized by exacerbations and remissions in most patients, but continuous neurological deterioration has been reported in up to 10% of cases (primary progressive MS). Patients with MS frequently report paresthesias, muscle weakness, and sensory disturbances. Acute symptoms, which are related to the site and extent of sclerosing CNS plaques, commonly include visual disturbances (diplopia, blurring, and field cuts), sensory abnormalities with numbness and paresthesia, pain, and electric shock sensation that radiates down the spine and into the limbs upon flexion of the neck (Lhermitte sign). Cranial nerve dysfunction, ataxia, and bladder and bowel disturbances are also common. Typically, there is a localized or, late in the course of disease, generalized muscle weakness with the legs affected more than the arms. Chronic symptoms can also include spastic paraparesis, appendicular tremor, psychiatric disturbances such as depression or euphoria (la

belle indifference), and dementia. In severe cases, respiration may be involved with the development of hypoxemia. As a rule, symptoms are closely related to the site affected within the CNS, and the number of symptoms is related to the extent of sclerosing CNS plaques. Notably, MS can be associated with impaired autonomic function, and hence an increased risk for exaggerated hemodynamic response to anesthetic induction agents, vasodilators, and sympathomimetic drugs.²³⁷

Diagnosing MS after a single, acute remitting clinically isolated syndrome is discouraged, whereas repeated attacks with increased CSF IgG and multifocal MRI abnormalities are strongly supportive of the diagnosis.²³⁸ Acute attacks are treated with various combinations of immunosuppression modalities including glucocorticoids or plasma exchange therapy, which have been shown to increase the rate of recovery but not the overall level of recovered function. Disease progression can, nevertheless, be modified with a novel humanized CD20 monoclonal antibody (ocrelizumab) in patients with primary-progressive or relapsing-remitting forms of MS. Other immunomodulatory treatment options include interferon β 1a or glatiramer acetate (a mixture of polypeptides synthesized to mimic myelin basic protein) in individuals with the relapsing-remitting MS, fingolimod, teriflunomide, or natalizumab, and the antineoplastic agent mitoxantrone. Teriflunomide is associated with hepatic injury, while mitoxantrone can be associated with cardiomyopathy. These patients may also receive treatments aimed at reducing spasticity (baclofen and benzodiazepines), as well as anticonvulsants or propranolol for tremor, oxybutynin and propantheline for bladder spasticity, and SSRIs or other antidepressive agents for mood disorders.

ANESTHETIC CONSIDERATIONS

It has been speculated that general anesthesia and surgery may increase the risk for aggravation of MS.²³⁹ Presently, there is no general consensus on this matter, and patients should therefore be informed of the potential for aggravated symptoms in the postoperative period. In general, preoperative chronic immunosuppressive medication should be continued during the perioperative period. Patients with MS are sensitive to physical (pain, fever, infection) and emotional stress, which makes it more likely that symptoms will be intensified in the perioperative period. Increased body temperature is often cited as an offending mechanism, possibly by causing a complete block of conduction in demyelinated nerves. Body temperature should therefore be closely monitored and controlled during the perioperative period. Great care must be exercised to minimize changes in fluid homeostasis, and central hemodynamics (preload, afterload) and to maintain respiration. Although intravenous induction agents and volatile anesthetics have been used safely, it is wise to avoid administering depolarizing neuromuscular blocking drugs to MS patients. MS-induced denervation, or misuse myopathy, may lead to a risk for succinylcholine-induced hyperkalemia, which can result in fatal cardiac arrhythmias. Nondepolarizing neuromuscular blockers are safe to use but should be dosed cautiously as both prolonged responses (increased sensitivity in patients with preexisting muscle weakness) and resistance to these NMBAs have

BOX 35.3 Perioperative Considerations for Patients with Multiple Sclerosis

1. Thoroughly inform the patient and family of the natural course of MS, and the risk for perioperative worsening of symptoms
2. Continue preoperative immunosuppressive therapy
3. Type of general anesthetics is unlikely to affect the course of disease
4. Minimize perioperative changes in fluid homeostasis and hemodynamics
5. Monitor body temperature closely, avoid hyperthermia
6. It is reasonable to avoid depolarizing neuromuscular blocking agents (NMBAs)
7. Nondepolarizing NMBAs can be used, but should be dosed cautiously with monitoring of the neuromuscular transmission
8. Epidural anesthesia has been used successfully, but spinal anesthesia is usually not recommended
9. Consider extended postoperative care in a monitored setting if patient has severe preoperative weakness or respiratory compromise

been reported. The use of rocuronium with sugammadex to ensure full reversal has been suggested as a safe alternative.²⁴⁰ It is speculated that the demyelination associated with MS renders the spinal cord susceptible to the neurotoxic effects of the local anesthetics. Epidural application of low concentrations of local anesthetics has, nevertheless, been successfully used in MS patients.²³⁹ Spinal anesthesia, on the other hand, has been implicated in postoperative exacerbations of symptoms in MS. As the blood–brain barrier may also be damaged by demyelination, spinal anesthesia is usually not recommended for these patients. A recent metaanalysis of 37 reports found that the MS symptoms were worsened in 10 of 231 patients, but despite the association no clear cause–effect relationship could be identified.²⁴¹ Notably, postpartum worsening of MS symptoms is noted in 20% of females. The need for postoperative care is dependent on the preoperative symptoms, type of surgery, and status of the patient at the end of the surgical procedure. In this context, MS patients with severe weakness and respiratory distress, including pharyngeal dysfunction, may need extended postoperative care, such as noninvasive respiratory support and intense physiotherapy, to avoid further impairment of their pulmonary function (Box 35.3).

Motor Neuron Disorders

Motor neuron disorders involve either the upper or the lower motor neurons of the cerebral cortex, brainstem, and spinal cord. Some forms are mixed, whereas others have predominately upper or lower motor neuron involvement. Amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease) is the most common disease within this group and involves both upper and lower motor neurons. Other examples of motor neuron disease are Kennedy disease (spinobulbar muscular atrophy), Friedreich ataxia (mixed upper and lower motor neurons), and spinal muscular atrophy (lower motor neurons).

ALS is characterized by degeneration of the anterior horn α -motoneurons in the spinal cord and brainstem motor nuclei, as well as the primary descending upper motor

neurons of the corticospinal tract. Degenerative loss of these neurons leads to progressive muscle weakness, muscle atrophy, and loss of neuronal mass in these locations. Patients present with gradually spreading focal weakness and muscle atrophy (typically of the hands), spasticity, and hyperreflexia of lower extremities. Dysarthria and dysphagia, tongue atrophy, and fasciculations may also occur. Progressive weakness can lead to respiratory failure and death. Sensory functions, including intellectual capacity and cognition, as well as bowel and bladder function, are not usually affected in ALS.

ALS has an incidence of about 2 in 100,000, and onset of the disease usually takes place around 40 to 50 years of age, with males more often affected than females. Most cases are sporadic, but rare familial forms (autosomal dominant and recessive forms) do exist. The underlying mechanism or mechanisms for this selective and progressive motor neuronal death are thus far unclear, but it has recently been suggested that superoxide dismutase (SOD) mutations may have a key role in the increased formation of free radicals seen in subsets of patients. SOD is an important antioxidant and its mutation can lead to decreased clearance of free radicals, increased oxidative stress, and mitochondrial dysfunction. Most familial forms are associated with the mutation of C9ORF72 on 9p21, TDP43, FUS, and VCP genes. The diagnosis is made by electrophysiology (electromyography [EMG] and electroneurography), neurologic examination, MRI imaging, and CSF analysis, which demonstrates early spastic weakness of the upper and lower extremities, typical subcutaneous muscle fasciculations, and bulbar involvement affecting pharyngeal function, speech, and the facial muscles. No curative treatment is currently available, and patients are therefore treated symptomatically. Riluzole, a glutamate release inhibitor, may provide neuroprotection and extend survival in these patients.²⁴² More recently, the antioxidant edaravone was shown to reduce the decline in daily functioning associated with ALS.²⁴³ Patients may also receive spasmolytic and analgesic agents. Those with advanced disease will ultimately require tracheostomy and gastrostomy surgeries and other supportive treatments including mechanical ventilation.

ANESTHETIC CONSIDERATIONS

Bulbar involvement in combination with respiratory muscle weakness leads to a risk for aspiration and pulmonary complications. Notably, these patients may have increased sensitivity to the respiratory depressant effects of sedatives and hypnotics. There are reports of sympathetic hyperreactivity and autonomic failure.²⁴⁴ Sympathetic hyperreactivity and autonomic dysfunction, often manifested as orthostatic hypotension and resting tachycardia but also significant hypotension or even pulseless electrical activity upon anesthesia induction, have been reported,²⁴⁵ and should be considered during the perioperative management of these patients.²⁴⁴ Succinylcholine should be avoided because of the risk for hyperkalemia as a result of denervation and immobilization. Nondepolarizing NMBA may cause prolonged and pronounced neuromuscular blockade and hence should be used with great caution.²⁴⁶ General anesthesia may be associated with exaggerated ventilatory depression. Regional anesthesia is also often avoided

BOX 35.4 Perioperative Considerations for Patients with Amyotrophic Lateral Sclerosis

1. Exaggerated respiratory depression and sensitivity to sedatives and hypnotics
2. Higher risk for aspiration and pulmonary complications
3. Autonomic dysfunction with risk for hemodynamic instability
4. Avoid depolarizing neuromuscular blocking agents (NMBAs) (risk for hyperkalemia); nondepolarizing NMBAs may cause prolonged and profound neuromuscular blockade
5. General and epidural anesthesia have been successfully administered; spinal anesthesia is often avoided

for fear of exacerbating disease symptoms. Both general and epidural anesthesia have, however, been successfully administered to these patients without reported complications (Box 35.4).

Guillain-Barré Syndrome

Guillain-Barré syndrome or acute inflammatory demyelinating polyradiculopathy is an acute inflammatory polyneuritis that is triggered by humoral and cell-mediated autoimmune response to a sensitizing event. Although the etiology is unknown, in many cases a timely association with a viral (influenza-like) or bacterial infection or even lymphomatous disease can be demonstrated.²⁴⁷ It typically presents as an ascending paralysis characterized by symmetric weakness that can vary from mild difficulty with walking to nearly complete paralysis of all extremities, facial, respiratory, and bulbar muscles. Mild variants can present with ataxia, ophthalmoplegia, or hyporeflexia without significant appendicular weakness. Fulminant cases can present with severe ascending weakness leading to complete tetraplegia, and paralysis of cranial nerves and phrenic and intercostal nerves with facial and respiratory muscle weakness necessitating tracheostomy and ventilatory support.²⁴⁸ Importantly, patients may also have autonomic involvement that could lead to hemodynamic instability and arrhythmias with risk for sudden circulatory collapse and fatal cardiac.

The diagnosis is made after careful neurologic examination such as areflexia and progressive motor weakness, clinical and electrophysiological studies,²⁴⁹ and CSF analysis. CSF analysis may show a typical increase in CSF protein in combination with a normal cell count, which is a classic sign of the disease. Electromyogram (EMG) and nerve conduction studies may be normal in the early acute period, but characteristic segmental demyelination and reduction of conduction velocity and dispersion or absence of F-waves are usually seen within 1 to 2 weeks.

Management is primarily supportive and includes nutritional support, respiratory support, and measures to prevent aspiration. Early plasma exchange, typically five exchanges with 5% albumin repletion, may mitigate the course but is contraindicated in setting of hemodynamic instability, marked dysautonomia, and active bleeding.²⁵⁰ Intravenous immunoglobulin (IVIG) is typically administered in the setting of dysautonomia, or if plasmapheresis and exchange transfusion are contraindicated.

BOX 35.5 Perioperative Considerations for Patients with Acute Inflammatory Demyelinating Polyradiculopathy

1. Autonomic dysfunction may be associated with hemodynamic instability and an exaggerated response to anesthesia induction agents, or to stimulating interventions such as laryngoscopy
2. Depolarizing neuromuscular blocking agents (NMBAs) should be avoided due to an upregulation of the acetylcholine receptors and risk for hyperkalemic response
3. Nondepolarizing NMBAs can be used but are commonly also avoided because of the risk for prolonged weakness
4. The use of regional anesthesia is controversial and may be associated with worsening symptoms

ANESTHETIC CONSIDERATIONS

Cranial nerve paralysis and autonomic dysfunction predispose these patients to an increased risk for aspiration. Aspiration precautions, including decompression of the stomach, should therefore be considered before the induction of anesthesia. Absence of compensatory cardiovascular responses may be associated with exaggerated hypotension at anesthesia induction or in response to hypovolemia. Conversely, laryngoscopy or noxious stimuli can be associated with an exaggerated increase in blood pressure. The hemodynamic instability is typically short-lived and self-limited, but small doses of short-acting and titratable vasoactive medications may be required.²⁵¹ Careful hemodynamic monitoring is essential and continuous monitoring of the blood pressure with an arterial catheter is often considered. These patients may also exhibit abnormal responses to NMBA; succinylcholine should not be used because of the risk of hyperkalemia. Nondepolarizing muscle relaxants are not contraindicated but should be avoided as a result of the increased sensitivity and risk for prolonged muscle weakness in the postoperative period. The risk for autonomic dysfunction, respiratory failure, and aspiration may require assisted or mechanical ventilation, even in the postoperative period. If these agents are used, the neuromuscular transmission should be closely monitored with a nerve stimulator as both resistance and sensitivity to these agents have been reported. Great care should be taken to maintain circulatory stability, including adequate cardiac preload and afterload. Careful hemodynamic monitoring is therefore essential in these patients.

Regional anesthesia is employed by some practitioners²⁵² but its use remains controversial as it has been reported to cause worsening of neurological symptoms.²⁵³ General anesthesia can be used; however, the combination of general anesthesia and epidural anesthesia is more controversial (Box 35.5).²⁵⁴

CRITICAL ILLNESS POLYNEUROPATHY AND CRITICAL ILLNESS MYOPATHY

Despite earlier reports of a rapid development of weakness, muscle atrophy, and polyneuropathy in critically ill patients, it was not until the 1987 report by Bolton and associates that the characteristic widespread axonal degeneration of motor and sensory fibers and the extensive denervation atrophy of limb and respiratory muscle associated with this polyneuropathy were clearly identified.²⁵⁵ Although the

BOX 35.6 Perioperative Considerations for Patients with Critical Illness Polyneuropathy

1. Particular attention should be made to protect peripheral nerves, in particular the ulnar and peroneal nerves, during positioning of these patients
2. Monitor and correct electrolyte and glucose abnormalities
3. Steroids have been implicated in the pathophysiology of the disease and should therefore be avoided
4. Neuromuscular blocking agents are best avoided altogether, but if needed only nondepolarizing agents should be considered

true incidence of critical illness polyneuropathy (CIP) is difficult to determine, critical illness neuropathy and myopathy are believed to affect up to 50% of all patients remaining in the intensive care unit for more than 2 weeks.²⁵⁶ It is typically manifested as profound symmetric limb weakness, with reduced or absent tendon reflexes and diaphragmatic and intercostal weakness. It affects the lower extremities to a greater extent than upper extremities, and distal muscle groups more severely than the proximal. The autonomic function is not affected and the extraocular eye movements remain intact. In CIP, there is no evidence of neuromuscular junction disorder and the electromyography and nerve conduction study findings are consistent with axonal motor and sensory polyneuropathy, with amplitude reduction of motor and sensory action potentials, and slowed conduction velocities. Serum CK levels are usually normal. Conversely, a sensory nerve action potential is often normal in critical illness myopathy but compound muscle action potentials are diminished and electromyography is consistent with myopathy. Serum CK levels may be elevated. No specific treatments are currently available, and management is supportive with aggressive and early rehabilitation. Use of sedation, paralytics, and corticosteroids should be limited,²⁵⁷ and aggressive control of hyperglycemia has been suggested to reduce the incidence of CIP by 44%.²⁵⁸

ANESTHETIC CONSIDERATIONS

Anesthetic considerations in CIP patients are similar to those with other acquired neuropathies (see above), and include protection of nerve compression sites, particularly the ulnar and peroneal nerves. Prolonged immobility in critically ill patients is associated with a relative increase in immature acetylcholine receptors that can lead to an insensitivity to nondepolarizing NMBA.²⁵⁹ Conversely, the sensitivity to depolarizing neuromuscular blockers is increased, with a risk for increased potassium efflux after succinylcholine administration (Box 35.6).²⁶⁰

Hereditary Motor-Sensory Neuropathies, including Charcot-Marie-Tooth Disease

Hereditary motor-sensory neuropathies include a spectrum of peripheral neurologic disorders, among which Charcot-Marie-Tooth (CMT) disease is often listed. They are caused

by a specific mutation in one of several myelin genes that result in defects in myelin structure, maintenance, and formation. Hereditary motor-sensory neuropathies have been classified into seven types and multiple subtypes according to the age at onset, mode of inheritance, predominately involved muscle groups, and genotypes.^{261,262} CMT types 1 and 2 are the most common hereditary peripheral neuropathies, with an estimated prevalence of 40 per 100,000.²⁶² Patients with CMT disease typically experience slow and progressive distal muscle weakness and wasting. Damage to sensory axons may also lead to sensory loss resulting in frequent tripping and falls. Neuropathic pain may develop in some patients. CMT patients usually have normal life expectancy. CMT type 3, also known as Dejerine-Sottas disease, is a very severe condition with an early onset of hypotonia during infancy. Nerve conduction velocity is typically significantly reduced to less than 10 ms.²⁶² The genetic inheritance pattern for CMT disease is heterogeneous.

ANESTHETIC CONSIDERATIONS

The anesthesia experience in patients with CMT disease is limited because of the small number of cases. Major considerations include the use of hypnotic agents, muscle relaxants, volatile agents, and neuraxial techniques. CMT type 1 patients have been reported to have significantly increased sensitivity to thiopental at induction that correlates with the severity of both motor and sensory defects. However, total intravenous anesthesia (TIVA) has been performed successfully in a number of cases without any reported problems.²⁶³⁻²⁶⁵

Because of the reduced number of acetylcholine receptors, sensitivity to nondepolarizing muscle relaxants is elevated and the response to succinylcholine is also reduced.²⁶⁶ Although succinylcholine has been used without adverse effect,^{267,268} the risk of an exaggerated hyperkalemic response may be sufficient to preclude it from being used in patients with suspected muscular denervation.²⁶⁸ Prolonged neuromuscular blockade with vecuronium has been reported.²⁶⁹ As a result of the large variety of disabilities in this patient group, careful baseline assessment of neuromuscular status should be conducted before the use of nondepolarizing neuromuscular relaxants. Normal response to atracurium and mivacurium has been demonstrated.^{270,271} Both TIVA and volatile anesthetics have been used safely in CMT patients in a series of cases.²⁶⁷ Neuraxial techniques for obstetric procedures have been reported to generally be successful in CMT patients.²⁷²⁻²⁷⁵ However, the use of regional anesthesia can be controversial given that the possible complications may exacerbate the neurologic symptoms.²⁷⁶ Similar medicolegal concerns may apply to the surgical and anesthesia positioning of CMT patients because of the sensory deficits and limb deformities.

Duchenne Muscular Dystrophy and Becker Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is the most common and severe type of muscular dystrophy, with an incidence of 1 per 3500 live male births²⁷⁷ and a total male prevalence of about 50 to 60×10^{-6} .²⁷⁸ Becker muscular dystrophy (BMD) is relatively rare and has an incidence of about 1 in

18,000 live male births and a prevalence of 23.8×10^{-6} .²⁷⁸ Both DMD and BMD are X-linked recessive diseases. The defect is located on the short arm of the X chromosome at the Xp21 region, which contains the gene for the large protein Dp427, also known as dystrophin. The dystrophin gene is 2500 kilobases long with more than 70 exons.²⁷⁸ Dystrophin is distributed not only in skeletal, cardiac, and smooth muscle but also in the brain.²⁷⁹ Because of the large size of the dystrophin gene, spontaneous new mutations are common and account for a third of new cases.²⁸⁰

The most common form of mutation is a deletion within the gene (65%-70% of cases of DMD and >80% of BMD). Duplication and point mutations are responsible for the rest. It also appears that there are “hot spots” within the first 20 exons and in the central region of the gene (exons 45-55) where deletion and duplication are likely to occur.²⁷⁸ Female cases of DMD have been reported with the 45,X and 46,XX karyotypes. The disease mechanism for the female 46,XX karyotype was thought to be preferential loss of the paternal X chromosome by postzygotic nondisjunction and manifestation of the DMD gene from the maternal X chromosome in muscle cells.²⁸¹ BMD is usually milder in severity than DMD because disruption of the translation process occurs in the relatively distal part of the gene, which leads to a reduced amount of truncated dystrophin protein.^{278,282}

Dystrophin, along with dystrophin-associated glycoproteins (DAGs), is involved in sarcolemmal stability. Dystrophin is responsible for maintenance of muscle membrane integrity despite the fact that it accounts for only approximately 0.002% of the protein in striated muscle.²⁸³ Dystrophin aggregates and links to actin (at its N terminus) and the DAG complex (at its C terminus) to form a stable structure that interacts with laminin in the extracellular matrix (Fig. 35.4). Lack or dysfunction of dystrophin leads to cellular and membrane instability, with progressive leakage of intracellular components and elevation of creatine

phosphokinase (CPK) levels. Eventually, damaged muscle cell units are invaded by macrophages and destroyed. Current study suggests that cytotoxic T cells are probably the culprit. Consequently, clinical pseudohypertrophy of the muscle occurs when the dead muscle shells are replaced by fibrofatty infiltrates. Loss of muscle units accounts for the weakness and contracture.²⁷⁹

Both DMD and BMD are characterized by progressive weakness and wasting of predominantly the proximal musculature. Pseudohypertrophy of the calves and other muscle groups is common. As the more severe of the two diseases, DMD tends to be symptomatic early in life. Seventy-four percent of children with DMD were found to manifest the disease by 4 years of age.²⁷⁷ DMD patients do not usually begin to walk until they are about 18 months of age or later.

The initial clinical findings include a waddling gait, frequent falling, and difficulty climbing stairs because of proximal muscle weakness in the pelvic girdle. The classic Gower maneuver describes rising from a sitting to a standing position with the help of both arms. Patients may also show weakness in the shoulder girdle and trunk erectors that leads to thoracolumbar scoliosis. The earlier the onset of disease, the more rapid the disease will take its course. In most cases, children with DMD are unable to walk by the age of 9 to 11. Proximal deep tendon reflexes in the upper extremities and patella may also disappear despite the lack of denervation.²⁸² Nevertheless, the Achilles tendon reflex remains intact even in later stages of the disease. Sixty percent of patients will have pseudohypertrophy of the calves, and thirty percent will have macroglossia. Some may also suffer from pain in the calves with activity.

The intellectual impairment that can be associated with the disease was thought to be related to limitation of educational opportunities. However, with equalization of educational opportunities, psychometric studies have revealed a significantly lower average intelligence quotient in DMD

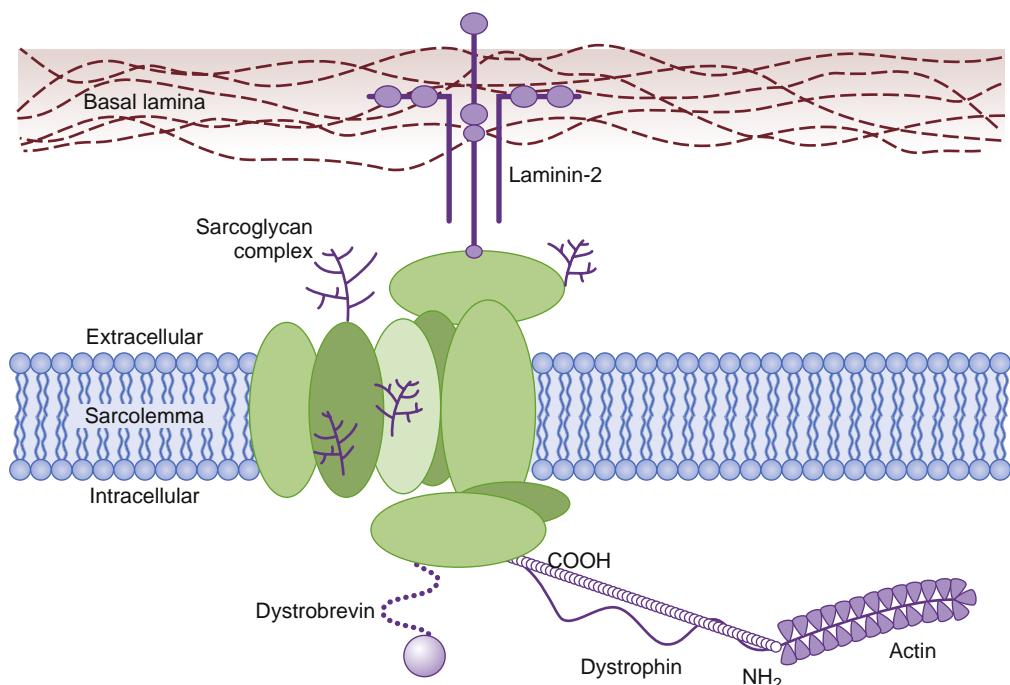


Fig. 35.4 Diagram of the cell-surface and cytoskeleton protein complex.

patients than in healthy groups.²⁸⁴ This implies a possible effect of dysfunctional dystrophin in the brain on learning.

Death in patients with DMD is commonly due to cardio-pulmonary compromise in their 30s.²⁷⁷ BMD is a mild form of DMD. The mutation that causes BMD produces dystrophin that retains partial function. The onset of symptoms occurs in the second or third decade of life. As a result, the life span of BMD patients can reach the early 40s. Pneumonia is the most common cause of death (Fig. 35.5).²⁸⁴

The heart is also affected to various degrees, depending on the stage of the disease and the type of mutation. Cardiac degeneration is due to replacement of myocardium by connective tissue or fat, which leads to dilated cardiomyopathy.²⁸⁵ Cardiac involvement starts early in the course of the disease, although clinical signs are not usually obvious in the early stage. No correlation has been established between the severity of cardiac disease and the severity of skeletal disease. Studies of necropsy have shown that the cardiomyopathy in DMD involves the posterobasal and contiguous lateral left ventricular walls as

initial and primary sites of myocardial dystrophy in the absence of small vessel coronary artery disease in these areas.²⁸⁶ Typical initial manifestations on the electrocardiogram (ECG) in DMD and BMD are sinus tachycardia, tall R waves in the right precordial leads, prominent left precordial Q waves, increased QT dispersion, and inverted T waves from scarring of the posterobasal portion of the left ventricle. Initially, the echocardiography is normal or shows regional wall motion abnormalities in areas of fibrosis. With the spreading of fibrosis, left ventricular dysfunction can be seen and ventricular arrhythmias frequently occur as well. In the final stages of the disease, systolic dysfunction may lead to heart failure and sudden death. Sub-clinical or clinical cardiac involvement is present in about 90% of DMD/BMD patients, but it is the cause of death in only 20% of DMD and 50% of BMD patients. Angiotensin-converting enzyme inhibitors are recommended in early stages of the disease, and β -blockers may be an additional option if indicated.²⁸⁵

Pulmonary insufficiency is a leading cause of morbidity and mortality in DMD.²⁸⁷ Usually, expiratory muscle function is affected first, because of the early onset of abdominal muscle weakness. By contrast, inspiratory muscle function is relatively preserved in the first decade, implying sparing of the diaphragm.²⁸⁸ Vital capacity (VC) increases in the first decade because of overall body growth, plateaus in early adolescence, and then declines dramatically as the diaphragmatic weakness progresses.²⁸⁸ Other measured lung volumes such as inspiratory reserve volume and total lung capacity (TLC) follow the same pattern. A disproportionate loss of VC and TLC relative to the respiratory muscle dysfunction results in part from additional factors, such as altered chest wall and lung mechanics, modifications in the distribution of surfactant, micro-atelectasis, and local fibrosis secondary to recurrent pneumonia.²⁸⁸ Scoliosis further impairs pulmonary function. On average, for each 10 degrees of thoracic scoliosis curvature, forced vital capacity (FVC) decreases by 4%.²⁸³ In 90% of patients, a curvature of greater than 20 degrees develops 3 to 4 years after they are wheelchair bound. Respiratory failure inevitably occurs in the second decade of life and is the most common cause of death.²⁸⁹

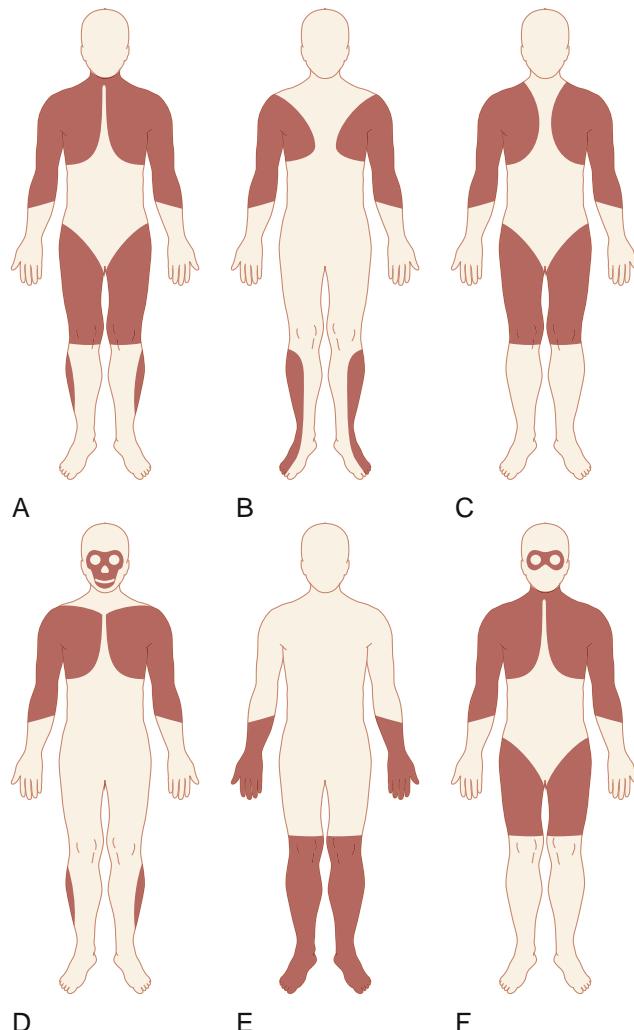


Fig. 35.5 Distribution of predominant muscle weakness in different types of dystrophy: (A) Duchenne type and Becker type; (B) Emery-Dreifuss; (C) limb girdle; (D) facioscapulohumeral; (E) distal; and (F) oculopharyngeal. (Redrawn from Emery AE. The muscular dystrophies. *BMJ* 1998;317:991–995.)

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Chronic elevation of the serum CPK level is a general indication of muscle disease. Three serum tests showing elevated CPK levels obtained one month apart is diagnostic of muscular dystrophy. CPK represents leakage of enzyme from muscle cells and does not correlate with severity of the disease. CPK could reach 50 to 300 times the normal value in early stages of the disease. The level tends to decrease with the loss of muscle mass. Elevation of the MB fraction of CK precludes its use as a marker for cardiac injury.²⁸² EMG can be supportive of the diagnosis; however, it can be very difficult to perform on children. Muscle biopsy, followed by immunostaining or Western blot analysis for dystrophin, is recommended for diagnostic testing. Multiple polymerase chain reactions are also useful in detecting more than 98% of the existing deletions.²⁷⁹ The result is usually available within 24 hours, which may render muscle biopsy, the old “gold standard,” obsolete.

ANESTHETIC CONSIDERATIONS

Patients with DMD and BMD may require anesthesia for muscle biopsy, correction of scoliosis, release of contractures, and exploratory laparotomy for ileus,²⁸² as well as for dental²⁹⁰ and obstetric²⁹¹ procedures. As the natural course of the disease progresses, the risk of surgery increases concomitant with the increased comorbid conditions associated with the later phase of the disease. However, perioperative complications are not proportional to the severity of the disease. They occur even in mildly affected patients. Consequently, patients should undergo careful preoperative consultation and evaluation.

Fifty to seventy percent of patients with muscular dystrophy demonstrate some cardiac abnormality, although it is clinically significant in only ten percent.²⁸² Preoperative cardiology assessment with an ECG and echocardiography is essential. Continuous cardiac Holter monitoring is necessary if an arrhythmia is captured on the ECG or if the patient describes symptoms that can be related to cardiac arrhythmias. An echocardiography will demonstrate mitral valve prolapse in 10% to 25% of patients. It may also show posterobasilar hypokinesis in a thin-walled ventricle and a slow relaxation phase with normal contraction characterizing the cardiomyopathy seen in DMD.²⁸² However, echocardiography may not always reflect the ability of the diseased myocardium to respond to perioperative stress. A stress echocardiography using angiotensin to detect latent heart failure and identify inducible contraction abnormalities has been advocated.²⁹²

An estimated 30% of deaths in individuals with DMD are due to respiratory causes.²⁹³ Therefore careful preoperative pulmonary assessment is important. Webster demonstrated that the manual muscle strength test has a strong statistical correlation with all of the timed functional tests. Peak expiratory flow was not only easy to perform, but also correlated statistically with all timed functional tests.²⁹⁴ The correlation was not significant for VC or forced expiratory volume in 1 second (FEV₁).

Intraoperatively, in terms of airway management, patients with DMD and BMD may have decreased laryngeal reflexes and prolonged gastric emptying time, which increases the risk for aspiration.²⁹⁵ Decreased ability to cough up the accumulation of oral secretions predisposes muscular dystrophy patients to postoperative respiratory tract infections.²⁸² Masseter spasm is also a possible complication during induction of anesthesia in these patients.²⁹⁶ Preparedness for a difficult airway is necessary, especially in patients with potential airway problems.

Postoperatively, DMD patients are at an increased risk for respiratory compromise.²⁹⁷ Retrospective reviews have indicated that the incidence of prolonged postoperative ventilation (>36 hours) was greatest in DMD patients who had a preoperative FVC of less than 40% of the predicted value.^{298,299} Preoperative pulmonary function studies are valuable in determining the postoperative course. Patients with a VC of greater than 30% of the predicted value can usually be extubated immediately after surgery.²⁸² Sleep apnea may also compound the condition and contribute to the development of pulmonary hypertension. Continuous positive airway pressure and bilevel positive airway pressure have been demonstrated to be effective in the

management of postoperative respiratory depression. Delayed pulmonary insufficiency may occur up to 36 hours postoperatively despite the apparent recovery of skeletal muscle strength.³⁰⁰

Reports have suggested a relationship between DMD/BMD and MH, but this association is not based on good rational grounds.³⁰¹ Whereas the risk for an MH mutation in DMD/BMD patients is similar to that of the general population, the incidence of MH-like anesthetic events has been reported to be 0.002 with DMD and 0.00036 with BMD. Unexplained cardiac arrest^{296,302} and acute heart failure³⁰³ have been reported in DMD/BMD patients. Succinylcholine is contraindicated in these patients because of the potential for rhabdomyolysis and hyperkalemia as a result of their unstable sarcolemmal membranes. Succinylcholine-induced hyperkalemia during acute rhabdomyolysis is more likely to result in cardiac arrest and unsuccessful resuscitation than is the potassium efflux resulting from upregulation of acetylcholine receptors in burn patients.³⁰⁰ Although the use of nondepolarizing muscle relaxants is usually accompanied by an increase in both maximal effect and duration of action,³⁰⁴ proper and rapid reversal with sugammadex may put some of these concerns to rest. Current off-label experience in infants and children has been favorable. Narcotics can be used, but small incremental dosing and short-acting medications are recommended given the respiratory depression associated with these medications, as well as the reports of inadvertent reactions to volatile anesthetics.²⁸²

Recently, TIVA has become more popular.³⁰⁵ However, consideration needs to be given to the myocardial status of the patient when propofol or barbiturates are used because they may lead to profound hypotension and reduced organ perfusion.^{282,306} Regional anesthesia may be a good alternative to general anesthesia because it avoids the risk of triggering agents and respiratory depression and enables the use of local anesthetics for postoperative analgesia. It may also facilitate chest physiotherapy.³⁰⁷

Recent breakthroughs in gene therapy are shining new lights into the management of these relatively common disorders. We have not seen reports on anesthesia management for DMD/BMD patients who had received gene therapy.

Limb-Girdle Muscular Dystrophy

Limb-girdle muscular dystrophy (LGMD) is a group of disorders with heterogeneous causes. To date, at least 18 genes have been identified as being responsible for this disease, with 7 being autosomal dominant and 11 autosomal recessive.³⁰⁸ Mutations within the same gene may result in different phenotypes that sometimes are not consistent with LGMD. Proximal muscle (shoulder or pelvic) girdle weakness is the characteristic feature of this group of diseases. Given the marked genetic heterogeneity, clinical manifestations of the disease vary. Autosomal recessive forms are about 10 times more common than autosomal dominant forms. Fukutin-related protein (FKRP) and calpain 3 (CAPN3) gene mutations have been associated with LGMD. In addition, a number of other disorders, not strictly included under LGMD in this classification, may have

LGMD-like phenotypes.³⁰⁸ Sporadic cases of LGMD have been reported in the anesthesia literature.³⁰⁹⁻³¹¹ General approaches to these patients are the same as those for DMD/BMD.

Myotonic Dystrophy

Myotonic dystrophy (MD) is an inherited muscular disorder characterized by progressive muscle weakness and wasting. Two types of MD result from a mutation in either the *dystrophin myotonia–protein kinase (DMPK)* gene, located on chromosome 19q13.3 (MD1, also known as Steinert disease), or the *CysCysHisCys (CCHC)*-type zinc finger, nucleic acid binding protein (*CNBP*) gene, located on chromosome 3q21 (MD2).³¹²

The incidence of MD is 1 in 8000. MD1 is by far the most common of the two types and accounts for about 98% of all cases. MD1 is caused by expansion of a CTG trinucleotide repeat in the *DMPK* gene and is inherited in an autosomal dominant manner.³¹² Typical signs and symptoms include muscle weakness and wasting (most prominent in the cranial and distal limb musculature), periodic myotonia, progressive myopathy, insulin resistance, defects in cardiac conduction, neuropsychiatric impairment, cataracts, testicular atrophy, and frontal balding in males. The typical cranial muscle weakness and wasting are manifested not only in the facial, temporalis, masseter, and sternocleidomastoid muscles but also in the vocal cord apparatus. Mitral valve prolapse is found in 20% of patients.³⁰⁰ The severity of the disease is related to the number of extra trinucleotide repeats.⁹⁴ MD1 patients may also have mildly elevated CK levels. Myotonic discharges can be identified on EMG, as well as an inability to relax from a handgrip. During pregnancy, the symptoms may be exacerbated. Uterine atony and a retained placenta may also complicate vaginal delivery. First-degree atrioventricular heart block is a common finding on the ECG before the onset of symptoms.³⁰⁰

MD2 is also called proximal myotonic myopathy. Intron 1 of the *CNBP* gene contains a complex repeat motif, (TG)n(TCTG)n(CCTG)n, and expansion of the CCTG repeat was determined as the cause of MD2. Patients with MD2 suffer from myotonia (90% of those affected), muscle dysfunction (82% weakness, pain, and stiffness), and less commonly, cardiac conduction defects, iridescent posterior subcapsular cataracts, insulin-insensitive type 2 diabetes mellitus, and testicular failure.

There is no case report in the literature linking MD to MH.³¹³ Lehmann-Horn and associates performed IVCT in 44 patients with myotonias and periodic paralyses, which revealed 4 positive, 10 equivocal, and 30 negative results.³¹⁴

ANESTHETIC CONSIDERATIONS

General considerations for MD are similar to those for other muscular dystrophies. Mathieu and coworkers conducted a retrospective study on the anesthetic and surgical complications of MD. The majority of complications were found to be pulmonary related and significantly more frequent in patients undergoing upper abdominal operations and those with severe disability, as assessed by the presence of proximal limb weakness.³¹⁵ The pulmonary complications

of MD are the result of hypotonia, chronic aspiration, and central and peripheral hypoventilation.²⁸² Smooth muscle atrophy, which leads to poor gastric motility, when coupled with a diminished cough reflex, promotes aspiration.

Succinylcholine will produce contractions lasting for several minutes, thus making intubation and ventilation a challenge. These contractions are not antagonized by nondepolarizing muscle relaxants. Other agents, including methohexitol, etomidate, propofol, and even neostigmine, may also induce myotonic reactions. Short-acting nondepolarizing muscle relaxants or avoidance of relaxation is therefore advised.²⁸² Case reports have demonstrated normal responses to sugammadex when rocuronium was used as the neuromuscular blockade.³¹⁶⁻³¹⁸

Triggering factors, such as hypothermia, shivering, and mechanical or electrical stimulation, may cause a myotonic reaction.³¹⁹ The reaction can be treated with phenytoin (4-6 mg/kg/day) or quinine (0.3-1.5 g/day).²⁸² Furthermore, MD patients can be very sensitive to anesthetic agents, with hypersomnolence and CO₂ retention sometimes being observed. Careful titration with relatively short-acting anesthetic agents may be beneficial. Close cardiac monitoring is required for MD patients. Pacing equipment should be readily available because a third of first-degree atrioventricular blocks may not respond to atropine.²⁸² All patients should be treated as though they have both cardiomyopathy and conduction defects.

Myotonia Congenita

Myotonia congenita (MC) is a congenital form of muscular dystrophy characterized by uncontrolled temporary skeleton muscle excitability as a result of mutations in the muscle chloride channel gene (*CLCN1*). There are two forms of MC, one with autosomal dominant and the other with recessive inheritance. The former is also known as Thomsen disease and the later as Becker myotonia. The myotonia in MC patients is usually initiated by a forceful muscle contraction, particularly after being at rest for at least 10 minutes. The myotonic muscle stiffness then becomes increasingly obvious after a second and third short, but forceful contraction. Further contractions usually dampen the myotonia.³²⁰

Thomsen disease was the first myotonic disease to be described. Patients may have a hypertrophic and athletic appearance. The sign of percussion myotonia is described as an indenting-appearing myotonia triggered by tapping the muscle. Lid lag is common and muscle stretch reflexes are normal.³²⁰ Myotonia symptoms in Becker myotonia usually start at 10 to 14 years of age or even later and are more severe than those of Thomsen disease. Becker myotonia may be associated with severe generalized stiffness resulting in falling. It can frequently be misdiagnosed as epilepsy. Antiepileptic medications do improve the symptoms, however.³²⁰

ANESTHETIC CONSIDERATIONS

As with many muscle diseases, there have been reports that MC patients are predisposed to MH, but as is the case for almost all of them, there are no data to support this

hypothesis.³²¹⁻³²³ However, depolarizing muscle relaxants can lead to severe masseter spasms in MC patients. Generalized spasms involving the respiratory and skeletal muscles have been reported.³²¹ The findings resemble those of MH, so dantrolene is sometimes administered.³²⁰ Because dantrolene is an inhibitor of calcium release from the SR, it can usually abolish the myotonia effectively.^{321,322} Some believe that local anesthetics and class Ib antiarrhythmic drugs such as lidocaine should be used for myotonic reactions rather than dantrolene.³²⁴ Because shivering in the operating room can trigger the myotonic reaction, MC patients should be kept normothermic during surgery.³²⁰

Myotubular Myopathy

Myotubular myopathy (MTM) is pathologically defined by the presence of centrally placed nuclei in the majority of extrafusal muscle fibers, an appearance resembling fetal myotubes during normal muscle development. Consequently, MTM is also called centronuclear myopathy (CNM).³²⁵ However, MTM now mostly refers to the X-linked form of the disease, whereas CNM is used for the autosomal form.³²⁵

MTM and CNM are rare. The estimated incidence of MTM is 1 in 50,000 newborn males.³²⁵ MTM has been linked to the myotubularin (*MTM1*) gene on Xq28. Pregnancy is often complicated by polyhydramnios and reduced fetal movements. Affected males typically have severe floppiness and weakness and respiratory distress at birth. Cardiac muscles are not generally involved. The patient usually has a normal response to pain, but tendon reflexes are absent. The long-term prognosis for MTM is extremely poor.³²⁵ In patients who survive the first year of life, most are either completely or partially ventilator dependent.³²⁶ These patients often have abnormal liver function.³²⁶ Both autosomal recessive and autosomal dominant forms have been observed in CNM patients. Its clinical features include respiratory distress, hypotonia, bulbar weakness, ophthalmoplegia, ptosis, and facial diplegia. Although the exact genetic mechanism is not fully understood, the *MTM1*, myotubularin-related protein (*MTMR2*), and myotubularin-related phosphatase (*MTMR3*) genes have been implicated.³²⁵ Pathologically, MTM and CNM share a similar, characteristic histologic feature: predominantly type 1 fiber with centrally placed nuclei seen on hematoxylin-eosin staining of formalin-fixed, paraffin-embedded tissue.³²⁵

ANESTHETIC CONSIDERATIONS

Reports of anesthesia for patients with MTM are sparse.³²⁷⁻³³² Nontriggering general anesthesia has been used because of the unfounded concern of possible susceptibility to MH. Agents such as propofol, fentanyl, remifentanil, and nitrous oxide have been used successfully without adverse effects.³²⁷⁻³³² The possibility of a prolonged effect of nondepolarizing muscle relaxants has been suggested with mechanomyography.³²⁷⁻³³² However, in reality, intubation of such patients may not require any muscle relaxant because of their hypotonic state. Costi and van der Walt suspected that the defect in MTM is distal to the neuromuscular junction,³²⁸ whereas Dorchie and coworkers suggested that muscles in MTM might be intrinsically normal, with myotubularin-deficient motor neurons involved in development of the disease.³³³

Metabolic Myopathies

Two major energy sources for muscle exist: glycogen and fatty acid. Glycogen serves as a dynamic, but limited reservoir of glucose, mainly stored in skeletal muscle and liver. Glycogen storage disorders (GSDs) are a group of metabolism disorders caused by enzyme deficiency or dysfunction. They reduce effective glucose storage by interfering with normal glycogen synthesis and degradation. Synthetic errors cause decreased normal glycogen, whereas degradation errors tend to block the breakdown of glycogen. Subsequently, hypoglycemia and accumulation of glycogen in tissues could occur as a result of substrate use. There are more than 12 types of GSD that are assigned roman numerals based on the enzyme deficiencies. Types I and II are discussed here.

Glycogen Storage Disease Type I

The incidence of GSD I is approximately 1 in 100,000 live newborns.³³⁴ The incidence in non-Ashkenazi Jews from North Africa may be as high as 1 in 5420 people.³³⁴ The defective enzyme causing the disease is glucose-6-phosphatase, which is the enzyme that converts glucose 6-phosphate (G6P) to glucose in the liver. Type Ia (von Gierke disease) is due to a deficiency in G6P hydrolase (catalytic subunit) activity and accounts for more than 80% of cases. Types Ib (G6P transporter deficiency), Ic, and Id represent allelic defects in the translocase associated with G6P. Their inheritance is autosomal recessive. The G6P gene (*G6PC*) encoding the hydrolase resides at 17q21, with the gene encoding G6P translocase (*G6PT*) located at 11q23. Mutations responsible for GSD I have been described in both type Ia and Ib patients.³³⁴

Impaired glycogenolysis results in accumulation of glycogen and G6P in the liver, kidney, intestine, skeletal muscle, and heart and is manifested as hepatomegaly, renomegaly, proximal tubular dysfunction, and diarrhea.³³⁵ Fasting hypoglycemia is the initial manifestation of the disease. As a result, upregulation of the synthesis and transport of counter-regulatory hormones, such as glucagon, cortisol, catecholamines, and growth hormone, becomes obvious and leads to the release of pyruvate, lactate, and free fatty acid. Lipid deposition in lean tissues such as the liver, skeletal muscle, cardiac muscle, and pancreas results in lipotoxicity and organ failure, including pulmonary hypertension, steatohepatitis, end-stage renal disease, insulin resistance, cardiac contractile dysfunction, and pancreatic β cell failure.³³⁴ For type Ib disease, specific problems such as neutropenia and neutrophil dysfunction are prominent. Patients may have recurrent infections and inflammatory bowel disease.³³⁶

ANESTHESIA CONSIDERATIONS

Anesthesia case reports for GSD I patients are rare.^{337,338} Patients with GSD I diseases should be given intravenous glucose-containing fluid preoperatively when they have fasted. Lactate-containing solutions should be avoided because these patients are not able to convert the lactic acid to glycogen.²⁸² Patients need to be monitored frequently to avoid hypoglycemia.

Glycogen Storage Disease Type II (Acid Maltase Deficiency)

The incidence of acid maltase deficiency (AMD) is estimated to be 1 in every 14,000 to 40,000 births. Its inheritance is autosomal recessive with a few exceptions.^{339,340} Mutations of the acid maltase gene on chromosome 17q25 cause deficiency of lysosomal acid maltase (acid α -1,4-glucosidase).³⁴⁰ Cases of AMD have been arbitrarily classified into three groups—infantile, childhood, and adult—according to the age at onset or death, rate of progression, and tissue-organ involvement.³⁴⁰

Acid maltase is a lysosomal enzyme that catalyzes the one-way hydrogenation of glycogen to G6P and is found in all tissues, including skeletal and cardiac muscle.³⁴¹ Consequently, glycogen accumulates within the muscle tissues of maltase-deficient patients. Infantile AMD, also known as Pompe disease, is usually manifested within the first few months of life as rapidly progressive weakness and hypotonia and enlargement of the tongue, heart, and liver. Massive amounts of glycogen (8%–15% of the wet weight of the tissue) accumulate in the heart, liver, and skeletal muscle, with relatively smaller deposits in smooth muscle, eyes, kidneys, endothelial cells, lymphocytes, brain, and spinal cord. Accumulation of glycogen in cardiac muscle leads to cardiac failure in the infantile form.³⁴⁰ Echocardiography demonstrates marked thickening of the interventricular septum and posterior left ventricular wall, left ventricular outflow obstruction, and trabecular hypertrophy.³⁴⁰ Ventricular wall thickness may be increased to up to 25 mm.³⁴² Wolff-Parkinson-White syndrome has been reported.³⁴³ The signs and symptoms of infantile AMD may resemble those of DMD. Death usually results from cardiorespiratory decompensation within several years of disease progression.³⁴⁴

Childhood AMD occurs in infancy to early childhood and is manifested by clinical signs of myopathy. Respiratory muscles tend to be selectively affected. Calf enlargement can also occur. The disease progresses relatively slowly in this form, with a few patients surviving beyond the second decade of life.³⁴⁰ Tongue, heart, and liver enlargement occur infrequently.³⁴⁵ However, involvement of vascular smooth muscle is more severe than in the infantile form. There has been a report of extensive glycogen deposition in the arterial wall causing basilar aneurysms.³⁴⁵

Adult AMD usually occurs after age 20 and is characterized by slow progressive myopathy or symptoms of respiratory failure.³⁴⁰ The weakness in proximal muscles is more prominent than the weakness in distal muscles. A third of adult AMD patients suffer from respiratory failure with a restrictive pattern. Weakness in the diaphragm causes extensive atelectasis. VC may be significantly reduced.³⁴⁰

ANESTHETIC CONSIDERATIONS

Anesthesia reports in AMD patients are rare.^{346–349} Isolated intraoperative cardiac arrest during halothane anesthesia in infantile AMD has been documented.³⁴⁹ Despite the problem noted with halothane, enflurane³⁴⁷ and sevoflurane³⁴⁸ have been used without complications. Theoretically, total intravenous general anesthesia with propofol may cause a reduction in afterload leading to an increased risk for myocardial ischemia. This may become significant when the patient is tachycardic.³⁴⁸

Subendocardial ischemia may occur in patients with a thickened ventricular wall and results in higher left ventricular end-diastolic pressure at lower ventricular volume.^{348,350} Close cardiac monitoring is therefore necessary. A central venous or pulmonary artery catheter is not essential in patients who are normovolemic without preexisting heart failure.³⁴⁸ Adequate filling pressure and normal to high systemic vascular resistance (SVR) are required to ensure effective coronary perfusion.³⁴⁸ Ketamine has been used successfully in a number of cases because of its ability to maintain SVR and contractility. Respiratory failure and muscle weakness are the other concerns for anesthesiologists. A spectrum of uses of muscle relaxants from none³⁴⁷ to atracurium³⁴⁶ to rocuronium³⁴⁸ have been attempted. Low-dose rocuronium, 0.5 mg/kg, with close monitoring of neuromuscular function and adequate use of reversal agents, has been sufficient to prevent prolonged postoperative weakness.³⁴⁸ Depolarizing agents should be avoided because of the potential risk of hyperkalemia and rhabdomyolysis.^{348,349}

Mitochondrial Myopathies

Mitochondrial diseases refer to defects in the five main steps of mitochondrial metabolism: substrate transport, substrate utilization, the Krebs cycle, the electron transport chain, and oxidation-phosphorylation coupling.³⁵¹ However, the term *mitochondrial myopathy* has been reserved for disorders caused by defects in the respiratory chain.³⁵¹ The respiratory chain is composed of five multimeric complexes (I–V) embedded in the inner mitochondrial membrane, plus two small mobile electron carriers, coenzyme Q₁₀ (CoQ₁₀) and cytochrome *c*, for a total of more than 80 proteins,³⁵¹ among which 13 are encoded by mitochondrial DNA (mtDNA) and all others by nuclear DNA (nDNA). mtDNA is different from nDNA in several aspects: (1) mtDNA is circular and contains no intron, (2) it has larger numbers of copies than nDNA does and a much higher spontaneous mutation rate, and (3) its inheritance is maternal. Diagnosis of mitochondrial diseases is difficult because of their clinical heterogeneity.

Primary mtDNA mutations may include point mutations in polypeptide, tRNA, or rRNA encoding regions and large-scale rearrangements, duplications, or deletions.³⁵² Some of the common conditions caused by point mutations include myoclonic epilepsy with ragged-red fibers (MERRF); mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS); neuropathy, ataxia, and retinitis pigmentosa (NARP); maternally inherited Leigh syndrome; and Leber hereditary optic neuropathy.³⁵¹ Sporadic large-scale mutations may lead to Kearns-Sayre syndrome, progressive external ophthalmoplegia, and Pearson syndrome.³⁵¹ nDNA mutations can cause deficiencies in complexes I to IV and CoQ₁₀ of the electron transport chain.³⁵¹

Mitochondrial diseases present a diagnostic challenge due to their clinical heterogeneity. Since mitochondria are ubiquitous; every tissue in the body can be affected by mtDNA mutations. Disorders due to nDNA mutations follow a Mendelian pattern and are thus phenotypically “all or none,” while inheritance of mtDNA is stochastic, leading to greater variability. Mitochondrial myopathy is estimated to have an incidence of 1 in 4000.³⁵³ Among all the

mitochondrial functions, abnormalities in electron transport and oxidative phosphorylation are the most common causes of mitochondrial myopathies.³⁵⁴ Mitochondrial myopathies are characterized by proximal muscle weakness. Common laboratory findings include a very high lactate to pyruvate ratio (50-250:1 instead of a normal ratio of <25:1), increased blood levels of free carnitine, and occasionally low levels of folate (for instance in Kearns-Sayre syndrome). The hallmark of mitochondrial myopathies is the “ragged red fiber” when muscle biopsy specimens are stained with modified Gomori trichrome stain,³⁵⁵ and specific defects in the activity of these enzymes have been demonstrated in patients with mitochondrial disease.³⁵⁶ Fatigue and poor stamina are prominent clinical features. Movement disorders such as ataxia, dystonia, myoclonus, chorea, athetosis, and tremors have also been described as being due to mitochondrial abnormalities.³⁵⁶ CT and MRI scans of the brain may be very helpful—for example, patients with MELAS demonstrate basal ganglia calcifications and stroke-like patterns not confined to vascular territories.³⁵⁷ Clinical features of two relatively common encephalomyopathies, MELAS and MERRF, are briefly discussed below.

MITOCHONDRIAL MYOPATHY, ENCEPHALOPATHY, LACTIC ACIDOSIS, AND STROKE-LIKE EPISODES

MELAS is the most common mitochondrial encephalomyopathy. Onset is most commonly before age 20. Seizures are common and stroke-like episodes (“stroke-like” because they do not conform to vascular distributions) may produce hemiparesis, hemianopia, and cortical blindness. Any patient with a stroke below the age of 40 should be worked up for MELAS. Associated findings include diabetes mellitus, hearing loss, pituitary and thyroid hypofunction, and lack of secondary sexual characteristics. In its full expression, MELAS leads to dementia, a bedridden state, and death. There is no specific treatment.³⁵⁸

MYOCLONIC EPILEPSY WITH RAGGED RED FIBERS

MERRF is a multisystem disorder characterized by myoclonus, generalized epilepsy, ataxia, and ragged red fibers on muscle biopsy. Other clinical features may include hearing loss, peripheral neuropathy, optic atrophy, dementia, short stature, and exercise intolerance.³⁵⁹ Cardiomyopathy is occasionally present. Laboratory features include an increased lactate at rest and exercise, and a myopathic picture on EMG and electroencephalogram showing generalized spike and wave discharges with background slowing. Only supportive treatment is available.

ANESTHETIC CONSIDERATIONS

The anesthesiologist may be involved in the care of patients with mitochondrial disease in multiple situations—often in the setting of obtaining a muscle biopsy in a child with an undiagnosed myopathy.³⁶⁰ These patients may also present for surgery for procedures related to the disease (such as implantation of a permanent pacemaker in a patient with KSS³⁶¹), for incidental medical problems, as well as in the

labor and delivery suite for labor analgesia.³⁶² The diversity of clinical presentations encountered in the mitochondrial myopathies discourages a “one size fits all” approach to anesthesia. Rather, each patient should be thoroughly evaluated and the anesthetic plan tailored to the patient’s specific needs.

PREOPERATIVE EVALUATION

Given the heterogeneous types of mitochondrial disease, patients with mitochondrial disease will need a comprehensive preoperative evaluation with a particular focus on neurologic, cardiac, respiratory, musculoskeletal, endocrinopathic, and metabolic compromise. An ECG and echocardiogram should be considered in patients with signs and symptoms of cardiomyopathy or conduction defects (or both). Although normal lactate and glucose levels cannot rule out mitochondrial diseases, laboratory studies consisting of glucose, electrolytes with anion gap, complete blood count, blood urea nitrogen, lactate, pyruvate, ammonia, CK, biotinidase, acyl carnitines, and blood and urine amino and organic acids could be used as initial investigation for suspected mitochondrial disorders.³⁶³ Further workup should include an erythrocyte sedimentation rate, glycosylated hemoglobin (HbA_{1c}), liver and renal profiles, thyroid function tests, arterial blood gas, and urinalysis.^{353,356} Multidisciplinary consultation with special laboratory and imaging studies may be required.³⁵⁶

INDUCTION AND MAINTENANCE OF ANESTHESIA

Anesthesia has a significant impact on mitochondrial function. Both barbiturates and propofol inhibit complex I of the electron transport chain.³⁶³ Local anesthetics have been demonstrated to disrupt oxidative phosphorylation and decrease the bioenergetic capacity of mitochondria.³⁶³ Sensitivity to intravenous barbiturates and etomidate has been reported.^{364,365} Fortunately, notwithstanding the potential pitfalls mentioned above, almost every anesthetic technique has been safely used in patients with mitochondrial disease.^{366,367} Midazolam,³⁶⁸ thiopental,³⁶⁹ propofol,^{370,371} remifentanil,³⁷² and ketamine³⁷¹ have all been used safely. Notably, propofol and midazolam are known to inhibit the mitochondrial respiratory chain in a dose-dependent manner.³⁷³ Indeed, mitochondrial dysfunction has been postulated as a mechanism for the propofol infusion syndrome.³⁷⁴ It is safe to use propofol as an anesthetic induction agent, but the use of a propofol infusion for long periods should probably be avoided.

Premedication should avoid respiratory depression caused by impaired respiratory responses to hypoxemia. Volatile agents such as halothane, isoflurane, and sevoflurane have been shown to inhibit complex I.³⁶³ This direct inhibition of mitochondrial electron transport system enzymes and altered mitochondrial bioenergetics in the heart were thought to be the mechanism of cardiac preconditioning by volatile anesthetics.^{375,376} Inhaled sevoflurane has been widely used for induction because of its low pungency.³⁷⁷ In some cases, halothane³⁶⁸ and isoflurane^{368,378} have also been used. Isoflurane has been recommended as the agent of choice in patients with Kearns-Sayre syndrome

because rhythm disturbances have been reported with halothane in such patients.^{368,378} In addition, artificial pacing capability is recommended when dealing with this specific subset of patients.³⁷⁷ With use of the bispectral index, higher sensitivity to volatile agents has been suggested in children with mitochondrial diseases, especially with dysfunction of complex I.³⁷⁹ However, its methodology has been criticized.³⁸⁰ A decreased minimum alveolar concentration of halothane in patients with mental retardation has also been reported.³⁸¹

Despite no real evidence and the fact that volatile anesthetics are frequently the anesthetic of choice when muscle relaxants are considered, several papers have expressed concern that these myopathies are associated with increased sensitivity to MH. This conclusion is not supported by any data. Increased sensitivity to nondepolarizing muscle relaxants has been documented for mivacurium,³⁸² atracurium,³⁸³ and rocuronium.^{383,384} In contrast, normal responses to depolarizing and nondepolarizing neuromuscular blockers such as pancuronium,³⁸⁵ vecuronium,³⁸⁶ and atracurium^{370,387} are also reported. Although muscle relaxants are not absolutely contraindicated based on current literature and research, it is necessary for anesthesia practitioners to cautiously administer depolarizing or nondepolarizing neuromuscular blockers to those patients with mitochondrial diseases and to use neuromuscular monitoring.³⁵³ Presently, there is no evidence to support an association between MH and mitochondrial disease. However, it may be prudent to avoid succinylcholine in patients with extensive myopathy to minimize the risk of hyperkalemia, although the safe use of succinylcholine has been documented in at least one patient with KSS.³⁸⁵

Nonsteroidal antiinflammatory drugs³⁷⁷ and regional techniques consisting of local,^{377,388} spinal,³⁸⁹ and epidural administration have been reported. However, it is suggested that regional anesthesia be performed when neurologic abnormalities of the spinal cord and peripheral nerves have definitely been ruled out.³⁸⁹ Importantly, coagulation function should be assessed because of the possibility of hepatic dysfunction.³⁷⁷

Opioids should be used with caution because of the increased risk for respiratory depression and their potential to induce respiratory acidosis in addition to the underlying metabolic acidosis.³⁷⁷ Because patients with mitochondrial diseases have dysfunctional aerobic metabolism, any increase in the basic metabolic rate should be prevented.³⁵⁶ Shivering, hypoxia, fasting, and hypotension in such patients may exacerbate the lactic acidosis and should therefore be avoided.³⁹⁰ Finally, the increased postoperative infection rate in patients with mitochondrial diseases may be due to low hepatic mitochondrial activity, phagocytosis by Kupffer cells, and decreased activity of the reticuloendothelial system.³⁹¹

Perhaps more important than the specific choice of anesthetic agents are the implications of patients' comorbidities and metabolic status. Normothermia should be maintained during surgeries, and intravenous fluids should be warmed to body temperature. Lactated Ringer (LR) should probably be avoided given the risk of preexisting lactic acidosis (although there is no evidence that LR has worsened acidosis when it has been used³⁶⁶). There have been multiple reports of hyponatremia (and

BOX 35.7 Perioperative Considerations for Patients with Mitochondrial Disease

1. Carefully assess and document the extent of organ system involvement preoperatively (including cardiac abnormalities in the KSS patients).
2. Minimize fasting period, avoid hypovolemia and glucose store depletion.
3. Minimize perioperative stress that may provoke increased energy requirement.
4. Pay particular attention to perioperative temperature control given that the mitochondrial respiratory chain is responsible for thermogenesis.
5. It is reasonable to administer glucose-containing solutions perioperatively, and to avoid lactate-containing fluids (e.g., lactated Ringer solution), particularly in children who are prone to lactic acidosis.
6. Every class of anesthetic agents is associated with theoretical risk of complications, but both volatile anesthetics and propofol have been successfully used in these patients.
7. Although there is no clear evidence of an association between malignant hyperthermia and mitochondrial disease, it is important to avoid succinylcholine.
8. Neuraxial anesthesia can be considered, but requires careful attention to preoperative neurologic dysfunction.

occasional hyperkalemia) in these patients.^{366,392,393} Adrenal insufficiency should be considered in such a picture, particularly when accompanied by hypotension.³⁶⁶ Finally, these patients are at increased risk of cardiac conduction abnormalities and cardiomyopathy that should be taken into consideration while formulating an anesthetic plan (Box 35.7).

Myasthenia Gravis

Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction. Autoantibodies against the α -subunit of the muscle-type nicotinic acetylcholine receptor destroy acetylcholine receptors of the neuromuscular junction and cause classic transmission failure with muscle weakness and fatigue. Sparing of other α -subunits of neuronal-type nicotinic acetylcholine receptors provides an explanation for the lack of autonomic or CNS involvement of the disease. The incidence of MG varies between geographic regions, being 1.2 per million in Japan and about 14 per 100,000 in some areas of the United States.^{394,395} In younger age groups, females are affected more often than males, whereas in elderly age groups (>60 years), males are more frequently affected.

There is a striking association between MG and hyperplasia of the thymus, with more than 70% of MG patients having thymus hyperplasia and 10% having thymomas.³⁹⁵ MG may also be seen as a part of a paraneoplastic syndrome.³⁹⁵

Typically, patients first report bulbar symptoms consisting of diplopia and ptosis. The bulbar symptoms are often followed by unevenly distributed muscle weakness and fatigue of the extremities and face. Speech and chewing may be affected, as well as pharyngeal function and coordination of swallowing, with a subsequent increased frequency of aspiration of oral contents. The muscle weakness is often

BOX 35.8 Risk Factors of Postoperative Ventilation for Patients with Myasthenia Gravis³⁹⁶

- Vital capacity <2-2.9 L
- Duration of MG >6 years
- Pyridostigmine dosage >750 mg/day
- History of chronic pulmonary disease
- Preoperative bulbar symptoms
- History of myasthenic crisis
- Intraoperative blood loss >1000 mL
- Serum antiacetylcholine receptor antibody >100 nmol/mL
- Pronounced decremental response on low frequency repetitive nerve stimulation

MG, Myasthenia gravis.

Modified from Anesthesia for the patient with myasthenia gravis.

<https://www.uptodate.com/contents/anesthesia-for-the-patient-with-myasthenia-gravis>; 2018. Accessed April 8, 2019.

exacerbated during exercise and throughout the course of the day. Apart from the patchy distribution of muscle weakness, symptoms may also vary from day to day, and there may be periods of remission of varying duration.

The diagnosis of MG is made by neurologic examination and testing of the tendency to fatigue and exhibit increased weakness during exercise or repeated contractions. The diagnosis can be confirmed by the Tensilon test (administration of an anticholinesterase, e.g., edrophonium). Improvement is usually seen within 5 minutes after administration of the drug and lasts for about 10 minutes. In addition, electrophysiologic evaluation is often performed and shows a classic decrement in the compound muscle action potential after repetitive nerve stimulation (Box 35.8).³⁹⁶

ANESTHETIC CONSIDERATIONS

Ideally, careful neurologic consultation in addition to preoperative evaluation should be performed on MG patients with the aim of optimizing drug therapy and preparing for postoperative care. Pulmonary function tests may be indicated to determine the need for mechanical ventilation postoperatively.³⁸² In addition, a number of risk factors have been associated with the necessity for postoperative ventilation.

As a general rule, patients should keep taking their anticholinesterase medication and be informed about the possibility of postoperative ventilator support. Succinylcholine can be used if needed for rapid tracheal intubation. However, patients with MG might need larger than normal doses (1.5-2.0 mg/kg body weight) because of the decreased number of functional acetylcholine receptors.³⁹⁷ On the other hand, as a result of the decrease in cholinesterase activity achieved by anticholinesterase treatment, neuromuscular blocks with succinylcholine or mivacurium are frequently prolonged.^{398,399} Traditionally, nondepolarizing neuromuscular blockers can be used in patients with MG but should be given with caution because their effects are highly unpredictable and the distribution of muscle weakness is often uneven. Most anesthesiologists used to dose nondepolarizing muscle relaxants in small increments corresponding to 0.1 to 0.2 times the 95% effective dose (ED₉₅) until the desired

neuromuscular blocking effect is achieved. Perioperative anticholinesterase treatment will modify the response to traditional reversal agents, because of the already existing acetylcholinesterase block, and in some cases, will reportedly prolong the recovery of neuromuscular function after the administration of a reversal agent.⁴⁰⁰ With the adoption of a newly modified γ -cyclodextrin neuromuscular reversal agent, sugammadex, the management of airway and steroid neuromuscular blockade agents, such as rocuronium or vecuronium, becomes simplified in patients with MG.^{401,402}

Sugammadex has a lower affinity to vecuronium than rocuronium; however, the reversal with sugammadex for vecuronium is still very satisfactory because fewer vecuronium molecules are present for equivalent blockade due to its higher potency to rocuronium. Although FDA has not approved its use in pediatric populations, current reported cases were favorable. On a separate note, sugammadex does have conflicting effects on progesterone, cortisol, aldosterone, and testosterone levels and may alter some coagulation parameters such as activated thromboplastin time and prothrombin time, or INR.⁴⁰³

Potent volatile anesthetics have been used successfully in MG patients. Because of the impaired margin of safety at the neuromuscular junction, a volatile anesthetic usually provides adequate muscular paralysis to allow most surgical procedures to be performed without the need for a neuromuscular blocking agent. Epidural and spinal anesthesia can be used in MG patients in addition to general anesthesia, provided that muscle function and ventilation are carefully monitored perioperatively. For a more detailed review, see Baraka⁴⁰⁴ and Abel and Eisenkraft.⁴⁰⁵

EATON-LAMBERT MYASTHENIC SYNDROME

Eaton-Lambert myasthenic syndrome (ELMS) is an immune-mediated channelopathy caused by decreased release of acetylcholine as a result of autoantibodies against presynaptic voltage-gated calcium channels and other presynaptic elements.⁴⁰⁶ Patients with ELMS have muscle weakness and fatigability, generally of the proximal limb muscles, with the lower extremities affected more often than the extraocular and bulbar muscle groups. The syndrome is frequently part of a paraneoplastic phenomenon, usually combined with small cell lung carcinoma. Unlike MG, patients with ELMS are usually worse in the morning with gradual improvement throughout the day. Improvement of muscle function with exercise is due to the accumulation of presynaptic calcium and subsequent improved release of acetylcholine.⁴⁰⁷ A minority of patients exhibit autonomic dysfunction. The diagnosis of ELMS is made by careful physical examination combined with clinical electrophysiology showing the typical facilitation of motor action potential with high-frequency nerve stimulation (30-50 Hz). Anticholinesterase treatment has little effect on patients with ELMS. Plasmapheresis, immunoglobulin therapy, and 3,4-diaminopyridine (DAP) result in transient improvement.

ANESTHETIC CONSIDERATIONS

As in patients with MG, those with ELMS should be carefully evaluated for the risk of postoperative respiratory

failure and the need for prolonged respiratory monitoring in the postoperative period. Sensitivity to depolarizing and nondepolarizing NMBA is usually increased. In patients treated with DAP or an anticholinesterase agent, reversal of a neuromuscular blockade may be ineffective.

Periodic Paralysis (Hyperkalemic, Hypokalemic, and Normokalemic)

The periodic paralyses are a group of disorders that are characterized by alterations of function in voltage-gated ion channels; hence these diseases are sometimes termed “skeletal muscle channelopathies.”⁴⁰⁸ The symptomatology of the particular channelopathy depends on the specific ion channel involved and can be divided into three broad categories: (1) chloride channelopathies (myotonia without paralysis e.g., MC, see earlier), (2) sodium channelopathies (myotonia with paralysis, such as hyperkalemic periodic paralysis [HyperPP]), and (3) other cation channelopathies (paralysis without myotonia, such as hypokalemic periodic paralysis [HypoPP]).⁴⁰⁹

HyperPP is an autosomal dominant disorder first described by Tyler and associates in 1951.³²⁰ It is characterized by attacks of flaccid weakness associated with increased serum potassium.⁴¹⁰ Precipitating factors include potassium rich foods, and rest after exercise. In addition, a cold environment, emotional stress, fasting, glucocorticoids, and pregnancy can provoke or worsen the attacks. The paralysis may last for 15 minutes to an hour, with decreased tendon reflexes. In the interictal state, HyperPP is usually associated with mild myotonia that does not impede voluntary movements.³²⁰

The pathogenesis of HyperPP involves mutations in *SCN4A*, encoding the voltage-gated sodium channel $\text{Na}_V1.4$ of mature muscle fibers; and such mutations lead to pathologically increased sodium current and an increased tendency of the muscle fiber to become depolarized.^{320,410} Influx of sodium into the muscle is accompanied by simultaneous efflux of potassium and hyperkalemia. Mutant channels exhibit sustained sodium currents that lead to prolonged membrane depolarization, which will then cause myotonia followed by membrane desensitization (or inactivation) and will eventually result in paralysis. In HyperPP patients, serum CK can be elevated, sometimes 5 to 10 times above the normal limit, whereas serum sodium and potassium levels are normal in the interictal state.³²⁰ EMG recordings will often show myotonic discharges during and between attacks. Muscle biopsies may show small peripheral vacuoles in the sarcoplasm. Recent studies supported that normokalemic periodic paralysis is a variant of the HyperPP, not a distinct disease, because all the subjects exhibited clinical and laboratory features of the HyperPP.⁴¹¹⁻⁴¹³ Treatment includes medication with acetazolamide (a carbonic anhydrase inhibitor) and mexiletine (an antiarrhythmic with a mechanism of action similar to lidocaine). Behavioral modification, such as avoiding potassium containing foods, strenuous exercise, fasting, and exposure to cold are also important.⁴⁰⁹

HypoPP is characterized by a decrease in potassium levels in blood. Attacks of HypoPP can be triggered by rigorous exercise, stress, high-carbohydrate or high-salt meals,

pregnancy, menstruation, hypothermia, or drugs such as insulin.^{414,415} EMG does not usually show myotonia.⁴¹⁰ The severity of attacks is usually greater than those occurring in patients with HyperPP. HypoPP is an autosomal dominant disease with higher penetration in males. The disease is due to loss of function of one of the two different ion channel types: $\text{Ca}_V1.1$ and $\text{Na}_V1.4$.⁴¹⁰ The most common muscle groups affected are those in the arms and legs; however, the disorder can also affect swallowing and respiratory muscles, which can be fatal in severe cases. The diagnosis of HypoPP is made by laboratory tests demonstrating hypokalemia during attacks and normokalemia between attacks. Mutations in the skeletal muscle voltage-gated calcium channel encoded by *CACNA1S* (HypoPP type 1) and *SCN4A* (HypoPP type 2) have been identified.³¹³ Theoretical association of HypoPP to MH was made because a few MH patients were known to have mutations in the *CACNA1S*.³¹³ It is generally accepted that the risk of susceptibility of HypoPP patients to MH is similar to that of the general population. It is still unclear the exact mechanisms that lead to hypokalemic paralysis. It is important to remain aware of the differences in the clinical features between HyperPP and HypoPP. HypoPP is not associated with myotonia, a spontaneous attack is associated with hypokalemia (a diagnostic criterion), potassium is a remedy, and glucose triggers an attack.⁴⁰⁹ Treatment is centered on the identification and avoidance of triggers. Potassium administration can be useful in the treatment of an acute attack. The prophylactic medication of choice in HypoPP type 1 is acetazolamide⁴¹⁶—however, acetazolamide can worsen symptoms in type 2 HypoPP.⁴¹⁷ Such patients may respond to potassium-sparing diuretics such as spironolactone.⁴¹⁸

Clinically resembling HypoPP, thyrotoxic periodic paralysis (TPP) occurs later in life than HypoPP. It has a strong male predominance, and is much more common in patients of oriental descent. Loss of function mutations in the inward rectifying potassium channel ($\text{K}_{ir}2.6$) may be involved in some cases of TPP.⁴¹⁹ The condition responds to antithyroid medications such as methimazole.⁴⁰⁹

ANESTHETIC CONSIDERATIONS

Potassium, cholinesterase inhibitors, and depolarizing muscle relaxants will aggravate the myotonia in HyperPP patients.³²⁰ Prolonged muscle weakness has been reported when succinylcholine is used.⁴²⁰ Although one third of patients had no signs of myotonia,⁴²¹ masseter spasm and respiratory and skeletal muscles stiffness could still occur during intubation and ventilation.³²⁰ Therefore neostigmine and succinylcholine should be contraindicated in HyperPP patients. Nondepolarizing muscle relaxants may be safely used.^{422,423} The safe use of both volatile agents and propofol has been documented.⁴²²⁻⁴²⁴ Ideally, all patients with HyperPP need to be admitted preoperatively so that proper preoperative fasting can be accompanied by the administration of dextrose-containing potassium-free maintenance fluid.⁴²³ Postoperatively, HyperPP patients may remain paralyzed for up to several hours. Preventive measures such as maintaining normal body temperature and low serum potassium levels and avoiding hypoglycemia are helpful in limiting such paralysis.⁴²² Although patients

with sodium channel pathology have often been considered to be susceptible to MH, there is no increased risk for MH in these patients.³¹⁴ General anesthesia with and without nondepolarizing muscle relaxants has been shown to have satisfactory outcomes.^{420,422,423,425,426} Regional techniques may also be appropriate for this patient group.^{421,425,426} Abortion of the hyperkalemic attack may be accomplished by administering glucose, insulin, epinephrine, and calcium supplements, or, alternatively, glucagon may be used. β -Adrenergic treatment with metaproterenol has also been shown to prevent attacks and facilitate recovery.⁴²³

Management of HypoPP patients should focus on avoiding triggers and medications causing a shift of potassium. General anesthesia, postoperative stress, glucose-containing intravenous solutions, and long-acting neuromuscular blockers are associated with postoperative paralytic events.⁴¹⁴ Patients with HypoPP undergoing general anesthesia have been reported to exhibit weakness and respiratory distress in the postoperative period.^{427,428} While safe use of intermediate and short-acting nondepolarizing muscle relaxants, such as atracurium and mivacurium, have been documented,⁴²⁹⁻⁴³¹ and it is probably prudent to avoid long-acting muscle relaxants.⁴³² Epidural analgesia has been shown to reduce both pain-related hyperventilation and serum catecholamines, thereby minimizing changes in serum potassium levels.⁴¹⁴ The sympathomimetic effect of epinephrine-containing local anesthetics may also precipitate hypokalemia.⁴¹⁴ Unlike HyperPP, an association between HypoPP and MH cannot be categorically ruled out,⁴³³ although the use of isoflurane in HypoPP has been reported.⁴³¹ There are a number of reports of MH-like metabolic crises in patients with HypoPP.⁴³⁴⁻⁴³⁶ Contracture-like responses to succinylcholine have also been described.⁴³⁷ In one of the above descriptions, it seemed likely that there were two unrelated mutations conferring both HypoPP and sensitivity to MH in the same patient.⁴³⁶ Therefore while the probability of MH in a given patient with HypoPP is likely to be remote, it cannot be ruled out, and the safest course might be the use of a nontriggering anesthetic. If volatile agents are used, they should be used with extra vigilance.⁴³³

Summary

MH is a subclinical myopathy featuring an eerie and erratic metabolic mayhem that is unmasked on exposure to potent volatile anesthetics or succinylcholine. Skeletal muscle acutely and unexpectedly increases its sarcoplasmic Ca^{2+} concentration, thereby leading to increased oxygen consumption and lactate production, and resulting in greater heat production, respiratory and metabolic acidosis, muscle rigidity, sympathetic stimulation, and increased cellular permeability. MHS skeletal muscle differs from normal muscle in that it is always closer to loss of control of Ca^{2+} concentration within the muscle fiber, and it can involve a generalized alteration in cellular or subcellular membrane permeability. This is an EC coupling defect resulting from an alteration in protein-protein interaction in the CRU. It is a homozygous, single point mutation of *RyR1* in swine and a heterozygous disorder in humans, in whom there may also be a modification of *RyR1* protein function by interacting structures,

membranes, or enzymes. Diagnosis rests on acute awareness of the signs and symptoms of this syndrome, of which hyperthermia is a late sign. Specific treatment includes administration of dantrolene to lower muscle Ca^{2+} levels, and symptomatic treatment consists of reversal of the acid-base and temperature changes. Evaluation of affected families is guided by analysis of drug-induced muscle contractures (by European IVCT and North American CHCT protocols) and genetic testing of DNA samples. General or regional anesthesia is safe for patients susceptible to MH, provided that care is taken to specially prepare the anesthesia machine and avoid all potent volatile anesthetics and succinylcholine. Research on MH has yielded insight into the physiology of metabolism and into the molecular biology of genetic muscle disorders. Challenges that remain include identification of all genetic mutations responsible for human MH, elucidation of the mechanism that links exposure to subsequent loss of control of Ca^{2+} , development of noninvasive and nondestructive testing for susceptibility, and determination of the mode of action of dantrolene.

Acknowledgment

This chapter is a consolidation of two chapters in the 8th edition, *Chapter 42*, Neuromuscular Disorders and other Genetic Disorders and *Chapter 43*, Malignant Hyperthermia and Muscle-Related Disorders. The editors, publisher, and the returning authors, would like to thank the following authors: Aranya Bagchi, Richa Saxena, and Diptiman Bose for their contributions to the prior edition of this work. It has served as the foundation for the current.

 Complete references available online at expertconsult.com.

References

1. Lerman J. *Br J Anaesth*. 2011;107(suppl 1):i79.
2. Rosenberg H, Pollock N, Schiemann A, Bulger T, Stowell K. Malignant hyperthermia: a review. *Orphanet J Rare Dis*. 2015;10:93.
3. Sumitani M, et al. *Anesthesiology*. 2011;114:84.
4. Suyama H, et al. *J Anesth*. 2002;16:207.
5. Monnier N, et al. *Anesthesiology*. 2002;97:1067.
6. Brady JE, et al. *Anesth Analg*. 2009;109:1162.
7. Yuen B, et al. *FASEB J*. 2012;26:1311.
8. Rosenberg H, Shutack JG. *Paediatr Anaesth*. 1996;6:87.
9. Rosenberg H, et al. *Orphanet J Rare Dis*. 2007;2:21.
10. Robinson R, et al. *Hum Mutat*. 2006;27:977.
11. Harrison GG, Isaacs H. *Anaesthesia*. 1992;47:54.
12. Gronert BJ, Antognini JF. Malignant hyperthermia. In: Miller RD, ed. *Anesthesia*. New York: Churchill Livingstone; 1994:1075.
13. Ombrédanne L. *Rev Med Française*. 1929;10:617.
14. Denborough MA, et al. *Br J Anaesth*. 1962;34:395.
15. Kalow W, et al. *Lancet*. 1970;296:895.
16. Britt BA, et al. *Can Anaesth Soc J*. 1969;16:89.
17. Ball RA, et al. *Vet Med Small Anim Clin*. 1973;68:1156.
18. Briskley EJ. *Adv Food Res*. 1964;13:89.
19. Hall LW, et al. *Br Med J*. 1966;2:1305.
20. Fujii J, et al. *Science*. 1991;253:448.
21. Harrison GG. *Br J Anaesth*. 1975;47:62.
22. Kolb ME, et al. *Anesthesiology*. 1982;56:254.
23. Lopez JR, et al. *Acta Cient Venez*. 1985;36:102.
24. Lopez JR, et al. *Muscle Nerve*. 1986;9:85.
25. Lopez JR, et al. *Muscle Nerve*. 1988;11:82.
26. Lopez JR, et al. *Anesthesiology*. 1992;76:711.
27. Choi RH, et al. *Proc Natl Acad Sci U S A*. 2017;114:4811.
28. Cherednichenko G, et al. *Molecular Pharmacology*. 2008;73:1203.
29. Pessah IN, et al. *Biochem Biophys Res Commun*. 1985;128:449.

30. Pessah IN, et al. *Biochem Biophys Res Commun*. 1986;139:235.
31. MacKenzie AE, et al. *Am J Hum Genet*. 1990;46:1082.
32. Otsu K, et al. *Genomics*. 1993;17:507.
33. Sorrentino V, et al. *Genomics*. 1993;18:163.
34. Collins JH. *Biochem Biophys Res Commun*. 1991;178:1288.
35. Jayaraman T, et al. *J Biol Chem*. 1992;267:9474.
36. Lam E, et al. *J Biol Chem*. 1995;270:26511.
37. Timerman AP, et al. *J Biol Chem*. 1996;271:20385.
38. Beam KG, et al. *Ann N Y Acad Sci*. 1989;560:127.
39. Tanabe T, et al. *Nature*. 1990;346:567.
40. Nakai J, et al. *J Biol Chem*. 1998;273:24983.
41. Nakai J, et al. *Two Regions of the Ryanodine Receptor Involved in Coupling with L-Type Ca²⁺ Channels*. 1998.
42. Sheridan DC, et al. *Proc Natl Acad Sci U S A*. 2006;103:19760.
43. Flucher BE, Franzini-Armstrong C. *Proc Natl Acad Sci U S A*. 1996;93:8101.
44. Cherednichenko G, et al. *Proc Natl Acad Sci U S A*. 2004;101:15793.
45. Gaburjakova M, et al. *J Biol Chem*. 2001;276:16931.
46. Meissner G. *Front Biosci*. 2002;7:d2072.
47. Ward CW, et al. *J Biol Chem*. 2004;279:5781.
48. Pessah IN, et al. *Pharmacol Ther*. 2010;125:260.
49. Perni S, et al. *De Novo Reconstitution Reveals the Proteins Required for Skeletal Muscle Voltage-Induced Ca(2+) Release*. 2017.
50. Polster A, et al. *Proc Natl Acad Sci U S A*. 2016;113:10986.
51. Cherednichenko G, et al. *Mol Pharmacol*. 2008;73:1203–1212.
52. Yang T, et al. *J Biol Chem*. 2007;282:37471.
53. Yang T, et al. *Am J Physiol Cell Physiol*. 2007;292:C1591.
54. Eltit JM, et al. *Proc Natl Acad Sci U S A*. 2012;109:7923.
55. Eltit JM, et al. *J Biol Chem*. 2010;285:38453.
56. Eltit JM, et al. *Proc Natl Acad Sci U S A*. 2011;108:7046.
57. Bannister RA, et al. *J Gen Physiol*. 2010;135:629.
58. Esteve E, et al. *J Gen Physiol*. 2010;135:619.
59. Wappler F, et al. *Eur J Anaesthesiol*. 2003;20:528.
60. Yang T, et al. *J Biol Chem*. 2003;278:25722.
61. Reuter DA, et al. *Can J Anaesth*. 2003;50:643.
62. Capacchione JF, Muldoon SM. *Anesth Analg*. 2009;109:1065.
63. Pessah IN, et al. *Mol Pharmacol*. 1987;31:232.
64. Zimanyi I, Pessah IN. *Brain Res*. 1991;561:181.
65. Jona I, et al. *Pflugers Arch*. 2001;441:729.
66. Laver D. *Clin Exp Pharmacol Physiol*. 2001;28:675.
67. Laver DR, et al. *J Membr Biol*. 1997;156:213.
68. Voss AA, et al. *Biochem Biophys Res Commun*. 2008;366:988.
69. Lamb GD. *J Muscle Res Cell Motil*. 1993;14:554.
70. Laver DR, et al. *Biophys J*. 1997;73:1913.
71. Barrientos GC, et al. *J Biol Chem*. 2012;287:2863.
72. Feng W, et al. *Mol Pharmacol*. 2011;79:420.
73. Chelu MG, et al. *FASEB J*. 2006;20:329.
74. Yang T, et al. *Anesthesiology*. 2006;105:1164.
75. Lopez JR, et al. *Am J Physiol Cell Physiol*. 2005;288:C606.
76. Ikemoto N, Yamamoto T. *Front Biosci*. 2002;7:d671.
77. Samso M, et al. *PLoS Biol*. 2009;7:e85.
78. Zalk R, Marks AR. *Ca(2+) Release Channels Join the 'Resolution Revolution'*. 2017.
79. Carpenter D, et al. *BMC Med Genet*. 2009;10:104.
80. Toppin PJ, et al. *Can J Anaesth*. 2010;57:689.
81. Pironi A, et al. *Am J Physiol Cell Physiol*. 2010;299:C1345.
82. Weiss RG, et al. *Am J Physiol Cell Physiol*. 2004;287:C1094.
83. Bannister RA, Beam KG. *J Muscle Res Cell Motil*. 2009;30:217.
84. Jones DE, et al. *Anesthesiology*. 1988;83:A344.
85. Hurne AM, et al. *J Biol Chem*. 2005;280:36994.
86. Bannister RA, et al. *J Gen Physiol*. 2009;133:79.
87. Sultana N, et al. *Development*. 2016;143:1547.
88. Putney JW, et al. *J Cell Sci*. 2001;114:2223.
89. Kurebayashi N, Ogawa Y. *J Physiol*. 2001;533:185.
90. Ma J, Pan Z. *Front Biosci*. 2003;8:d242.
91. Pan Z, et al. *Nat Cell Biol*. 2002;4:379.
92. Zhao X, et al. *J Biol Chem*. 2006;281:33477.
93. Desmedt JE, Hainaut K. *J Physiol*. 1977;265:565.
94. Krivickas LS, et al. *Muscle Nerve*. 2000;23:529.
95. Yamaguchi N, et al. *J Biochem (Tokyo)*. 1997;121:432.
96. Paul-Pletzer K, et al. *J Biol Chem*. 2002;277:34918.
97. Monnier N, et al. *Am J Hum Genet*. 1997;60:1316.
98. Sambuughin N, et al. *Anesthesiology*. 2001;95:594.
99. Brown RL, et al. *Hum Mol Genet*. 2000;9:1515.
100. Girard T, et al. *Hum Mutat*. 2001;18:357.
101. Brandt A, et al. *Hum Mol Genet*. 1999;8:2055.
102. Rueffert H, et al. *Am J Med Genet A*. 2004;124:248.
103. Robinson R, et al. *Hum Genet*. 2003;112:217.
104. Gillard EF, et al. *Genomics*. 1991;11:751.
105. Sei Y, et al. *Anesthesiology*. 2004;101:824.
106. Davis M, et al. *Br J Anaesth*. 2002;88:508.
107. Oyamada H, et al. *Jpn J Pharmacol*. 2002;88:159.
108. Yeh HM, et al. *Anesth Analg*. 2005;101:1401.
109. Fletcher JE, et al. *Br J Anaesth*. 1995;75:307.
110. Lynch PJ, et al. *Anesthesiology*. 1997;86:620.
111. Monnier N, et al. *Hum Mol Genet*. 2003;12:1171.
112. Rueffert H, et al. *Br J Anaesth*. 2001;87:240.
113. No authors listed. A protocol for the investigation of malignant hyperpyrexia (MH) susceptibility. *Br J Anaesth*. 1984;56:1267.
114. Ording H, et al. *Acta Anaesthesiol Scand*. 1997;41:955.
115. Hopkins PM, et al. *Br J Anaesth*. 2015;115:531.
116. Larach MG. *Anesth Analg*. 1989;69:511.
117. Allen GC, et al. *Anesthesiology*. 1998;88:579.
118. Metterlein T, et al. *Cardiovasc Ther*. 2010;28:356.
119. Metterlein T, et al. *Muscle Nerve*. 2011;44:208.
120. Gerbershagen MU, et al. *Eur J Anaesthesiol*. 2011;29:42.
121. Johannsen S, et al. *Anesth Analg*. 2012;115:925.
122. Bendahan D, et al. *Acta Anaesthesiol Scand*. 2004;48:1019.
123. Baur CP, et al. *Anesth Analg*. 2000;90:200.
124. Metterlein T, et al. *Eur J Anaesthesiol*. 2011;28:251.
125. Metterlein T, et al. *Minerva Anestesiol*. 2011;77:768.
126. Migita T, et al. *Acta Anaesthesiol Scand*. 2011;56:351.
127. Zhou H, et al. *Am J Hum Genet*. 2006;79:859.
128. Urwyler A, et al. *Br J Anaesth*. 2001;86:283.
129. Robinson RL, et al. *Hum Mutat*. 2002;20:88.
130. Rueffert H, et al. *Acta Anaesthesiol Scand*. 2002;46:692.
131. Larach MG, et al. *Anesth Analg*. 2010;110:498.
132. Allen GC, Brubaker CL. *Anesth Analg*. 1998;86:1328.
133. Shulman M, et al. *Anesthesiology*. 1981;54:259.
134. Gronert GA. *Anesthesiology*. 1980;53:395.
135. Hall GM, et al. *Br J Anaesth*. 1976;48:270.
136. Denborough M, Hopkinson KC. *Lancet*. 1988;1:191.
137. Bendixen D, et al. *Acta Anaesthesiol Scand*. 1997;41:480.
138. Larach MG, et al. *Anesthesiology*. 1994;80:771.
139. Gronert GA, et al. *Anesth Analg*. 1980;59:377.
140. Haverkort-Poels PJ, et al. *Muscle Nerve*. 1987;10:45.
141. Denborough MA, et al. *Br Med J (Clin Res Ed)*. 1988;296:1442.
142. Hackl W, et al. *Br J Anaesth*. 1991;66:138.
143. Hopkins PM, et al. *Lancet*. 1991;338:1491.
144. Kochling A, et al. *Anaesth Intensive Care*. 1998;26:315.
145. Reynolds AC, et al. *Lancet*. 1981;2:303.
146. Gronert GA, et al. *Anesthesiology*. 1977;47:411.
147. Gronert GA, White DA. *Pflugers Arch*. 1988;411:226.
148. Wappler F, et al. *Anesthesiology*. 2001;94:95.
149. Anetseder M, et al. *Neurology*. 1994;44:2393.
150. Ryan JF, Tedeschi LG. *J Clin Anesth*. 1997;9:66.
151. *Adverse Effects of Heat and Exercise in Relation to MH Susceptibility*. 2018. <https://www.mhaus.org/healthcare-professionals/mhaus-recommendations/adverse-effects-of-heat-and-exercise-in-relation-to-mh-susceptibility/>.
152. Butler-Browne GS, et al. *Muscle Nerve*. 1988;11:610.
153. Morgan DL, Proske U. *Physiol Rev*. 1984;64:103.
154. van der Spek AF, et al. *Br J Anaesth*. 1990;64:21.
155. Magee KR, Shy GM. *Brain*. 1956;79:610.
156. Norwood FL, et al. *Brain*. 2009;132:3175.
157. Jungbluth H, et al. *Semin Pediatr Neurol*. 2011;18:239.
158. Engel AG, et al. *Mayo Clin Proc*. 1971;46:666.
159. Klingler W, et al. *Anesth Analg*. 2009;109:1167.
160. Koch BM, et al. *Arch Neurol*. 1985;42:1204.
161. Osada H, et al. *Gynecol Obstet Invest*. 2004;58:32.
162. Allanson JE. Noonan syndrome. *J Med Genet*. 1987;24:9–13.
163. Bencic J, Hogan K. *Anesth Analg*. 2009;109:1049.
164. Briggs BJ, Dickerman JD. *Pediatr Blood Cancer*. 2012;58:167.
165. Tartaglia M, et al. *Mol Syndromol*. 2010;1:2.
166. Hunter A, Pinsky L. *J Pediatr*. 1975;86:412.
167. Sharathkumar AA. *Pediatr Blood Cancer*. 2012;59:592.
168. Bajwa SJ, et al. *Saudi J Anaesth*. 2011;5:345.
169. Dadabhooy ZP, Winnie AP. *Anesthesiology*. 1988;68:636.
170. Campbell AM, Bousfield JD. *Anaesthesia*. 1992;47:131.
171. McBain J, et al. *Can J Anaesth*. 2006;53:274.

172. Isaacs H, Badenhorst ME. *Muscle Nerve*. 1992;15:740.
173. Heiman-Patterson TD, et al. *Pediatr Neurol*. 1986;2:175.
174. King JO, Denborough MA. *J Pediatr*. 1973;83:37.
175. McPherson EW, Taylor CA. *Am J Med Genet*. 1981;8:159.
176. Kaplan AM, et al. *J Pediatr*. 1977;91:431.
177. Isaacs H, Barlow MB. *Br J Anaesth*. 1973;45:901.
178. Isaacs H, et al. *Br J Anaesth*. 1973;45:860.
179. Isaacs H, Barlow MB. *J Neurol Neurosurg Psychiatry*. 1973;36:228.
180. Reed W, et al. *Blood*. 2003;101:351.
181. Habib AS, et al. *Can J Anaesth*. 2003;50:589.
182. D'Arcy CE, et al. *Neurology*. 2008;71:776.
183. Dowling JJ, et al. *Neuromuscul Disord*. 2011;21:420.
184. Glahn KP, et al. *Br J Anaesth*. 2010;105:417.
185. Birgenheier N, et al. *Anesth Analg*. 112:1363.
186. Kugler Y, Russell WJ. *Anaesth Intensive Care*. 2011;39:84.
187. Rosenberg H. *Anesthesiol*. 2010;20, News.
188. Flewellen EH, et al. *Anesthesiology*. 1983;59:275.
189. Brandom BW, et al. *Anesth Analg*. 2011;112:1115.
190. Oh ST, et al. *J Surg Res*. 1997;71:79.
191. Korolkiewicz RP, et al. *J Physiol Pharmacol*. 2000;51:821.
192. Gener B, et al. *Pediatrics*. 2010;125:e1514.
193. Lerman J, et al. *Anesthesiology*. 1989;70:625.
194. Burkman JM, et al. *Anesthesiology*. 2007;106:901; quiz 1077.
195. Hopkins PM. *Anesthesiology*. 2007;106:893.
196. Gallant EM, et al. *Anesth Analg*. 1985;64:601.
197. Harrison GG, et al. *Anaesth Intensive Care*. 1988;16:197.
198. Migita T, et al. *J Anesth*. 2012;26:579.
199. Metterlein T, et al. *Anesth Analg*. 2011;112:1174.
200. Choi RH, et al. *Proceedings of the National Academy of Sciences*; 2017;4811.
201. Larach MG, et al. *Anesth Analg*. 2012;114:94.
202. Wong CA, Denholm B. *Anesthsiol News*. 2011;17.
203. Aderibigbe T, et al. *Anesthesiology*. 2014;120:1333.
204. MacCani RM, et al. *Anesth Analg*. 1996;82:790.
205. McGraw TT, Keon TP. *Can J Anaesth*. 1989;36:530.
206. Whitty RJ, et al. *Can J Anaesth*. 2009;56:497.
207. Crawford MW, et al. *Anesthesiology*. 2007;106:289.
208. Prinzenhausen H, et al. *Can J Anaesth*. 2006;53:885.
209. Petroz GC, Lerman J. *Anesthesiology*. 2002;96:941.
210. Brunner HW, et al. *Acta Anaesthesiol Scand*. 2011;55:1118.
211. Shanahan H, et al. *Eur J Anaesthsiol*. 2012;29:229.
212. Gunter JB, et al. *Anesth Analg*. 2008;107:1936.
213. Jones C, et al. *Anaesth Intensive Care*. 2012;40:490.
214. Schonell LH, et al. *Anaesth Intensive Care*. 2003;31:58.
215. Feldman JM. *Anesthesiology*. 2011;115:434; author reply 6.
216. Block FE. *Anesth Analg*. 2011;112:1270.
217. Jantzen JP, et al. *Anaesthetist*. 1989;38:639.
218. Preparation of Anesthesia Workstations to Anesthetize MH Susceptible Patients. <https://www.mhaus.org/healthcare-professionals/mhaus-recommendations/preparation-of-anesthesia-workstations-to-anesthetize-mh-susceptible-patients/>. Accessed 30.05.18.
219. Criteria for a recommended standard. *Occupational Exposure to Waste Anesthetic Gases and Vapors*; 1977. <http://www.cdc.gov/niosh/pdfs/77-140a.pdf>
220. Anesthetic Gases. *Guidelines for Workplace Exposures*; 2000. <https://www.osha.gov/dts/osta/anestheticgases/index.html>
221. Anetseder M, et al. *Lancet*. 2003;362:494.
222. Bina S, et al. *Anesthesiology*. 2006;104:90.
223. Schuster F, et al. *Anesthesiology*. 2007;107:616.
224. Schuster F, et al. *Anesth Analg*. 2006;102:468.
225. Bina S, et al. *Eur J Anaesthsiol*. 2007;25:48.
226. Girard T, et al. *J Biol Chem*. 2001;276:48077.
227. Litman RS, Rosenberg H. *JAMA*. 2005;293:2918.
228. McKinney LC, et al. *Anesthesiology*. 2006;104:1191.
229. Ordung H, et al. *Br J Anaesth*. 1990;64:341.
230. Sei Y, et al. *Anesthesiology*. 2002;97:1052.
231. Gareau PJ, et al. *Free Radic Res Commun*. 1993;19:43.
232. Payen JF, et al. *Anesthesiology*. 1993;78:848.
233. Nanson JK, Sheikh A. *Int J Obstet Anesth*. 2000;9:276.
234. Stowell K, et al. *Anaesth Intensive Care*. 2007;35:454.
235. Girard T, et al. *Anesthesiology*. 2006;104:1353.
236. Suggested guidelines for management of the pregnant-patient not believed to be at risk for MH, but whose partners is susceptible to malignant hyperthermia. 2009. <https://www.mhaus.org/healthcare-professionals/mhaus-recommendations/parturient-with-mhs-partner/>.
237. Tombul T, et al. *Acta neurologica Belgica*. 2011;111:116.
238. Freedman MS, et al. *Arch Neurol*. 2005;62:865.
239. Bader AM, et al. *J Clin Anesth*. 1988;1:21.
240. Staikou C, Rekatsina M. *Saudi J Anaesth*. 2017;11:472.
241. Bornemann-Cimenti H, et al. *Rev Bras Anestesiol*. 2016;67:404.
242. Ludolph AC, et al. *Curr Opin Neurol*. 2012;25:530.
243. Rothstein JD. *Cell*. 2017;171:725.
244. Shimizu T, et al. *Neurology*. 2000;54:1534.
245. You TM, Kim S. *J Dent Anesth Pain Med*. 2017;17:235.
246. Rosenbaum KJ, et al. *Anesthesiology*. 1971;35:638.
247. Jacobs BC, et al. *Neurology*. 1998;51:1110.
248. Lawn ND, et al. *Arch Neurol*. 2001;58:893.
249. Asbury AK. *Arch Neurol*. 1981;(suppl 9):1.
250. Hughes RA, et al. *Cochrane Database Syst Rev*. 2012;7:CD002063.
251. Asahina M, et al. *Acta Neurol Scand*. 2002;105:44.
252. McGrady EM. *Anaesthesia*. 1987;42:899.
253. Steiner I, et al. *Neurology*. 1985;35:1473.
254. Brooks H, et al. *Anaesthesia*. 2000;55:894.
255. Zochodne DW, et al. *Brain*. 1987;110(Pt 4):819.
256. Bolton CF. *Muscle Nerve*. 2005;32:140.
257. Dodson BA, et al. *Crit Care Med*. 1995;23:815.
258. Hermans G, et al. *Am J Respir Crit Care Med*. 2007;175:480.
259. Gronert GA. *Anesthesiology*. 1981;55:547.
260. O'Neill GN. *Int Anesthesiol Clin*. 2006;44:107.
261. Rudnik-Schneborn S, et al. Spinal muscular atrophies. In Engel A, Franzini-Armstrong C, eds: *Myology*, 3rd ed, New York: McGraw-Hill; 2004:1845.
262. Charcot-Marie-Tooth disease. Genetics, clinical features, and diagnosis. *UpToDate*. 2018. <https://www.uptodate.com/contents/charcot-marie-tooth-disease-genetics-clinical-features-and-diagnosis>.
263. Ginz HF, et al. *Anaesthetist*. 2001;50:767.
264. Gratarola A, et al. *Minerva Anestesiol*. 1998;64:357.
265. Sugino S, et al. *Masui*. 2002;51:1016.
266. Baur CP, et al. *Anasthesiol Intensivmed Notfallmed Schmerzther*. 2002;37:125.
267. Antognini JF. *Can J Anaesth*. 1992;39:398.
268. Baranov D, et al. Neurological diseases. In: Fleisher L, ed. *Anesthesia and Uncommon Diseases*. 5th ed. Philadelphia: Saunders; 2006.
269. Pogson D, et al. *Br J Anaesth*. 2000;85:914.
270. Naguib M, Samarkandi AH. *Can J Anaesth*. 1998;45:56.
271. Schmitt HJ, Munster T. *Can J Anaesth*. 2006;53:984.
272. Reah G, et al. *Anaesthesia*. 1998;53:586.
273. Scull T, Weeks S. *Can J Anaesth*. 1996;43:1150.
274. Sugai K, Sugai Y. *Masui*. 1989;38:688.
275. Tanaka S, et al. *Masui*. 1994;43:931.
276. Schmitt HJ, et al. *Can J Anaesth*. 2004;51:1049.
277. Dubowitz V. *Muscle Disorders in Childhood*. 2nd ed. Philadelphia: Saunders; 1995.
278. Dalakas M, et al. The muscular dystrophies. In: Barnes P, Hilton-Jones D, eds. *Myopathies in Clinical Practice*. 1st ed. London: Martin Dunitz; 2003.
279. *Muscular Dystrophy*. 2017. <https://emedicine.medscape.com/article/1259041-overview>.
280. Emery A. *Neuromuscul Disord*. 1991;1:19.
281. Sano M, et al. *Jinruidengaku Zasshi*. 1987;32:257.
282. Urban M, Lahliou S. Muscle diseases. In: Fleisher L, ed. *Anesthesia and Uncommon Diseases*. Philadelphia: Saunders; 2006:303.
283. Hoffman E. *Cell*. 1987;51:919.
284. Leibowitz D, Dubowitz V. *Dev Med Child Neurol*. 1981;23:577.
285. Finsterer J, Stollberger C. *Cardiology*. 2003;99:1.
286. Perloff JK, et al. *Circulation*. 1984;(69):33.
287. Morris P. *Paediatr Anaesth*. 1997;7:1.
288. Hahn A, et al. *Arch Phys Med Rehabil*. 1997;78:1.
289. Ames WA, et al. *Paediatr Anaesth*. 2005;15:3.
290. Kawaai H, et al. *Anesth Prog*. 2005;52:12.
291. Molyneux MK. *Int J Obstet Anesth*. 2005;14:58.
292. Angermann C, et al. *Z Kardiol*. 1986;75:542.
293. Smith CL, Bush GH. *Br J Anaesth*. 1985;57:1113.
294. Webster R. *Respiratory Function as a Measure of Muscle Strength in Young Boys with Duchenne Muscular Dystrophy*. School of Women and Children's Health, University of N.S.W; 2003.
295. Stevens RD. *Curr Opin Anaesthsiol*. 2001;14:693.
296. Breuckling E, et al. *Anaesthetist*. 2000;49:187.

297. Benson ER, et al. *Spine*. 1998;23:2308.
298. Miller F, et al. *Dev Med Child Neurol*. 1992;34:775.
299. Jenkins JG, et al. *Crit Care Med*. 1982;10:645.
300. Stoelting R, Dierdorf S. In: *Anesthesia and Co-Existing Disease*. Philadelphia: Churchill Livingstone; 2002:505.
301. Gurnaney H, et al. *Anesth Analg*. 2009;109:1043.
302. Farrell PT. *Anaesth Intensive Care*. 1994;22:597.
303. Schummer W, Schummer C. *Br J Anaesth*. 2004;92:149.
304. Ririe DG, et al. *Anesthesiology*. 1998;88:351.
305. Yemen TA, McClain C. *Paediatr Anaesth*. 2006;16:105.
306. Fairfield MC. *Anesthesia*. 1993;48:1013.
307. Murat I, et al. *Anesthesiology*. 1987;67:249.
308. Kirschner J, Bonnemann CG. *Arch Neurol*. 2004;61:189.
309. Moro C, et al. *Ann Fr Anesth Reanim*. 2007;26:359.
310. Egi M, et al. *Masui*. 2002;51:196.
311. Pash MP, et al. *Can J Anaesth*. 1996;43:959.
312. Myotonic dystrophy. *Etiology, Clinical Features, and Diagnosis*. 2018. <https://www.uptodate.com/contents/myotonic-dystrophy-etiology-clinical-features-and-diagnosis>.
313. Parness J, et al. *Anesth Analg*. 2009;109:1054.
314. Lehmann-Horn F, Iaizzo PA. *Br J Anaesth*. 1990;65:692.
315. Mathieu J, et al. *Neurology*. 1997;49:1646.
316. Matsuki Y, et al. *Eur J Anaesthesiol*. 2011;28:145.
317. Stourac P, et al. *Br J Anaesth*. 2013;110:657.
318. Ahmed S, et al. *Cardiol Res*. 2018;9:50.
319. Catena V, et al. *Minerva Anestesiol*. 2007;73:475.
320. Lehmann-Horn F, et al. Nondystrophic myotonias and periodic paralyses. In: Engel A, Franzini-Armstrong C, eds. *Myology*. 3rd ed. New York: McGraw-Hill; 2004:1257–1300.
321. Farbu E, et al. *Acta Anaesthesiol Scand*. 2003;47:630.
322. Newberg LA, et al. *Br J Anaesth*. 1983;55:57.
323. Beck CL, et al. *Proc Natl Acad Sci U S A*. 1996;93:11248.
324. Rosenbaum HK. *Anesthesiol Clin North America*. 2002;20:623.
325. North K. Congenital myopathies. In: Engel A, Franzini-Armstrong C, eds. *Myology*. New York: McGraw-Hill; 2004:1473.
326. Herman GE, et al. *J Pediatr*. 1999;134:206.
327. Breslin D, et al. *Anesthesia*. 2000;55:471.
328. Costi D, van der Walt JH. *Paediatr Anaesth*. 2004;14:964.
329. Garcia-Aguado R, et al. *Rev Esp Anestesiol Reanim*. 1994;41:302.
330. Gottschalk A, et al. *Anesthesiology*. 1998;89:1018.
331. Schmid E. *Paediatr Anaesth*. 2006;16:218.
332. Tokarz A, et al. *Eur J Anaesthesiol*. 2002;19:842.
333. Dorchies OM, et al. *Neuromuscul Disord*. 2001;11:736.
334. Glucose-6-phosphatase deficiency (glycogen storage disease I, von Gierke disease). 2018. <https://www.uptodate.com/contents/glucose-6-phosphatase-deficiency-glycogen-storage-disease-i-von-gierke-disease>. Accessed 30.05.18.
335. Rake JP, et al. *Eur J Pediatr*. 2002;161(suppl 1):S112.
336. Visser G, et al. *Eur J Pediatr*. 2002;161(suppl 1):S120.
337. Kakinohana M, et al. *Masui*. 1998;47:1104.
338. Kawai T. *Masui*. 2005;54:924.
339. Loonen MC, et al. *Neurology*. 1981;31:1209.
340. Engel A, et al. Acid maltase deficiency. In: Engel A, Franzini-Armstrong C, eds. *Myology*. New York: McGraw-Hill; 2004:1559.
341. Type II glycogen storage disease (pompe disease). <https://emedicine.medscape.com/article/119506-overview>. 2017.
342. Ehlers KH, et al. *Circulation*. 1962;25:96.
343. Bulkley BH, Hutchins GM. *Am Heart J*. 1978;96:246.
344. Weinik M, King F. Acid maltase deficiency myopathy. *eMedicine*. 2012.
345. Makos MM, et al. *Ann Neurol*. 1987;22:629.
346. Giltin MC, et al. *Anesth Analg*. 1993;77:392.
347. Kotani N, et al. *Anesth Analg*. 1996;82:182.
348. Ing RJ, et al. *Paediatr Anaesth*. 2004;14:514.
349. McFarlane HJ, Soni N. *Anaesthesia*. 1986;41:1219.
350. Mohiddin SA, Fananapazir L. *Tex Heart Inst J*. 2002;29:290.
351. DiMauro S, Bonilla E. Mitochondrial encephalomyopathies. In: Engel A, Franzini-Armstrong C, eds. *Myology*. 3rd ed. New York: McGraw-Hill; 2004:1623.
352. Siciliano G, et al. *Biosci Rep*. 2007;27:53.
353. Wisely NA, Cook PR. *Eur J Anaesthesiol*. 2001;18:333.
354. Mehndiratta MM, et al. *Neurol India*. 2002;50:162.
355. Swash M, et al. *J Neurol Sci*. 1978;38:347.
356. Shipton EA, Prosser DO. *Eur J Anaesthesiol*. 2004;21:173.
357. Swash M, et al. *J Neurol Sci*. 1978;38:347.
358. Amato AA, Brown RH. Muscle dystrophies and other muscle diseases. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, eds. *Harrison's Principles of Internal Medicine*. 18th ed. McGraw-Hill; 2012.
359. DiMauro S, Bonilla E. Mitochondrial encephalomyopathies. In: Engel AG, Franzini-Armstrong C, eds. *Myology*. 3rd ed. McGraw-Hill; 2004:1623–1662.
360. Allison KR. Muscular dystrophy versus mitochondrial myopathy: the dilemma of the undiagnosed hypotonic child. In: *Paediatric Anaesthesia*. 2007; 17:1–6.
361. Hara K, et al. *J Clin Anesth*. 2004;16:539.
362. Mautura M, et al. *Int J Obstet Anesth*. 2008;17:370.
363. Levy E, Muravchick S. Mitochondrial diseases. In: Fleisher L, ed. *Anesthesia and Uncommon Diseases*. Philadelphia: Saunders; 2006:455.
364. James RH. *Anaesthesia*. 1985;40:88.
365. James RH. *Anaesthesia*. 1986;41:216.
366. Gurrieri C, et al. *Can J Anaesth*. 2011;58:751.
367. Footitt EJ, et al. *Br J Anaesth*. 2008;100:436.
368. Driessens J, et al. *Paediatr Anaesth*. 2007;17:16.
369. Burns AM, Shelly MP. *Anaesthesia*. 1989;44:975.
370. Kelly A, O'Connor M. *Anaesthesia*. 1990;45:596.
371. Ramchandra DS, et al. *Can J Anaesth*. 1990;37:474.
372. Guasch E, et al. *Anaesthesia*. 2003;58:607.
373. Sharma AD, et al. *Paediatr Anaesth*. 2001;11:488.
374. Vanlander AV, et al. *Acta Anaesthesiol Scand*. 2012;56:520.
375. Stowe DF, Kevin LG. *Antioxid Redox Signal*. 2004;6:439.
376. Stadnicka A, et al. *J Anesth*. 2007;21:212.
377. Wallace JJ, et al. *Paediatr Anaesth*. 1998;8:249–254.
378. Lauwers MH, et al. *Anaesthesia*. 1994;49:876.
379. Morgan PG, et al. *Anesthesiology*. 2002;96:1268.
380. Allen GC. *Anesthesiology*. 2003;98:282.
381. Frei FJ, et al. *Anaesthesia*. 1997;52:1056.
382. Naguib M, et al. *Anesthesiology*. 1996;84:1506.
383. Finsterer J, et al. *Can J Anaesth*. 1998;45:781.
384. Sharma AD, et al. *Paediatr Anaesth*. 2001;11:488.
385. D'Ambra MN, et al. *Anesthesiology*. 1979;51:343.
386. Wiesel S, et al. *Anesth Analg*. 1991;72:696.
387. Rowe RW, Helander E. *Anesth Analg*. 1990;71:295.
388. Rosaeg OP, et al. *Can J Anaesth*. 1994;43:403.
389. Hsiao PN, et al. *Acta Anaesthesiol Sin*. 2000;38:107.
390. Sasano N, et al. *J Anesth*. 2007;21:72.
391. Farag E, et al. *Can J Anaesth*. 2002;49:958.
392. Sasano N, et al. *J Anesth*. 2009;23:587.
393. Kubota H, et al. *J Child Neurol*. 2005;20:116.
394. Vincent A, et al. *Lancet*. 2001;357:2122.
395. Lindstrom JM. *Muscle Nerve*. 2000;23:453.
396. Anesthesia for the patient with myasthenia gravis. 2018. <https://www.uptodate.com/contents/anesthesia-for-the-patient-with-myasthenia-gravis>. Accessed April 8, 2019.
397. Eisenkraft JB, et al. *Anesthesiology*. 1988;69:760.
398. Baraka A. *Anaesthesia*. 1992;47:217.
399. Seigne RD, Scott RP. *Br J Anaesth*. 1994;72:468.
400. Kim JM, Mangold J. *Br J Anaesth*. 1989;63:497.
401. Sungur Ulke Z, et al. *Acta Anaesthesiol Scand*. 2013;57:745.
402. de Boer HD, et al. *Rev Esp Anestesiol Reanim*. 2010;57:181.
403. BRIDION(R) (sugammadex) Injection - First and Only Selective Relaxant Binding Agent - Approved in European Union. 2008. <http://www.evaluategroup.com/Universal/View.aspx?type=Story&id=160887>.
404. Baraka A. *Br J Anaesth*. 1992;69:227.
405. Abel M, Eisenkraft JB. *Mt Sinai J Med*. 2002;69:31.
406. Takamori M, et al. *Neurosci Res*. 2000;36:183.
407. Hewett SJ, Atchison WD. *Brain Res*. 1991;566:320.
408. Burge JA, Hanna MG. *Curr Neurol Neurosci Rep*. 2012;12:62.
409. Lehmann-Horn F, Rudel R, Jurkat-Rott K. Nondystrophic myotonias and periodic paralyses. In: Engel AG, Franzini-Armstrong C, eds. *Myology*. McGraw-Hill; 2004:1257–1300.
410. Jurkat-Rott K, Lehmann-Horn F. *J Neurol*. 2006;253:1391.
411. Chinnery PF, et al. *Ann Neurol*. 2002;52:251.
412. Song YW, et al. *Muscle Nerve*. 2012;46:914.
413. Vicart S, et al. *Neurology*. 2004;63:2120.
414. Visconti CM, et al. *Anesth Analg*. 1999;88:1081.
415. Robinson JE, et al. *Can J Anaesth*. 2000;47:160.
416. Griggs RC, et al. *Ann Intern Med*. 1970;73:39.
417. Bendahhou S, et al. *Ann Neurol*. 2001;50:417.
418. LoVecchio F, Jacobson S. *Emerg Med Clin North Am*. 1997;15:605.

419. Lin SH, Huang CL. *J Am Soc Nephrol*. 2012;23:985.
420. Depoix JP, et al. *Anesth Analg*. 2004;99:302.
421. Aouad R, Atanassoff PG. *Can J Anaesth*. 2004;51:92.
422. Ashwood EM, et al. *Anaesthesia*. 1992;47:579.
423. Aarons JJ, et al. *Anesthesiology*. 1989;71:303.
424. Cone AM, Sansome AJ. *Anaesthesia*. 1992;47:1097.
425. Weller JF, et al. *Anesthesiology*. 2002;97:259.
426. Barker MC. *AANA J*. 2012;78:191.
427. Siler JN, Discavage WJ. *Anesthesiology*. 1975;43:489.
428. Melnick B, et al. *Anesthesiology*. 1983;58:263.
429. Rooney RT, et al. *Anesth Analg*. 1988;67:782.
430. Hofer C, et al. *Anaesthesia*. 2001;56:1082.
431. Chitra S, Korula G. *Indian J Anaesth*. 2009;53:226.
432. Visconti CM, et al. *Anesth Analg*. 1999;88:1081.
433. Parness J, et al. *Anesth Analg*. 2009;109:1054.
434. Lambert C, et al. *Anesth Analg*. 1994;79:1012.
435. Rajabally YA, El Lahawi M. *Muscle Nerve*. 2002;25:453.
436. Marchant CL, et al. *Muscle Nerve*. 2004;30:114.
437. Neuman GG, Kopman AF. *Anesth Analg*. 1993;76:426.

References

1. Lerman J. Perioperative management of the paediatric patient with coexisting neuromuscular disease. *Br J Anaesth.* 2011;107(suppl 1):i79–89.
2. Rosenberg H, Pollock N, Schiemann A, Bulger T, Stowell K. Malignant hyperthermia: a review. *Orphanet J Rare Dis.* 2015;10:93.
3. Sumitani M, Uchida K, Yasunaga H, et al. Prevalence of malignant hyperthermia and relationship with anesthetics in Japan: data from the diagnosis procedure combination database. *Anesthesiology.* 2011;114:84–90.
4. Suyama H, Kawamoto M, Yuge O. Prevention and treatment of malignant hyperthermia in certified training hospitals in Japan: a questionnaire. *J Anesth.* 2002;16:207–210.
5. Monnier N, Krivosic-Horber R, Payen JF, et al. Presence of two different genetic traits in malignant hyperthermia families: implication for genetic analysis, diagnosis, and incidence of malignant hyperthermia susceptibility. *Anesthesiology.* 2002;97:1067–1074.
6. Brady JE, Sun LS, Rosenberg H, Li G. Prevalence of malignant hyperthermia due to anesthesia in New York State, 2001–2005. *Anesth Analg.* 2009;109:1162–1166.
7. Yuen B, Boncompagni S, Feng W, et al. Mice expressing T482I-RYR1 are viable but exhibit sex- and genotype-dependent susceptibility to malignant hyperthermia and muscle damage. *FASEB J.* 2012;26:1311–1322.
8. Rosenberg H, Shutack JG. Variants of malignant hyperthermia. Special problems for the paediatric anaesthesiologist. *Paediatr Anaesth.* 1996;6:87–93.
9. Rosenberg H, Davis M, James D, Pollock N, Stowell K. Malignant hyperthermia. *Orphanet J Rare Dis.* 2007;2:21.
10. Robinson R, Carpenter D, Shaw MA, Halsall J, Hopkins P. Mutations in RYR1 in malignant hyperthermia and central core disease. *Human mutation.* 2006;27:977–989.
11. Harrison GG, Isaacs H. Malignant hyperthermia. An historical vignette. *Anesthesia.* 1992;47:54–56.
12. Gronert BJ, Antognini JF. Malignant hyperthermia. In: Miller RD, ed. *Anesthesia.* New York: Churchill Livingstone; 1994:1075–1090.
13. Ombrédanne L. De l'influence de l'anesthésique employé dans la ganèse des accidents post-opératoires de pâleurhyperthermie observés chez les nourrissons. *Rev Med Française.* 1929;10:617.
14. Denborough MA, Forster JF, Lovell RR, Maplestone PA, Villiers JD. Anaesthetic deaths in a family. *Br J Anaesth.* 1962;34:395–396.
15. Kalow W, Britt BA, Terreau ME, Haist C. Metabolic error of muscle metabolism after recovery from malignant hyperthermia. *Lancet.* 1970;296:895–898.
16. Britt BA, Locher WG, Kalow W. Hereditary aspects of malignant hyperthermia. *Can J Anaesth.* 1969;16:89–98.
17. Ball RA, Annis CL, Topel DG, Christian LL. Clinical and laboratory diagnosis of porcine stress syndrome. *Vet Med Small Anim Clin.* 1973;68:1156–1159.
18. Briskey EJ. Etiological status and associated studies of pale, soft, exudative porcine musculature. *Adv Food Res.* 1964;13:89–178.
19. Hall LW, Woolf N, Bradley JW, Jolly DW. Unusual reaction to suxamethonium chloride. *Br Med J.* 1966;2:1305.
20. Fujii J, Otsu K, Zorzato F, et al. Identification of a mutation in porcine ryanodine receptor associated with malignant hyperthermia. *Science.* 1991;448–451.
21. Harrison GG. Control of the malignant hyperpyrexic syndrome in MHS swine by dantrolene sodium. *Br J Anaesth.* 1975;47:62–65.
22. Kolb ME, Horne ML, Martz R. Dantrolene in human malignant hyperthermia. *Anesthesiology.* 1982;56:254–262.
23. Lopez JR, Alamo LA, Jones D, et al. [Determination of intracellular free calcium concentration, in vivo, in swine susceptible to malignant hyperthermia syndrome]. *Acta Cient Venez.* 1985;36:102–104.
24. Lopez JR, Alamo LA, Jones DE, et al. [Ca²⁺+]i in muscles of malignant hyperthermia susceptible pigs determined in vivo with Ca²⁺ selective microelectrodes. *Muscle Nerve.* 1986;9:85–86.
25. Lopez JR, Allen PD, Alamo L, Jones D, Srreter FA. Myoplasmic free [Ca²⁺] during a malignant hyperthermia episode in swine. *Muscle Nerve.* 1988;11:82–88.
26. Lopez JR, Gerardi A, Lopez MJ, Allen PD. Effects of dantrolene on myoplasmic free [Ca²⁺] measured in vivo in patients susceptible to malignant hyperthermia. *Anesthesiology.* 1992;76:711–719.
27. Choi RH, Koenig X, Launikonis BS. Dantrolene requires Mg²⁺ to arrest malignant hyperthermia. *Proc Natl Acad Sci U S A.* 2017;114:4811–4815.
28. Cherednichenko G, Ward CW, Feng W, et al. Enhanced excitation-coupled calcium entry in myotubes expressing malignant hyperthermia mutation r163c is attenuated by dantrolene. *Molecular Pharmacology.* 2008;73:1203–1212.
29. Pessah IN, Waterhouse AL, Casida JE. The calcium-ryanodine receptor complex of skeletal and cardiac muscle. *Biochem Biophys Res Commun.* 1985;128:449–456.
30. Pessah IN, Anderson KW, Casida JE. Solubilization and separation of Ca²⁺-ATPase from the Ca²⁺-ryanodine receptor complex. *Biochem Biophys Res Commun.* 1986;139:235–243.
31. MacKenzie AE, Korneluk RG, Zorzato F, et al. The human ryanodine receptor gene: its mapping to 19q13.1, placement in a chromosome 19 linkage group, and exclusion as the gene causing myotonic dystrophy. *Am J Hum Genet.* 1990;46:1082–1089.
32. Otsu K, Fujii J, Periasamy M, et al. Chromosome mapping of five human cardiac and skeletal muscle sarcoplasmic reticulum protein genes. *Genomics.* 1993;17:507–509.
33. Sorrentino V, Giannini G, Malzac P, Mattei MG. Localization of a novel ryanodine receptor gene (RYR3) to human chromosome 15q14-q15 by in situ hybridization. *Genomics.* 1993;18:163–165.
34. Collins JH. Sequence analysis of the ryanodine receptor: possible association with a 12K, FK506-binding immunophilin/protein kinase C inhibitor. *Biochem Biophys Res Commun.* 1991;178:1288–1290.
35. Jayaraman T, Brillantes AM, Timerman AP, et al. FK506 binding protein associated with the calcium release channel (ryanodine receptor). *J Biol Chem.* 1992;267:9474–9477.
36. Lam E, Martin MM, Timerman AP, et al. A novel FK506 binding protein can mediate the immunosuppressive effects of FK506 and is associated with the cardiac ryanodine receptor. *J Biol Chem.* 1995;270:26511–26522.
37. Timerman AP, Onoue H, Xin HB, et al. Selective binding of FKBP12.6 by the cardiac ryanodine receptor. *J Biol Chem.* 1996;271:20385–20391.
38. Beam KG, Tanabe T, Numa S. Structure, function, and regulation of the skeletal muscle dihydropyridine receptor. *Ann N Y Acad Sci.* 1989;560:127–137.
39. Tanabe T, Beam KG, Adams BA, Niidome T, Numa S. Regions of the skeletal muscle dihydropyridine receptor critical for excitation-contraction coupling. *Nature.* 1990;346:567–569.
40. Nakai J, Tanabe T, Konno T, Adams B, Beam KG. Localization in the II–III loop of the dihydropyridine receptor of a sequence critical for excitation-contraction coupling. *J Biol Chem.* 1998;273:24983–24986.
41. Nakai J, Sekiguchi N, Fau - Rando TA, Rando TA, Fau - Allen PD, Allen PD, Fau - Beam KG, Beam KG. Two Regions of the Ryanodine Receptor Involved in Coupling with L-Type Ca²⁺ Channels. 1998.
42. Sheridan DC, Takekura H, Franzini-Armstrong C, Beam KG, Allen PD, Perez CF. Bidirectional signaling between calcium channels of skeletal muscle requires multiple direct and indirect interactions. *Proc Natl Acad Sci.* 2006;103:19760–19765.
43. Flucher BE, Franzini-Armstrong C. Formation of junctions involved in excitation-contraction coupling in skeletal and cardiac muscle. *Proc Natl Acad Sci U S A.* 1996;93:8101–8106.
44. Cherednichenko G, Hurne AM, Fessenden JD, et al. Conformational activation of Ca²⁺ entry by depolarization of skeletal myotubes. *Proc Natl Acad Sci U S A.* 2004;101:15793–15798.
45. Gaburjakova M, Gaburjakova J, Reiken S, et al. FKBP12 binding modulates ryanodine receptor channel gating. *J Biol Chem.* 2001;276:16931–16935.
46. Meissner G. Regulation of mammalian ryanodine receptors. *Front Biosci.* 2002;7:d2072–2080.
47. Ward CW, Feng W, Tu J, Pessah IN, Worley PK, Schneider MF. Homer protein increases activation of Ca²⁺ sparks in permeabilized skeletal muscle. *J Biol Chem.* 2004;279:5781–5787.
48. Pessah IN, Cherednichenko G, Lein PJ. Minding the calcium store: Ryanodine receptor activation as a convergent mechanism of PCB toxicity. *Pharmacol Ther.* 2010;125:260–285.
49. Perni S, Lavorato M, Beam KG. De Novo Reconstitution Reveals the Proteins Required for Skeletal Muscle Voltage-Induced Ca(2+) Release; 2017.
50. Polster A, Nelson BR, Olson EN, Beam KG. Stac3 has a direct role in skeletal muscle-type excitation contraction coupling that is disrupted by a myopathy-causing mutation. *Proc Natl Acad Sci.* 2016;113:10986–10991.

51. Cherednichenko G, Ward CW, Feng W, et al. Enhanced excitation-coupled calcium entry (ECCE) in myotubes expressing malignant hyperthermia mutation R163C is attenuated by dantrolene. *Mol Pharmacol*. 2008.
52. Yang T, Allen PD, Pessah IN, Lopez JR. Enhanced excitation-coupled calcium entry in myotubes is associated with expression of RYR1 MH mutations. *J Biol Chem*. 2007.
53. Yang T, Esteve E, Pessah IN, Molinski TF, Allen PD, Lopez JR. Elevated resting $[Ca^{2+}]_i$ in myotubes expressing malignant hyperthermia RyR1 cDNAs is partially restored by modulation of passive calcium leak from the SR. *Am J Physiol*. 2007;292:C1591–1598.
54. Eltit JM, Bannister RA, Moua O, et al. Malignant hyperthermia susceptibility arising from altered resting coupling between the skeletal muscle L-type Ca^{2+} channel and the type 1 ryanodine receptor. *Proc Natl Acad Sci U S A*. 2012;109:7923–7928.
55. Eltit JM, Feng W, Lopez JR, et al. Ablation of skeletal muscle triadin impairs FKBP12/RyR1 channel interactions essential for maintaining resting cytoplasmic Ca^{2+} . *J Biol Chem*. 2010;285:38453–38462.
56. Eltit JM, Li H, Ward CW, et al. Orthograde dihydropyridine receptor signal regulates ryanodine receptor passive leak. *Proc Natl Acad Sci U S A*. 2011;108:7046–7051.
57. Bannister RA, Esteve E, Eltit JM, et al. A malignant hyperthermia-inducing mutation in RYR1 (R163C): consequent alterations in the functional properties of DHPR channels. *J Gen Physiol*. 2010;135:629–640.
58. Esteve E, Eltit JM, Bannister RA, et al. A malignant hyperthermia-inducing mutation in RYR1 (R163C): alterations in Ca^{2+} entry, release, and retrograde signaling to the DHPR. *J Gen Physiol*. 2010;135:619–628.
59. Wappler F, Anetseder M, Baur CP, et al. Multicentre evaluation of in vitro contracture testing with bolus administration of 4-chloro-m-cresol for diagnosis of malignant hyperthermia susceptibility. *Eur J Anaesthesiol*. 2003;20:528–536.
60. Yang T, Ta TA, Pessah IN, Allen PD. Functional defects in six ryanodine receptor isoform-1 (RyR1) mutations associated with malignant hyperthermia and their impact on skeletal excitation-contraction coupling. *J Biol Chem*. 2003;278:25722–25730.
61. Reuter DA, Anetseder M, Muller R, Roewer N, Hartung EJ. The ryanodine contracture test may help diagnose susceptibility to malignant hyperthermia. *Can J Anaesth*. 2003;50:643–648.
62. Capacchione JF, Muldoon SM. The relationship between exertional heat illness, exertional rhabdomyolysis, and malignant hyperthermia. *Anesth Analg*. 2009;109:1065–1069.
63. Pessah IN, Stambuk RA, Casida JE. Ca^{2+} -activated ryanodine binding: mechanisms of sensitivity and intensity modulation by Mg^{2+} , caffeine, and adenine nucleotides. *Mol Pharmacol*. 1987;31:232–238.
64. Zimanyi I, Pessah IN. Pharmacological characterization of the specific binding of [3 H]ryanodine to rat brain microsomal membranes. *Brain Research*. 1991;561:181–191.
65. Jona I, Szegedi C, Sarkozi S, Szentesi P, Csernoch L, Kovacs L. Altered inhibition of the rat skeletal ryanodine receptor/calcium release channel by magnesium in the presence of ATP. *Pflugers Arch*. 2001;441:729–738.
66. Laver D. The power of single channel recording and analysis: its application to ryanodine receptors in lipid bilayers. *Clin Exp Pharmacol Physiol*. 2001;28:675–686.
67. Laver DR, Baynes TM, Dulhunty AF. Magnesium inhibition of ryanodine-receptor calcium channels: evidence for two independent mechanisms. *J Membr Biol*. 1997;156:213–229.
68. Voss AA, Allen PD, Pessah IN, Perez CF. Allosterically coupled calcium and magnesium binding sites are unmasked by ryanodine receptor chimeras. *Biochem Biophys Res Commun*. 2008;366:988–993.
69. Lamb GD. Ca^{2+} inactivation, Mg^{2+} inhibition and malignant hyperthermia. *J Muscle Res Cell Motil*. 1993;14:554–556.
70. Laver DR, Owen VJ, Junankar PR, Taske NL, Dulhunty AF, Lamb GD. Reduced inhibitory effect of Mg^{2+} on ryanodine receptor- Ca^{2+} release channels in malignant hyperthermia. *Biophysical Journal*. 1997;73:1913–1924.
71. Barrientos GC, Feng W, Truong K, et al. Gene dose influences cellular and calcium channel dysregulation in heterozygous and homozygous T4826I-RYR1 malignant hyperthermia-susceptible muscle. *J Biol Chem*. 2012;287:2863–2876.
72. Feng W, Barrientos GC, Cherednichenko G, et al. Functional and biochemical properties of ryanodine receptor type 1 channels from heterozygous R163C malignant hyperthermia-susceptible mice. *Mol Pharmacol*. 2011;79:420–431.
73. Chelu MG, Goonasekera SA, Durham WJ, et al. Heat- and anesthesia-induced malignant hyperthermia in an RyR1 knock-in mouse. *FASEB J*. 2006;20:329–330.
74. Yang T, Riehl J, Esteve E, et al. Pharmacologic and functional characterization of malignant hyperthermia in the R163C RyR1 knock-in mouse. *Anesthesiology*. 2006;105:1164–1175.
75. Lopez JR, Linares N, Pessah IN, Allen PD. Enhanced response to caffeine and 4-chloro-m-cresol in malignant hyperthermia-susceptible muscle is related in part to chronically elevated resting $[Ca^{2+}]_i$. *Am J Physiol*. 2005;288:C606–612.
76. Ikemoto N, Yamamoto T. Regulation of calcium release by inter-domain interaction within ryanodine receptors. *Front Biosci*. 2002;7:d671–683.
77. Samso M, Feng W, Pessah IN, Allen PD. Coordinated movement of cytoplasmic and transmembrane domains of RyR1 upon gating. *PLoS Biol*. 2009;7:e85.
78. Carpenter D, Ringrose C, Leo V, et al. The role of CACNA1S in predisposition to malignant hyperthermia. *BMC Med Genet*. 2009;10:104.
79. Toppin PJ, Chandy TT, Ghanekar A, Kraeva N, Beattie WS, Riazi S. A report of fulminant malignant hyperthermia in a patient with a novel mutation of the CACNA1S gene. *Can J Anaesth*. 2010;57:689–693.
80. Pirone A, Schredelseker J, Tuluc P, et al. Identification and functional characterization of malignant hyperthermia mutation T1354S in the outer pore of the Cav1.1a-S-subunit. *Am J Physiol*. 2010;299:C1345–C1354.
81. Weiss RG, O'Connell KM, Flucher BE, Allen PD, Grabner M, Dirksen RT. Functional analysis of the R1086H malignant hyperthermia mutation in the DHPR reveals an unexpected influence of the III-IV loop on skeletal muscle EC coupling. *Am J Physiol*. 2004;287:C1094–C1102.
82. Bannister RA, Beam KG. Ryanodine modification of RyR1 retrogradely affects L-type Ca^{2+} channel gating in skeletal muscle. *J Muscle Res Cell Motil*. 2009;30:217–223.
83. Jones DE, Ryan JF, Taylor B, et al. Pancuronium in large doses protects susceptible swine from halothane induced malignant hyperthermia. *Anesthesiology*. 1988;83:A344.
84. Hurne AM, O'Brien JJ, Wingrove D, et al. Ryanodine receptor type 1 (RyR1) mutations C4958S and C4961S reveal excitation-coupled calcium entry (ECCE) is independent of sarcoplasmic reticulum store depletion. *J Biol Chem*. 2005;280:36994–37004.
85. Bannister RA, Pessah IN, Beam KG. The skeletal L-type Ca^{2+} current is a major contributor to excitation-coupled Ca^{2+} entry. *J Gen Physiol*. 2009;133:79–91.
86. Sultana N, Dienes B, Benedetti A, et al. Restricting calcium currents is required for correct fiber type specification in skeletal muscle. *Development*. 2016;143:1547–1559.
87. Putney JW, Broad LM, Braun FJ, Lievremont JP, Bird GS. Mechanisms of capacitative calcium entry. *J Cell Sci*. 2001;114:2223–2229.
88. Kurebayashi N, Ogawa Y. Depletion of Ca^{2+} in the sarcoplasmic reticulum stimulates Ca^{2+} entry into mouse skeletal muscle fibres. *J Physiol*. 2001;533:185–199.
89. Ma J, Pan Z. Junctional membrane structure and store operated calcium entry in muscle cells. *Front Biosci*. 2003;8:d242–d255.
90. Pan Z, Yang D, Nagaraj RY, et al. Dysfunction of store-operated calcium channel in muscle cells lacking mg29. *Nat Cell Biol*. 2002;4:379–383.
91. Zhao X, Weisleder N, Han X, et al. Azumolene inhibits a component of store-operated calcium entry coupled to the skeletal muscle ryanodine receptor. *J Biol Chem*. 2006;281:33477–33486.
92. Desmedt JE, Hainaut K. Inhibition of the intracellular release of calcium by Dantrolene in barnacle giant muscle fibres. *J Physiol*. 1977;265:565–585.
93. Krivickas LS, Ansved T, Suh D, Frontera WR. Contractile properties of single muscle fibers in myotonic dystrophy. *Muscle Nerve*. 2000;23:529–537.
94. Yamaguchi N, Igami K, Kasai M. Kinetics of depolarization-induced calcium release from skeletal muscle triads in vitro. *J Biol Chem*. 1997;121:432–439.

96. Paul-Pletzer K, Yamamoto T, Bhat MB, et al. Identification of a dantrolene-binding sequence on the skeletal muscle ryanodine receptor. *J Biol Chem.* 2002;277:34918–34923.
97. Monnier N, Procaccio V, Stieglitz P, Lunardi J. Malignant-hyperthermia susceptibility is associated with a mutation of the alpha 1-subunit of the human dihydropyridine-sensitive L-type voltage-dependent calcium-channel receptor in skeletal muscle. *Am J Hum Genet.* 1997;60:1316–1325.
98. Sambuughin N, Sei Y, Gallagher KL, et al. North American malignant hyperthermia population: screening of the ryanodine receptor gene and identification of novel mutations. *Anesthesiology.* 2001;95:594–599.
99. Brown RL, Pollock AN, Couchman KG, et al. A novel ryanodine receptor mutation and genotype-phenotype correlation in a large malignant hyperthermia New Zealand Maori pedigree. *Hum Mol Genet.* 2000;9:1515–1524.
100. Girard T, Urwyler A, Censier K, Mueller CR, Zorzato F, Treves S. Genotype-phenotype comparison of the Swiss malignant hyperthermia population. *Hum Mutat.* 2001;18:357–358.
101. Brandt A, Schleithoff L, Jurkat-Rott K, Klingler W, Baur C, Lehmann-Horn F. Screening of the ryanodine receptor gene in 105 malignant hyperthermia families: novel mutations and concordance with the in vitro contracture test. *Hum Mol Genet.* 1999;8:2055–2062.
102. Rueffert H, Olthoff D, Deutrich C, Schober R, Froster UG. A new mutation in the skeletal ryanodine receptor gene (RYR1) is potentially causative of malignant hyperthermia, central core disease, and severe skeletal malformation. *Am J Med Genet.* 2004;124:248–254.
103. Robinson R, Hopkins P, Carsana A, et al. Several interacting genes influence the malignant hyperthermia phenotype. *Hum Genet.* 2003;112:217–218.
104. Gillard EF, Otsu K, Fujii J, et al. A substitution of cysteine for arginine 614 in the ryanodine receptor is potentially causative of human malignant hyperthermia. *Genomics.* 1991;11:751–755.
105. Sei Y, Sambuughin NN, Davis EJ, et al. Malignant hyperthermia in North America: genetic screening of the three hot spots in the type I ryanodine receptor gene. *Anesthesiology.* 2004;101:824–830.
106. Davis M, Brown R, Dickson A, et al. Malignant hyperthermia associated with exercise-induced rhabdomyolysis or congenital abnormalities and a novel RYR1 mutation in New Zealand and Australian pedigrees. *Br J Anaesth.* 2002;88:508–515.
107. Oyamada H, Oguchi K, Saitoh N, et al. Novel mutations in C-terminal channel region of the ryanodine receptor in malignant hyperthermia patients. *Jpn J Pharmacol.* 2002;88:159–166.
108. Yeh HM, Tsai MC, Su YN, et al. Denaturing high performance liquid chromatography screening of ryanodine receptor type 1 gene in patients with malignant hyperthermia in Taiwan and identification of a novel mutation (Y522C). *Anesth Analg.* 2005;101:1401–1406.
109. Fletcher JE, Tripolitis L, Hubert M, Vita GM, Levitt RC, Rosenberg H. Genotype and phenotype relationships for mutations in the ryanodine receptor in patients referred for diagnosis of malignant hyperthermia. *Br J Anaesth.* 1995;75:307–310.
110. Lynch PJ, Krivosic-Horber R, Reyford H, et al. Identification of heterozygous and homozygous individuals with the novel RYR1 mutation Cys35Arg in a large kindred. *Anesthesiology.* 1997;86:620–626.
111. Monnier N, Ferreiro A, Marty I, Labarre-Vila A, Mezin P, Lunardi J. A homozygous splicing mutation causing a depletion of skeletal muscle RYR1 is associated with multi-minicore disease congenital myopathy with ophthalmoplegia. *Hum Mol Genet.* 2003;12:1171–1178.
112. Rueffert H, Olthoff D, Deutrich C, Thamm B, Froster UG. Homozygous and heterozygous Arg614Cys mutations (1840C→T) in the ryanodine receptor gene co-segregate with malignant hyperthermia susceptibility in a German family. *Br J Anaesth.* 2001;87:240–245.
113. A protocol for the investigation of malignant hyperpyrexia (MH) susceptibility. The European malignant hyperpyrexia group. *Br J Anaesth.* 1984;56:1267–1269.
114. Ording H, Brancadoro V, Cozzolino S, et al. In vitro contracture test for diagnosis of malignant hyperthermia following the protocol of the European MH Group: results of testing patients surviving fulminant MH and unrelated low-risk subjects. The European malignant hyperthermia group. *Acta Anaesthesiol Scand.* 1997;41:955–966.
115. Hopkins PM, Rueffert H, Snoeck MM, et al. European Malignant Hyperthermia Group guidelines for investigation of malignant hyperthermia susceptibility. *Br J Anaesth.* 2015;115:531–539.
116. Larach MG. Standardization of the caffeine halothane muscle contracture test. North American malignant hyperthermia group. *Anesth Analg.* 1989;69:511–515.
117. Allen GC, Larach MG, Kunselman AR. The sensitivity and specificity of the caffeine-halothane contracture test: a report from the North American Malignant Hyperthermia Registry. The North American Malignant Hyperthermia Registry of MHAUS. *Anesthesiology.* 1998;88:579–588.
118. Metterlein T, Schuster F, Tadda L, Hager M, Roewer N, Anetseder M. Statins alter intracellular calcium homeostasis in malignant hyperthermia susceptible individuals. *Cardiovasc Ther.* 2010;28:356–360.
119. Metterlein T, Schuster F, Tadda L, et al. Fluoroquinolones influence the intracellular calcium handling in individuals susceptible to malignant hyperthermia. *Muscle Nerve.* 2011;44:208–212.
120. Gerbershagen MU, Missler G, Schutte JK, et al. 3,4-Methylene-dioxymethamphetamine (Ecstasy) increases the sensitivity of the contractile apparatus to calcium ions in both malignant hyperthermia-susceptible and normal skeletal muscle fibres. *Eur J Anaesthesiol.* 2011;29:42–49.
121. Johannsen S, Roewer N, Schuster F. Ondansetron-induced muscular contractures in malignant hyperthermia-susceptible individuals. *Anesth Analg.* 2012.
122. Bendahan D, Guis S, Monnier N, et al. Comparative analysis of in vitro contracture tests with ryanodine and a combination of ryanodine with either halothane or caffeine: a comparative investigation in malignant hyperthermia. *Acta Anaesthesiol Scand.* 2004;48:1019–1027.
123. Baur CP, Bellon L, Felleiter P, et al. A multicenter study of 4-chlorom-cresol for diagnosing malignant hyperthermia susceptibility. *Anesth Analg.* 2000;90:200–205.
124. Metterlein T, Schuster F, Kranke P, Roewer N, Anetseder M. In-vitro contracture testing for susceptibility to malignant hyperthermia: can halothane be replaced? *Eur J Anaesthesiol.* 2011;28:251–255.
125. Metterlein T, Hartung E, Schuster F, Roewer N, Anetseder M. Sevoflurane as a potential replacement for halothane in diagnostic testing for malignant hyperthermia susceptibility: results of a preliminary study. *Minerva Anestesiol.* 2011;77:768–773.
126. Migita T, Mukaida K, Kobayashi M, Hamada H, Kawamoto M. The severity of sevoflurane-induced malignant hyperthermia. *Acta Anaesthesiol Scand.* 2011;56:351–356.
127. Zhou H, Brockington M, Jungbluth H, et al. Epigenetic allele silencing unveils recessive RYR1 mutations in core myopathies. *Am J Hum Genet.* 2006;79:859–868.
128. Urwyler A, Deufel T, McCarthy T, West S. Guidelines for molecular genetic detection of susceptibility to malignant hyperthermia. *Br J Anaesth.* 2001;86:283–287.
129. Robinson RL, Brooks C, Brown SL, et al. RYR1 mutations causing central core disease are associated with more severe malignant hyperthermia in vitro contracture test phenotypes. *Hum Mutat.* 2002;20:88–97.
130. Rueffert H, Olthoff D, Deutrich C, Meinecke CD, Froster UG. Mutation screening in the ryanodine receptor 1 gene (RYR1) in patients susceptible to malignant hyperthermia who show definite IVCT results: identification of three novel mutations. *Acta Anaesthesiol Scand.* 2002;46:692–698.
131. Larach MG, Gronert GA, Allen GC, Brandom BW, Lehman EB. Clinical presentation, treatment, and complications of malignant hyperthermia in North America from 1987 to 2006. *Anesth Analg.* 2010;110:498–507.
132. Allen GC, Brubaker CL. Human malignant hyperthermia associated with desflurane anesthesia. *Anesth Analg.* 1998;86:1328–1331.
133. Shulman M, Braverman B, Ivankovich AD, Gronert G. Sevoflurane triggers malignant hyperthermia in swine. *Anesthesiology.* 1981;54:259–260.
134. Gronert GA. Malignant hyperthermia. *Anesthesiology.* 1980;53:395–423.
135. Hall GM, Lucke JN, Lister D. Proceedings: neuromuscular blocking drugs in porcine malignant hyperthermia. *Br J Anaesth.* 1976;48:270–271.
136. Denborough M, Hopkinson KC. Propofol and malignant hyperpyrexia. *Lancet.* 1988;1:191.
137. Bendixen D, Skovgaard LT, Ording H. Analysis of anaesthesia in patients suspected to be susceptible to malignant hyperthermia before diagnostic in vitro contracture test. *Acta Anaesthesiol Scand.* 1997;41:480–484.

138. Larach MG, Localio AR, Allen GC, et al. A clinical grading scale to predict malignant hyperthermia susceptibility. *Anesthesiology*. 1994;80:771–779.
139. Gronert GA, Thompson RL, Onofrio BM. Human malignant hyperthermia: awake episodes and correction by dantrolene. *Anesth Analg*. 1980;59:377–378.
140. Haverkort-Poels PJ, Joosten EM, Ruitenberg W. Prevention of recurrent exertional rhabdomyolysis by dantrolene sodium. *Muscle Nerve*. 1987;10:45–46.
141. Denborough MA, Hopkinson KC, Banney DG. Firefighting and malignant hyperthermia. *Br Med J (Clin Res Ed)*. 1988;296:1442–1443.
142. Hackl W, Winkler M, Mauritz W, Sporn P, Steinbereithner K. Muscle biopsy for diagnosis of malignant hyperthermia susceptibility in two patients with severe exercise-induced myolysis. *Br J Anaesth*. 1991;66:138–140.
143. Hopkins PM, Ellis FR, Halsall PJ. Evidence for related myopathies in exertional heat stroke and malignant hyperthermia. *Lancet*. 1991;338:1491–1492.
144. Kochling A, Wappler F, Winkler G, Schulte am Esch JS. Rhabdomyolysis following severe physical exercise in a patient with predisposition to malignant hyperthermia. *Anaesth Intensive Care*. 1998;26:315–318.
145. Reynolds AC, Reynolds EV, Henschel EO. Physical exercise in malignant hyperthermia screening. *Lancet*. 1981;2:303.
146. Gronert GA, Milde JH, Theye RA. Role of sympathetic activity in porcine malignant hyperthermia. *Anesthesiology*. 1977;47:411–415.
147. Gronert GA, White DA. Failure of norepinephrine to initiate porcine malignant hyperthermia. *Pflugers Arch*. 1988;411:226–228.
148. Wappler F, Fiege M, Steinbath M, et al. Evidence for susceptibility to malignant hyperthermia in patients with exercise-induced rhabdomyolysis. *Anesthesiology*. 2001;94:95–100.
149. Anetseder M, Hartung E, Klepper S, Reichmann H. Gasoline vapors induce severe rhabdomyolysis. *Neurology*. 1994;44:2393–2395.
150. Ryan JF, Tedeschi LG. Sudden unexplained death in a patient with a family history of malignant hyperthermia. *J Clin Anesth*. 1997;9:66–68.
151. *Adverse Effects of Heat and Exercise in Relation to MH Susceptibility*. 2018. <https://www.mhaus.org/healthcare-professionals/mhaus-recommendations/adverse-effects-of-heat-and-exercise-in-relation-to-mh-susceptibility/>. Accessed April 8, 2019.
152. Butler-Browne GS, Eriksson PO, Laurent C, Thornell LE. Adult human masseter muscle fibers express myosin isozymes characteristic of development. *Muscle Nerve*. 1988;11:610–620.
153. Morgan DL, Proske U. Vertebrate slow muscle: its structure, pattern of innervation, and mechanical properties. *Physiol Rev*. 1984;64:103–169.
154. van der Spek AF, Reynolds PI, Fang WB, Ashton-Miller JA, Stohler CS, Schork MA. Changes in resistance to mouth opening induced by depolarizing and non-depolarizing neuromuscular relaxants. *Br J Anaesth*. 1990;64:21–27.
155. Magee KR, Shy GM. A new congenital non-progressive myopathy. *Brain*. 1956;79:610–621.
156. Norwood FL, Harling C, Chinnery PF, Eagle M, Bushby K, Straub V. Prevalence of genetic muscle disease in Northern England: in-depth analysis of a muscle clinic population. *Brain*. 2009;132:3175–3186.
157. Jungbluth H, Sewry CA, Muntoni F. Core myopathies. *Semin Pediatr Neurol*. 2011;18:239–249.
158. Engel AG, Gomez MR, Groover RV. Multicore disease. A recently recognized congenital myopathy associated with multifocal degeneration of muscle fibers. *Mayo Clin Proc*. 1971;46:666–681.
159. Klingler W, Rueffert H, Lehmann-Horn F, Girard T, Hopkins PM. Core myopathies and risk of malignant hyperthermia. *Anesth Analg*. 2009;109:1167–1173.
160. Koch BM, Bertorini TE, Eng GD, Boehm R. Severe multicore disease associated with reaction to anesthesia. *Arch Neurol*. 1985;42:1204–1206.
161. Osada H, Masuda K, Seki K, Sekiya S. Multi-minicore disease with susceptibility to malignant hyperthermia in pregnancy. *Gynecol Obstet Invest*. 2004;58:32–35.
162. Allanson JE. Noonan syndrome. *J Med Genet*. 1987;24:9–13.
163. Benca J, Hogan K. Malignant hyperthermia, coexisting disorders, and enzymopathies: risks and management options. *Anesth Analg*. 2009;109:1049–1053.
164. Briggs BJ, Dickerman JD. Bleeding disorders in Noonan syndrome. *Pediatr Blood Cancer*. 2012;58:167–172.
165. Tartaglia M, Zampino G, Gelb BD. Noonan syndrome: clinical aspects and molecular pathogenesis. *Mol Syndromol*. 2010;1:2–26.
166. Hunter A, Pinsky L. An evaluation of the possible association of malignant hyperpyrexia with the Noonan syndrome using serum creatine phosphokinase levels. *J Pediatr*. 1975;86:412–415.
167. Sharathkumar AA. Bleeding disorders and Noonan syndrome. *Pediatr Blood Cancer*. 2012;59:592; author reply 3.
168. Bajwa SJ, Gupta S, Kaur J, et al. Anesthetic considerations and difficult airway management in a case of Noonan syndrome. *Saudi J Anaesth*. 2011;5:345–347.
169. Dadabhoy ZP, Winnie AP. Regional anesthesia for cesarean section in a parturient with Noonan's syndrome. *Anesthesiology*. 1988;68:636–638.
170. Campbell AM, Bousfield JD. Anaesthesia in a patient with Noonan's syndrome and cardiomyopathy. *Anaesthesia*. 1992;47:131–133.
171. McBain J, Lemire EG, Campbell DC. Epidural labour analgesia in a parturient with Noonan syndrome: a case report. *Can J Anaesth*. 2006;53:274–278.
172. Isaacs H, Badenhorst ME. Dominantly inherited malignant hyperthermia (MH) in the King-Denborough syndrome. *Muscle Nerve*. 1992;15:740–742.
173. Heiman-Patterson TD, Rosenberg HR, Binning CP, Tahmoush AJ. King-Denborough syndrome: contracture testing and literature review. *Pediatr Neurol*. 1986;2:175–177.
174. King JO, Denborough MA. Anesthetic-induced malignant hyperpyrexia in children. *J Pediatr*. 1973;83:37–40.
175. McPherson EW, Taylor CA. The King syndrome: malignant hyperthermia, myopathy, and multiple anomalies. *Am J Med Genet*. 1981;8:159–165.
176. Kaplan AM, Bergeson PS, Gregg SA, Curless RG. Malignant hyperthermia associated with myopathy and normal muscle enzymes. *J Pediatr*. 1977;91:431–434.
177. Isaacs H, Barlow MB. Malignant hyperpyrexia occurring in a second Johannesburg family. *Br J Anaesth*. 1973;45:901–906.
178. Isaacs H, Frere G, Mitchell J. Histological, histochemical and ultra-microscopic findings in muscle biopsies from carriers of the trait for malignant hyperpyrexia. *Br J Anaesth*. 1973;45:860–868.
179. Isaacs H, Barlow MB. Malignant hyperpyrexia. Further muscle studies in asymptomatic carriers identified by creatinine phosphokinase screening. *J Neurol Neurosurg Psychiatry*. 1973;36:228–243.
180. Reed W, Smith R, Dekovic F, et al. Comprehensive banking of sibling donor cord blood for children with malignant and nonmalignant disease. *Blood*. 2003;101:351–357.
181. Habib AS, Millar S, Deballi P, Muir HA. Anesthetic management of a ventilator-dependent parturient with the King-Denborough syndrome. *Can J Anaesth*. 2003;50:589–592.
182. D'Arcy CE, Bjorksten A, Yiu EM, et al. King-Denborough syndrome caused by a novel mutation in the ryanodine receptor gene. *Neurology*. 2008;71:776–777.
183. Dowling JJ, Lillis S, Amburgey K, et al. King-Denborough syndrome with and without mutations in the skeletal muscle ryanodine receptor (RYR1) gene. *Neuromuscul Disord*. 2011;21:420–427.
184. Glahn KP, Ellis FR, Halsall PJ, et al. Recognizing and managing a malignant hyperthermia crisis: guidelines from the European Malignant Hyperthermia Group. *Br J Anaesth*. 2010;105:417–420.
185. Birgenheier N, Stoker R, Westenskow D, Orr J. Activated charcoal effectively removes inhaled anesthetics from modern anesthesia machines. *Anesth Analg*. 2011;112:1363–1370.
186. Kugler Y, Russell WJ. Speeding dantrolene preparation for treating malignant hyperthermia. *Anaesth Intensive Care*. 2011;39:84–88.
187. Rosenberg H. Current state of malignant hyperthermia and the use of dantrium IV as treatment. *Anesthesiol News*. 2010;20–21.
188. Flewellen EH, Nelson TE, Jones WP, Arens JF, Wagner DL. Dantrolene dose response in awake man: implications for management of malignant hyperthermia. *Anesthesiology*. 1983;59:275–280.
189. Brandom BW, Larach MG, Chen MS, Young MC. Complications associated with the administration of dantrolene 1987 to 2006: a report from the North American Malignant Hyperthermia Registry of the Malignant Hyperthermia Association of the United States. *Anesth Analg*. 2011;112:1115–1123.
190. Oh ST, Yedidag E, Conklin JL, Martin M, Bielefeldt K. Calcium release from intracellular stores and excitation-contraction coupling in intestinal smooth muscle. *J Surg Res*. 1997;71:79–86.

191. Korolkiewicz RP, Konstanski Z, Rekowski P, et al. Sources of activator Ca²⁺ for galanin-induced contractions of rat gastric fundus, jejunum and colon. *J Physiol Pharmacol*. 2000;51:821–831.
192. Gener B, Burns JM, Griffin S, Boyer EW. Administration of ondansetron is associated with lethal outcome. *Pediatrics*. 2010;125:e1514–e1517.
193. Lerman J, McLeod ME, Strong HA. Pharmacokinetics of intravenous dantrolene in children. *Anesthesiology*. 1989;70:625–629.
194. Burkman JM, Posner KL, Domino KB. Analysis of the clinical variables associated with recrudescence after malignant hyperthermia reactions. *Anesthesiology*. 2007;106:901–906. quiz 1077–1078.
195. Hopkins PM. Recrudescence of malignant hyperthermia. *Anesthesiology*. 2007;106:893–894.
196. Gallant EM, Foldes FF, Rempel WE, Gronert GA. Verapamil is not a therapeutic adjunct to dantrolene in porcine malignant hyperthermia. *Anesth Analg*. 1985;64:601–606.
197. Harrison GG, Wright IG, Morrell DF. The effects of calcium channel blocking drugs on halothane initiation of malignant hyperthermia in MHS swine and on the established syndrome. *Anaesth Intensive Care*. 1988;16:197–201.
198. Migita T, Mukaida K, Yasuda T, Hamada H, Kawamoto M. Calcium channel blockers are inadequate for malignant hyperthermia crisis. *J Anesth*. 2012;26:579–584.
199. Metterlein T, Schuster F, Kranke P, Hager M, Roewer N, Anetseder M. Magnesium does not influence the clinical course of succinylcholine-induced malignant hyperthermia. *Anesth Analg*. 2011;112:1174–1178.
200. Choi RH, Koenig X, Launikonis BS. Dantrolene requires Mg²⁺ to arrest malignant hyperthermia. *Proc Natl Acad Sci U S A*. 2017;114:4811–4815.
201. Larach MG, Dirksen SJ, Belani KG, et al. Special article: creation of a guide for the transfer of care of the malignant hyperthermia patient from ambulatory surgery centers to receiving hospital facilities. *Anesth Analg*. 2012;114:94–100.
202. Wong CA, Denholm B. Malignant hyperthermia diagnosis, treatment, and prevention. *Anesth News*. 2011;17–21.
203. Aderibigbe T, Lang BH, Rosenberg H, Chen Q, Li G. Cost-effectiveness analysis of stocking dantrolene in ambulatory surgery centers for the treatment of malignant hyperthermia. *Anesthesiology*. 2014;120:1333–1338.
204. Maccani RM, Wedel DJ, Hofer RE. Norepinephrine does not potentiate porcine malignant hyperthermia. *Anesth Analg*. 1996;82:790–795.
205. McGraw TT, Keon TP. Malignant hyperthermia and the clean machine. *Can J Anaesth*. 1989;36:530–532.
206. Whitty RJ, Wong GK, Petroz GC, Pehora C, Crawford MW. Preparation of the Drager Fabius GS workstation for malignant hyperthermia-susceptible patients. *Can J Anaesth*. 2009;56:497–501.
207. Crawford MW, Prinzhausen H, Petroz GC. Accelerating the washout of inhalational anesthetics from the Drager Primus anesthetic workstation: effect of exchangeable internal components. *Anesthesiology*. 2007;106:289–294.
208. Prinzhausen H, Crawford MW, O'Rourke J, Petroz GC. Preparation of the Drager Primus anesthetic machine for malignant hyperthermia-susceptible patients. *Can J Anaesth*. 2006;53:885–890.
209. Petroz GC, Lerman J. Preparation of the Siemens KION anesthetic machine for patients susceptible to malignant hyperthermia. *Anesthesiology*. 2002;96:941–946.
210. Brunner HW, Pohl S, Grond S. Washout of sevoflurane from the GE Avance and Aoming Carestation anesthetic machines. *Acta Anaesthesiol Scand*. 2011;55:1118–1123.
211. Shanahan H, O'Donoghue R, O'Kelly P, Synnott A, O'Rourke J. Preparation of the Drager Fabius CE and Drager Zeus anaesthetic machines for patients susceptible to malignant hyperthermia. *Eur J Anaesthesiol*. 2012;29:229–234.
212. Gunter JB, Ball J, Than-Win S. Preparation of the Drager Fabius anesthesia machine for the malignant-hyperthermia susceptible patient. *Anesth Analg*. 2008;107:1936–1945.
213. Jones C, Bennett K, Kim TW, Bulger TF, Pollock N. Preparation of Datex-Ohmeda Aestiva and Aisys anaesthetic machines for use in malignant hyperthermia susceptible patients. *Anaesth Intensive Care*. 2012;40:490–497.
214. Schonell LH, Sims C, Bulsara M. Preparing a new generation anaesthetic machine for patients susceptible to malignant hyperthermia. *Anaesth Intensive Care*. 2003;31:58–62.
215. Feldman JM. New device simplifies workstation preparation for malignant hyperthermia-susceptible patients. *Anesthesiology*. 2011;115:434. author reply 6–7.
216. Block FE. Malignant hyperthermia and charcoal absorbent: too hot to handle. *Anesth Analg*. 2011;112:1270–1271.
217. Jantzen JP, Eck J, Kleemann PP. [An activated charcoal filter for eliminating volatile anesthetics. A contribution to the management of malignant hyperthermia]. *Anaesthetist*. 1989;38:639–641.
218. Preparation of Anesthesia Workstations to Anesthetize MHSusceptible Patients. <https://www.mhaus.org/healthcare-professionals/mhaus-recommendations/preparation-of-anesthesia-workstations-to-anesthetize-mh-susceptible-patients/>. Accessed April 8, 2019.
219. Criteria for a recommended standard. *Occupational Exposure to Waste Anesthetic Gases and Vapors*; 1977. <http://www.cdc.gov/niosh/pdfs/77-140a.pdf>. Accessed April 8, 2019.
220. Anesthetic Gases. *Guidelines for Workplace Exposures*; 2000. <https://www.osha.gov/dts/osta/anestheticgases/index.html>. Accessed April 8, 2019.
221. Anetseder M, Hager M, Muller-Reible C, Roewer N. Regional lactate and carbon dioxide concentrations in a metabolic test for malignant hyperthermia. *Lancet*. 2003;362:494; discussion -5.
222. Bina S, Cowan G, Karaian J, Muldoon S, Mongan P, Bunger R. Effects of caffeine, halothane, and 4-chloro-m-cresol on skeletal muscle lactate and pyruvate in malignant hyperthermia-susceptible and normal swine as assessed by microdialysis. *Anesthesiology*. 2006;104:90–100.
223. Schuster F, Metterlein T, Negele S, et al. Intramuscular injection of sevoflurane detects malignant hyperthermia predisposition in susceptible pigs. *Anesthesiology*. 2007;107:616–620.
224. Schuster F, Scholl H, Hager M, Muller R, Roewer N, Anetseder M. The dose-response relationship and regional distribution of lactate after intramuscular injection of halothane and caffeine in malignant hyperthermia-susceptible pigs. *Anesth Analg*. 2006;102:468–472.
225. Bina S, Muldoon S, Bunger R. Effects of ryanodine on skeletal muscle lactate and pyruvate in malignant hyperthermia-susceptible and normal swine as assessed by microdialysis. *Eur J Anaesthesiol*. 2007;1–10.
226. Girard T, Cavagna D, Padovan E, et al. B-lymphocytes from malignant hyperthermia-susceptible patients have an increased sensitivity to skeletal muscle ryanodine receptor activators. *J Biol Chem*. 2001;276:48077–48082.
227. Litman RS, Rosenberg H. Malignant hyperthermia: update on susceptibility testing. *JAMA*. 2005;293:2918–2924.
228. McKinney LC, Butler T, Mullen SP, Klein MG. Characterization of ryanodine receptor-mediated calcium release in human B cells: relevance to diagnostic testing for malignant hyperthermia. *Anesthesiology*. 2006;104:1191–1201.
229. Ording H, Foder B, Scharff O. Cytosolic free calcium concentrations in lymphocytes from malignant hyperthermia susceptible patients. *Br J Anaesth*. 1990;64:341–345.
230. Sei Y, Brandom BW, Bina S, et al. Patients with malignant hyperthermia demonstrate an altered calcium control mechanism in B lymphocytes. *Anesthesiology*. 2002;97:1052–1058.
231. Gareau PJ, Janzen EG, Towner RA, Stewart WA. In vivo 31P NMR spectroscopy studies of halothane induced porcine stress syndrome. No effect of C-phenyl N-tert-butyl nitrone (PBN). *Free Radic Res Commun*. 1993;19:43–50.
232. Payen JF, Bosson JL, Bourdon L, et al. Improved noninvasive diagnostic testing for malignant hyperthermia susceptibility from a combination of metabolites determined in vivo with 31P-magnetic resonance spectroscopy. *Anesthesiology*. 1993;78:848–855.
233. Nanson JK, Sheikh A. Anaesthesia for emergency caesarean section in a parturient with bleeding placenta praevia and a potentially malignant hyperthermia-susceptible fetus. *Int J Obstet Anesth*. 2000;9:276–278.
234. Stowell K, Pollock N, Langton E. Perinatal diagnosis of malignant hyperthermia susceptibility. *Anaesth Intensive Care*. 2007;35:454–455.
235. Girard T, John M, Schaefer C, Urwyler A. Perinatal diagnosis of malignant hyperthermia susceptibility. *Anesthesiology*. 2006;104:1353–1354.
236. Suggested Guidelines for Management of the Pregnant-Patient not Believed to be at Risk for Mh, but whose Partners is Susceptible to Malignant Hyperthermia. 2009. <https://www.mhaus.org/healthcare-professionals/mhaus-recommendations/parturient-with-mhs-partner/>. Accessed April 8, 2019.
237. Tombul T, Anlar O, Tuncer M, Huseyinoglu N, Eryonucu B. Impaired heart rate variability as a marker of cardiovascular autonomic

- dysfunction in multiple sclerosis. *Acta Neurologica Belgica*. 2011; 111:116–120.
238. Freedman MS, Thompson EJ, Deisenhammer F, et al. Recommended standard of cerebrospinal fluid analysis in the diagnosis of multiple sclerosis: a consensus statement. *Arch Neurol*. 2005;62:865–870.
239. Bader AM, Hunt CO, Datta S, Naulty JS, Ostheimer GW. Anesthesia for the obstetric patient with multiple sclerosis. *J Clin Anesth*. 1988;1:21–24.
240. Staikou C, Rekatsina M. Use of rocuronium and sugammadex under neuromuscular transmission monitoring in a patient with multiple sclerosis. *Saudi J Anesth*. 2017;11:472–475.
241. Bornemann-Cimenti H, Sivro N, Toft F, Halb L, Sandner-Kiesling A. Neuralgia anesthesia in patients with multiple sclerosis – a systematic review. *Braz J Anesthesiol (English Edition)*. 2016;67:404–410.
242. Ludolph AC, Brettschneider J, Weishaupt JH. Amyotrophic lateral sclerosis. *Curr Opin Neurol*. 2012;25:530–535.
243. Rothstein JD. Edaravone: a new drug approved for ALS. *Cell*. 2017;171:725.
244. Shimizu T, Kawata A, Kato S, et al. Autonomic failure in ALS with a novel SOD1 gene mutation. *Neurology*. 2000;54:1534–1537.
245. You TM, Kim S. Pulseless electrical activity during general anesthesia induction in patients with amyotrophic lateral sclerosis. *J Dent Anesth Pain Med*. 2017;17:235–240.
246. Rosenbaum KJ, Neigh JL, Strobel GE. Sensitivity to nondepolarizing muscle relaxants in amyotrophic lateral sclerosis: report of two cases. *Anesthesiology*. 1971;35:638–641.
247. Jacobs BC, Rothbarth PH, van der Meche FG, et al. The spectrum of antecedent infections in Guillain-Barre syndrome: a case-control study. *Neurology*. 1998;51:1110–1115.
248. Lawn ND, Fletcher DD, Henderson RD, Wolter TD, Wijdicks EF. Anticipating mechanical ventilation in Guillain-Barre syndrome. *Arch Neurol*. 2001;58:893–898.
249. Asbury AK. Diagnostic considerations in Guillain-Barre syndrome. *Ann Neurol*. 1981;(suppl 9):1–5.
250. Hughes RA, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barre syndrome. *Cochrane Database Syst Rev*. 2012;7:CD002063.
251. Asahina M, Kuwabara S, Suzuki A, Hattori T. Autonomic function in demyelinating and axonal subtypes of Guillain-Barre syndrome. *Acta Neurol Scand*. 2002;105:44–50.
252. McGrady EM. Management of labour and delivery in a patient with Guillain-Barre syndrome. *Anaesthesia*. 1987;42:899.
253. Steiner I, Argov Z, Cahan C, Abramsky O. Guillain-Barre syndrome after epidural anesthesia: direct nerve root damage may trigger disease. *Neurology*. 1985;35:1473–1475.
254. Brooks H, Christian AS, May AE. Pregnancy, anaesthesia and Guillain Barre syndrome. *Anaesthesia*. 2000;55:894–898.
255. Zochodne DW, Bolton CF, Wells GA, et al. Critical illness polyneuropathy. A complication of sepsis and multiple organ failure. *Brain*. 1987;110(Pt 4):819–841.
256. Bolton CF. Neuromuscular manifestations of critical illness. *Muscle Nerve*. 2005;32:140–163.
257. Dodson BA, Kelly BJ, Braswell LM, Cohen NH. Changes in acetylcholine receptor number in muscle from critically ill patients receiving muscle relaxants: an investigation of the molecular mechanism of prolonged paralysis. *Crit Care Med*. 1995;23:815–821.
258. Hermans G, Wilmer A, Meersseman W, et al. Impact of intensive insulin therapy on neuromuscular complications and ventilator dependency in the medical intensive care unit. *Am J Respir Crit Care Med*. 2007;175:480–489.
259. Gronert GA. Disuse atrophy with resistance to pancuronium. *Anesthesiology*. 1981;55:547–549.
260. O'Neill GN. Acquired disorders of the neuromuscular junction. *Int Anesthesiol Clin*. 2006;44:107–121.
261. Rudnik-Schneborn S, De Visser M, Zerres K. Spinal Muscular Atrophies. In: Engel A, Franzini-Armstrong C, eds. *Myology*. 3rd ed. New York: McGraw-Hill; 2004:1845–1864.
262. Charcot-Marie-Tooth disease. Genetics, clinical features, and diagnosis. *UpToDate*. 2018. <https://www.uptodate.com/contents/charcot-marie-tooth-disease-genetics-clinical-features-and-diagnosis>. Accessed April 8, 2019.
263. Ginz HF, Ummenhofer WC, Erb T, Urwyler A. [The hereditary motor-sensory neuropathy Charcot-Marie-Tooth disease: anesthesiologic management-case report with literature review]. *Anesthesist*. 2001;50:767–771.
264. Gratarola A, Mameli MC, Pelosi G. Total intravenous anaesthesia in Charcot-Marie-Tooth disease. Case report. *Minerva Anestesiol*. 1998;64:357–360.
265. Sugino S, Yamazaki Y, Nawa Y, Sato K, Sonoda H, Namiki A. [Anesthetic management for a patient with Charcot-Marie-Tooth disease using propofol and nitrous oxide]. *Masui*. 2002;51:1016–1019.
266. Baur CP, Schara U, Schlecht R, Georgieff M, Lehmann-Horn F. [Anesthesia in neuromuscular disorders. Part 2: specific disorders]. *Anesthesiol Intensivmed Notfallmed Schmerzther*. 2002;37:125–137.
267. Antognini JF. Anaesthesia for Charcot-Marie-Tooth disease: a review of 86 cases. *Can J Anaesth*. 1992;39:398–400.
268. Baranov D, TK, McClung H, Scarfo K, Hecker J. Neurological diseases. In: Fleisher L, ed. *Anesthesia and Uncommon Diseases*. 5th ed. Philadelphia, Pa: Saunders; 2006.
269. Pogson D, Telfer J, Wimbush S. Prolonged vecuronium neuromuscular blockade associated with Charcot Marie Tooth neuropathy. *Br J Anaesth*. 2000;85:914–917.
270. Naguib M, Samarkandi AH. Response to atracurium and mivacurium in a patient with Charcot-Marie-Tooth disease. *Can J Anaesth*. 1998;45:56–59.
271. Schmitt HJ, Munster T. Mivacurium-induced neuromuscular block in adult patients suffering from Charcot-Marie-Tooth disease. *Can J Anaesth*. 2006;53:984–988.
272. Reah G, Lyons GR, Wilson RC. Anaesthesia for caesarean section in a patient with Charcot-Marie-Tooth disease. *Anaesthesia*. 1998;53:586–588.
273. Scull T, Weeks S. Epidural analgesia for labour in a patient with Charcot-Marie-Tooth disease. *Can J Anaesth*. 1996;43:1150–1152.
274. Sugai K, Sugai Y. [Epidural anaesthesia for a patient with Charcot-Marie-Tooth disease, bronchial asthma and hypothyroidism]. *Masui*. 1989;38:688–691.
275. Tanaka S, Tsuchida H, Namiki A. [Epidural anesthesia for a patient with Charcot-Marie-Tooth disease, mitral valve prolapse syndrome and IIInd degree AV block]. *Masui*. 1994;43:931–933.
276. Schmitt HJ, Muenster T, Schmidt J. Central neural blockade in Charcot-Marie-Tooth disease. *Can J Anaesth*. 2004;51:1049–1050.
277. Dubowitz V. *Muscle Disorders in Childhood*. 2nd ed. Philadelphia, Pa: WB Saunders; 1995.
278. Dalakas M, Palace J, Rose M. The muscular dystrophies. In: Barnes P, Hilton-Jones D, eds. *Myopathies in Clinical Practice*. 1st ed. London: Martin Dunitz; 2003:59–83.
279. *Muscular Dystrophy*. 2017. <https://emedicine.medscape.com/article/1259041-overview>. Accessed April 8, 2019.
280. Emery A. Population frequencies of inherited neuromuscular diseases—a world survey. *Neuromuscul Disord*. 1991;1:19–29.
281. Sano M, Saito F, Yamamoto K, Tonomura A, Tsukagoshi H. Duchenne muscular dystrophy in a female with 45,X/46,XX chromosome constitution. *Jinrui Idengaku Zasshi*. 1987;32:257–262.
282. Urban M, Lahliou S. Muscle diseases. In: Fleisher L, ed. *Anesthesia and Uncommon Diseases*. Philadelphia, Pa: Saunders Elsevier; 2006:303–325.
283. Hoffman E. Dystrophin: the protein product of the Duchenne muscular dystrophy locus. *Cell*. 1987;51:919–928.
284. Leibowitz D, Dubowitz V. Intellect and behaviour in Duchenne muscular dystrophy. *Dev Med Child Neurol*. 1981;23:577–590.
285. Finsterer J, Stollberger C. The heart in human dystrophinopathies. *Cardiology*. 2003;99:1–19.
286. Perloff JK, Henze E, Schelbert HR. Alterations in regional myocardial metabolism, perfusion, and wall motion in Duchenne muscular dystrophy studied by radionuclide imaging. *Circulation*. 1984;69:33–42.
287. Morris P. Duchenne muscular dystrophy: a challenge for the anaesthetist. *Paediatr Anaesth*. 1997;7:1–4.
288. Hahn A, Bach JR, Delaubier A, Renardel-Irani A, Guillou C, Rideau Y. Clinical implications of maximal respiratory pressure determinations for individuals with Duchenne muscular dystrophy. *Arch Phys Med Rehabil*. 1997;78:1–6.
289. Ames WA, Hayes JA, Crawford MW. The role of corticosteroids in Duchenne muscular dystrophy: a review for the anesthetist. *Paediatr Anaesth*. 2005;15:3–8.
290. Kawaai H, Tanaka K, Yamazaki S. Continuous infusion propofol general anesthesia for dental treatment in patients with progressive muscular dystrophy. *Anesthesia Progress*. 2005;52:12–16.

291. Molyneux MK. Anaesthetic management during labour of a manifesting carrier of Duchenne muscular dystrophy. *Int J Obstet Anesth.* 2005;14:58–61.
292. Angermann C, Spes C, Pongratz D. [Cardiac manifestation of progressive muscular dystrophy of the Duchenne type]. *Zeitschrift für Kardiologie.* 1986;75:542–551.
293. Smith CL, Bush GH. Anaesthesia and progressive muscular dystrophy. *Br J Anaesth.* 1985;57:1113–1118.
294. Webster R. *Respiratory Function as a Measure of Muscle Strength in Young Boys with Duchenne Muscular Dystrophy.* School of Women and Children's Health, University of N.S.W; 2003.
295. Stevens RD. Neuromuscular disorders and anaesthesia. *Curr Opin Anaesthesiol.* 2001;14:693–698.
296. Breucking E, Reimnitz P, Schara U, Mortier W. [Anesthetic complications. The incidence of severe anesthetic complications in patients and families with progressive muscular dystrophy of the Duchenne and Becker types]. *Anaesthesia.* 2000;49:187–195.
297. Benson ER, Thomson JD, Smith BG, Banta JV. Results and morbidity in a consecutive series of patients undergoing spinal fusion for neuromuscular scoliosis. *Spine.* 1998;23:2308–2317; discussion 18.
298. Miller F, Moseley CF, Koreska J. Spinal fusion in Duchenne muscular dystrophy. *Dev Med Child Neurol.* 1992;34:775–786.
299. Jenkins JG, Bohn D, Edmonds JF, Levison H, Barker GA. Evaluation of pulmonary function in muscular dystrophy patients requiring spinal surgery. *Crit Care Med.* 1982;10:645–649.
300. Stoelting R, Dierdorf S. *Anesthesia and Co-Existing Disease.* Philadelphia, Pa: Churchill Livingstone; 2002:505–549.
301. Gurnaney H, Brown A, Litman RS. Malignant hyperthermia and muscular dystrophies. *Anesth Analg.* 2009;109:1043–1048.
302. Farell P. Anesthesia-induced rhabdomyolysis causing cardiac arrest: case report and review of anesthesia and the dystrophinopathies. *Anesth Intensive Care.* 1994;22: 597–561.
303. Schummer W, Schummer C. Acute heart failure during spinal surgery in a boy with Duchenne muscular dystrophy. *Br J Anaesth.* 2004;92:149; author reply -50.
304. Ririe DG, Shapiro F, Sethna NF. The response of patients with Duchenne's muscular dystrophy to neuromuscular blockade with vecuronium. *Anesthesiology.* 1998;88:351–354.
305. Yemen TA, McClain C. Muscular dystrophy, anesthesia and the safety of inhalational agents revisited: again. *Paediatr Anaesth.* 2006;16:105–108.
306. Fairfield MC. Increased propofol requirements in a child with Duchenne muscular dystrophy. *Anesthesia.* 1993;48:1013.
307. Murat I, Esteve C, Montay G, Delleur MM, Gaudiche O, Saint-Maurice C. Pharmacokinetics and cardiovascular effects of bupivacaine during epidural anesthesia in children with Duchenne muscular dystrophy. *Anesthesiology.* 1987;67:249–252.
308. Kirschner J, Bonnemann CG. The congenital and limb-girdle muscular dystrophies: sharpening the focus, blurring the boundaries. *Arch Neurol.* 2004;61:189–199.
309. Moro C, Dangelser G, Veyckemans F. [Anesthetic management of a child with delta sarcoglycanopathy]. *Ann Fr Anesth Reanim.* 2007;26:359–362.
310. Egi M, Tokioka H, Chikai T, et al. [Propofol anesthesia for a patient with progressive muscular dystrophy]. *Masui.* 2002;51:196–198.
311. Pash MP, Balaton J, Eagle C. Anaesthetic management of a parturient with severe muscular dystrophy, lumbar lordosis and a difficult airway. *Can J Anaesth.* 1996;43:959–963.
312. Myotonic dystrophy: *Etiology, clinical features, and diagnosis.* 2018. <https://www.uptodate.com/contents/myotonic-dystrophy-etiology-clinical-features-and-diagnosis>. Accessed April 8, 2019.
313. Parness J, Bandschapp O, Girard T. The myotonias and susceptibility to malignant hyperthermia. *Anesth Analg.* 2009;109:1054–1064.
314. Lehmann-Horn F, Iaizzo PA. Are myotonias and periodic paralyses associated with susceptibility to malignant hyperthermia? *Br J Anaesth.* 1990;65:692–697.
315. Mathieu J, Allard P, Gobeil G, Girard M, De Braekeleer M, Begin P. Anesthetic and surgical complications in 219 cases of myotonic dystrophy. *Neurology.* 1997;49:1646–1650.
316. Matsuki Y, Hirose M, Tabata M, Nobukawa Y, Shigemi K. The use of sugammadex in a patient with myotonic dystrophy. *Eur J Anaesthesiol. (EJA).* 2011;28:145–146.
317. Stouras P, Krikava I, Seidlova J, et al. Sugammadex in a parturient with myotonic dystrophy. *Br J Anaesth.* 2013;110:657–658.
318. Ahmed S, Naguib A, Tumin D, Tobias JD. Use of sugammadex in a patient with myotonic dystrophy. *Cardiol Res.* 2018;9:50–52.
319. Catena V, Del Monte DD, Rubini A, et al. Anesthesia and myotonic dystrophy (Steinert's syndrome). The role of total intravenous anesthesia with propofol, cisatracurium and remifentanil. Case report. *Minerva Anestesiol.* 2007;73:475–479.
320. Lehmann-Horn F, Reinhardt R, Jurkat-Rott K. Altered excitability of the cell membrane. In: Engel A, Franzini-Armstrong C, eds. *Myology.* New York: McGraw-Hill; 2004:1257–1300.
321. Farbu E, Softeland E, Bindoff LA. Anaesthetic complications associated with myotonia congenita: case study and comparison with other myotonic disorders. *Acta Anaesthesiol Scand.* 2003;47:630–634.
322. Newberg LA, Lambert EH, Gronert GA. Failure to induce malignant hyperthermia in myotonic goats. *Br J Anaesth.* 1983;55:57–60.
323. Beck CL, Fahlke C, George AL. Molecular basis for decreased muscle chloride conductance in the myotonic goat. *Proc Natl Acad Sci U S A.* 1996;93:11248–11252.
324. Rosenbaum HK, Miller JD. Malignant hyperthermia and myotonic disorders. *Anesthesiol Clin North America.* 2002;20:623–664.
325. North K. Congenital myopathies. In: Engel A, Franzini-Armstrong C, eds. *Myology.* New York: McGraw-Hill; 2004. 1473–1433.
326. Herman GE, Finegold M, Zhao W, de Gouyon B, Metzenberg A. Medical complications in long-term survivors with X-linked myotubular myopathy. *J Pediatr.* 1999;134:206–214.
327. Breslin D, Reid J, Hayes A, Mirakhur RK. Anaesthesia in myotubular (centronuclear) myopathy. *Anaesthesia.* 2000;55:471–474.
328. Costi D, van der Walt JH. General anaesthesia in an infant with X-linked myotubular myopathy. *Paediatr Anaesth.* 2004;14:964–968.
329. Garcia-Aguado R, Nunez M, Tommasi Rosso M, Vivo M, Gil F, Bolinches R. [Myotubular myopathy (centronuclear) and expected difficult intubation. Anesthetic management]. *Rev Esp Anestesiol Reanim.* 1994;41:302–303.
330. Gottschalk A, Heiman-Patterson T, deQuevedo R, Quinn PD. General anaesthesia for a patient with centronuclear (myotubular) myopathy. *Anesthesiology.* 1998;89:1018–1020.
331. Schmid E, Johr M, Berger TM. X-linked myotubular myopathy: anaesthetic management for muscle biopsy. *Paediatr Anaesth.* 2006;16:218–220.
332. Tokarz A, Gaszynski T, Gaszynski W, Arkuszewski P. General anaesthesia with remifentanil and propofol for a patient with centronuclear(myotubular)myopathy. *Eur J Anaesthesiol.* 2002;19:842–844.
333. Dorchies OM, Laporte J, Wagner S, et al. Normal innervation and differentiation of X-linked myotubular myopathy muscle cells in a nerve-muscle coculture system. *Neuromuscul Disord.* 2001;11:736–746.
334. *Glucose-6-Phosphatase Deficiency (Glycogen Storage Disease I, Von Gierke Disease);* 2018. <https://www.uptodate.com/contents/glucose-6-phosphatase-deficiency-glycogen-storage-disease-i-von-gierke-disease>. Accessed April 8, 2019.
335. Rake JP, Visser G, Labrune P, Leonard JV, Ullrich K, Smit GP. Guidelines for management of glycogen storage disease type I - European Study on Glycogen Storage Disease Type I (ESGSD I). *Eur J Pediatr.* 2002;161(suppl 1):S112–S119.
336. Visser G, Rake JP, Labrune P, et al. Consensus guidelines for management of glycogen storage disease type 1b - European Study on Glycogen Storage Disease Type 1. *Eur J Pediatr.* 2002;161(suppl 1):S120–S123.
337. Kakinohana M, Tokumine J, Shimabukuro T, Taira Y, Okuda Y. [Patient-controlled sedation using propofol for a patient with von Gierke disease]. *Masui.* 1998;47:1104–1108.
338. Kawai T. [Anesthetic management for an emergency operation in a patient with von Gierke disease]. *Masui.* 2005;54:924–925.
339. Loonen MC, Busch HF, Koster JF, et al. A family with different clinical forms of acid maltase deficiency (glycogenosis type II): biochemical and genetic studies. *Neurology.* 1981;31:1209–1216.
340. Engel A, Hirschhorn R, Huie M. Acid maltase deficiency. In: Engel A, Franzini-Armstrong C, eds. *Myology.* New York: McGraw-Hill; 2004:1559–1586.
342. Ehlers KH, Hagstrom JW, Lukas DS, Redo SF, Engle MA. Glycogen storage disease of the myocardium with obstruction to left ventricular outflow. *Circulation.* 1962;25:96. 109.

343. Bulkley BH, Hutchins GM. Pompe's disease presenting as hypertrophic cardiomyopathy with Wolff-Parkinson-White syndrome. *Am Heart J.* 1978;96:246–252.
344. Weinik M, King F. Acid maltase deficiency myopathy. *eMedicine.* 2006.
345. Makos MM, McComb RD, Hart MN, Bennett DR. Alpha-glucosidase deficiency and basilar artery aneurysm: report of a sibship. *Ann Neurol.* 1987;22:629–633.
346. Gitlin MC, Jahr JS, Margolis MA, McCain J. Is mivacurium chloride effective in electroconvulsive therapy? A report of four cases, including a patient with myasthenia gravis. *Anesth Analg.* 1993;77:392–394.
347. Kotani N, Hirota K, Anzawa N, Takamura K, Sakai T, Matsuki A. Motor and sensory disability has a strong relationship to induction dose of thiopental in patients with the hypertropic variety of Charcot-Marie-Tooth syndrome. *Anesth Analg.* 1996;82:182–186.
348. Ing RJ, Cook DR, Bengur RA, et al. Anaesthetic management of infants with glycogen storage disease type II: a physiological approach. *Paediatr Anaesth.* 2004;14:514–519.
349. McFarlane HJ, Soni N. Pompe's disease and anaesthesia. *Anaesthesia.* 1986;41:1219–1224.
350. Mohiddin SA, Fananapazir L. Systolic compression of epicardial coronary and intramural arteries in children with hypertrophic cardiomyopathy. *Tex Heart Inst J.* 2002;29:290–298.
351. DiMauro S, Bonilla E. Mitochondrial encephalomyopathies. In: Engel A, Franzini-Armstrong C, eds. *Myology.* 3rd ed. New York: McGraw-Hill; 2004:1623–1662.
352. Siciliano G, Volpi L, Piazza S, Ricci G, Mancuso M, Murri L. Functional diagnostics in mitochondrial diseases. *Biosci Rep.* 2007;27:53–67.
353. Wisely NA, Cook PR. General anaesthesia in a man with mitochondrial myopathy undergoing eye surgery. *Eur J Anaesthesiol.* 2001;18:333–335.
354. Mehdiratta MM, Agarwal P, Tatke M, Krishnamurthy M. Neurological mitochondrial cytopathies. *Neurol India.* 2002;50:162–167.
355. Swash M, Schwartz MS, Sargeant MK. The significance of ragged-red fibres in neuromuscular disease. *J Neurol Sci.* 1978;38:347–355.
356. Shipton EA, Prosser DO. Mitochondrial myopathies and anaesthesia. *Eur J Anaesthesiol.* 2004;21:173–178.
357. Swash M, Schwartz MS, Sargeant MK. The significance of ragged-red fibres in neuromuscular disease. *J Neurol Sci.* 1978;38:347–355.
358. Amato AA, Brown RH. Muscle dystrophies and other muscle diseases. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, eds. *Harrison's Principles of Internal Medicine.* 18th ed. McGraw-Hill; 2012.
359. DiMauro S, Bonilla E. Mitochondrial encephalomyopathies. In: Engel AG, Franzini-Armstrong C, eds. *Myology.* 3rd ed. McGraw-Hill; 2004:1623–1662.
360. Allison KR. Muscular dystrophy versus mitochondrial myopathy: the dilemma of the undiagnosed hypotonic child. *Paediatric Anaesthesia.* 2007;17:1–6.
361. Hara K, Sata T, Shigematsu A. Anesthetic management for cardioverter-defibrillator implantation in a patient with Kearns-Sayre syndrome. *J Clin Anesth.* 2004;16:539–541.
362. Maurtua M, Torres A, Ibarra V, DeBoer G, Dolak J. Anesthetic management of an obstetric patient with MELAS syndrome: case report and literature review. *Int J Obstet Anesth.* 2008;17:370–373.
363. Levy E, Muravchick S. Mitochondrial diseases. In: Fleisher L, ed. *Anesthesia and Uncommon Diseases.* Philadelphia, Pa: Saunders Elsevier; 2006:455–467.
364. James RH. Thiopentone and ophthalmoplegia plus. *Anaesthesia.* 1985;40:88.
365. James RH. Induction agent sensitivity and ophthalmoplegia plus. *Anaesthesia.* 1986;41:216.
366. Gurrieri C, Kivela JE, Bojanic K, et al. Anesthetic considerations in mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome: a case series. *Can J Anaesth.* 2011;58:751–763.
367. Footitt EJ, Sinha MD, Raiman JA, Dhawan A, Moganasundram S, Champion MP. Mitochondrial disorders and general anaesthesia: a case series and review. *Br J Anaesth.* 2008;100:436–441.
368. Driessens J, Willems S, Dercksen S, Giele J, van der Staak F, Smeitink J. Anesthesia-related morbidity and mortality after surgery for muscle biopsy in children with mitochondrial defects. *Paediatr Anaesth.* 2007;17:16–21.
369. Burns AM, Shelly MP. Anaesthesia for patients with mitochondrial myopathy. *Anaesthesia.* 1989;44:975–977.
370. Kelly A, O'Connor M. Mitochondrial myopathy and anaesthesia. *Anaesthesia.* 1990;45:596.
371. Ramchandra DS, Anisya V, Gourie-Devi M. Ketamine monoanesthesia for diagnostic muscle biopsy in neuromuscular disorders in infancy and childhood: floppy infant syndrome. *Can J Anaesth.* 1990;37:474–476.
372. Guasch E, Civantos B, Aguilar JM, Torres MD, Gilsanz F. Progressive external ophthalmoplegia and ambulatory remifentanil-propofol based anaesthesia. *Anaesthesia.* 2003;58:607–608.
373. Sharma AD, Erb T, Schulman SR, Sreeram G, Slaughter TF. Anaesthetic considerations for a child with combined Prader-Willi syndrome and mitochondrial myopathy. *Paediatr Anaesth.* 2001;11:488–490.
374. Vanlander AV, Jorens PG, Smet J, et al. Inborn oxidative phosphorylation defect as risk factor for propofol infusion syndrome. *Acta Anaesthesiol Scand.* 2012;56:520–525.
375. Stowe DF, Kevin LG. Cardiac preconditioning by volatile anesthetic agents: a defining role for altered mitochondrial bioenergetics. *Antioxid Redox Signal.* 2004;6:439–448.
376. Stadnicka A, Marinovic J, Ljubkovic M, Bienengraeber MW, Bosnjak ZJ. Volatile anesthetic-induced cardiac preconditioning. *J Anesth.* 2007;21:212–219.
377. Wallace JJ, Perndt H, Skinner M. Anaesthesia and mitochondrial disease. *Paediatr Anaesth.* 1998;8:249–254.
378. Lauwers MH, Van Lersberghe C, Camu F. Inhalation anaesthesia and the Kearns-Sayre syndrome. *Anaesthesia.* 1994;49:876–878.
379. Morgan PG, Hoppel CL, Sedensky MM. Mitochondrial defects and anesthetic sensitivity. *Anesthesiology.* 2002;96:1268–1270.
380. Allen GC. Bispectral index and mitochondrial myopathies. *Anesthesiology.* 2003;98:282; author reply 3.
381. Frei FJ, Haemmerle MH, Brunner R, Kern C. Minimum alveolar concentration for halothane in children with cerebral palsy and severe mental retardation. *Anaesthesia.* 1997;52:1056–1060.
382. Naguib M, el Dawlatly AA, Ashour M, al-Bunyan M. Sensitivity to mivacurium in a patient with mitochondrial myopathy. *Anesthesiology.* 1996;84:1506–1509.
383. Finsterer J, Stratil U, Bittner R, Sporn P. Increased sensitivity to rocuronium and atracurium in mitochondrial myopathy. *Can J Anaesth.* 1998;45:781–784.
384. Sharma AD, Erb T, Schulman SR, Sreeram G, Slaughter TF. Anaesthetic considerations for a child with combined Prader-Willi syndrome and mitochondrial myopathy. *Paediatr Anaesth.* 2001;11:488–490.
385. D'Ambra MN, Dedrick D, Savarese JJ. Kearns-Sayre syndrome and pancuronium–succinylcholine-induced neuromuscular blockade. *Anesthesiology.* 1979;51:343–345.
386. Wiesel S, Bevan JC, Samuel J, Donati F. Vecuronium neuromuscular blockade in a child with mitochondrial myopathy. *Anesth Analg.* 1991;72:696–699.
387. Rowe RW, Helander E. Anesthetic management of a patient with systemic carnitine deficiency. *Anesth Analg.* 1990;71:295–297.
388. Rosaeg OP, Morrison S, MacLeod JP. Anaesthetic management of labour and delivery in the parturient with mitochondrial myopathy. *Can J Anaesth.* 1996;43:403–407.
389. Hsiao PN, Cheng YJ, Tseng HC, Chuang YH, Kao PF, Tsai SK. Spinal anesthesia in MELAS syndrome: a case with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes. *Acta Anaesthesiol Sin.* 2000;38:107–110.
390. Sasano N, Fujita Y, So M, Sobue K, Sasano H, Katsuya H. Anesthetic management of a patient with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) during laparotomy. *J Anesth.* 2007;21:72–75.
391. Farag E, Argalious M, Narouze S, DeBoer GE, Tome J. The anesthetic management of ventricular septal defect (VSD) repair in a child with mitochondrial cytopathy. *Can J Anaesth.* 2002;49:958–962.
392. Sasano N, Tamura T, Azami T, Sasano H. Severe hyponatremia occurring after surgical stress in a patient with mitochondrial disease. *J Anesth.* 2009;23:587–590.
393. Kubota H, Tanabe Y, Takanashi J, Kohno Y. Episodic hyponatremia in mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS). *J Child Neurol.* 2005;20:116–120.
394. Vincent A, Palace J, Hilton-Jones D. Myasthenia gravis. *Lancet.* 2001;357:2122–2128.
395. Lindstrom JM. Acetylcholine receptors and myasthenia. *Muscle Nerve.* 2000;23:453–477.

396. *Anesthesia for the Patient with Myasthenia Gravis*. 2018. <https://www.uptodate.com/contents/anesthesia-for-the-patient-with-myasthenia-gravis>. Accessed April 8, 2019.
397. Eisenkraft JB, Book WJ, Mann SM, Papatestas AE, Hubbard M. Resistance to succinylcholine in myasthenia gravis: a dose-response study. *Anesthesiology*. 1988;69:760–763.
398. Baraka A. Suxamethonium block in the myasthenic patient. Correlation with plasma cholinesterase. *Anesthesia*. 1992;47:217–219.
399. Seigne RD, Scott RP. Mivacurium chloride and myasthenia gravis. *Br J Anaesth*. 1994;72:468–469.
400. Kim JM, Mangold J. Sensitivity to both vecuronium and neostigmine in a sero-negative myasthenic patient. *Br J Anaesth*. 1989;63:497–500.
401. Sungur Ulke Z, Yavru A, Camci E, Ozkan B, Toker A, Senturk M. Rocuronium and sugammadex in patients with myasthenia gravis undergoing thymectomy. *Acta Anaesthesiol Scand*. 2013;57:745–748.
402. de Boer HD, van Egmond J, Driessen JJ, Booij LH. A new approach to anesthesia management in myasthenia gravis: reversal of neuromuscular blockade by sugammadex. *Rev Esp Anestesiol Reanim*. 2010;57:181–184.
403. BRIDION(R) (sugammadex) Injection - First and Only Selective Relaxant Binding Agent - Approved in European Union. 2008. <https://www.fiercebiotech.com/biotech/bridion-r-sugammadex-injection-first-and-only-selective-relaxant-binding-agent-approved>. Accessed April 8, 2019.
404. Baraka A. Onset of neuromuscular block in myasthenic patients. *Br J Anaesth*. 1992;69:227–228.
405. Abel M, Eisenkraft JB. Anesthetic implications of myasthenia gravis. *Mt Sinai J Med*. 2002;69:31–37. New York.
406. Takamori M, Maruta T, Komai K. Lambert-Eaton myasthenic syndrome as an autoimmune calcium-channelopathy. *Neurosci Res*. 2000;36:183–191.
407. Hewett SJ, Atchison WD. Serum and plasma from patients with Lambert-Eaton Myasthenic Syndrome reduce depolarization-dependent uptake of 45Ca2+ into rat cortical synaptosomes. *Brain Res*. 1991;566:320–324.
408. Burge JA, Hanna MG. Novel insights into the pathomechanisms of skeletal muscle channelopathies. *Curr Neurol Neurosci Rep*. 2012;12:62–69.
409. Lehmann-Horn F, Rudel R, Jurkat-Rott K. Nondystrophic myotonias and periodic paralyses. In: Engel AG, Franzini-Armstrong C, eds. *Myology*. McGraw-Hill; 2004:1257–1300.
410. Jurkat-Rott K, Lehmann-Horn F. Paroxysmal muscle weakness: the familial periodic paralyses. *J Neurol*. 2006;253:1391–1398.
411. Chinnery PF, Walls TJ, Hanna MG, Bates D, Fawcett PR. Normokalemic periodic paralysis revisited: does it exist? *Ann Neurol*. 2002;52:251–252.
412. Song YW, Kim SJ, Heo TH, Kim MH, Kim JB. Normokalemic periodic paralysis is not a distinct disease. *Muscle Nerve*. 2012.
413. Vicart S, Sternberg D, Fournier E, et al. New mutations of SCN4A cause a potassium-sensitive normokalemic periodic paralysis. *Neurology*. 2004;63:2120–2127.
414. Visconti CM, Ptacek LJ, Dudley D. Anesthetic management of familial hypokalemic periodic paralysis during parturition. *Anesth Analg*. 1999;88:1081–1082.
415. Robinson JE, Morin VI, Douglas MJ, Wilson RD. Familial hypokalemic periodic paralysis and Wolff-Parkinson-White syndrome in pregnancy. *Can J Anaesth*. 2000;47:160–164.
416. Griggs RC, Engel WK, Resnick JS. Acetazolamide treatment of hypokalemic periodic paralysis. Prevention of attacks and improvement of persistent weakness. *Ann Intern Med*. 1970;73:39–48.
417. Bendaouhou S, Cummins TR, Griggs RC, Fu YH, Ptacek LJ. Sodium channel inactivation defects are associated with acetazolamide-exacerbated hypokalemic periodic paralysis. *Ann Neurol*. 2001;50:417–420.
418. LoVecchio F, Jacobson S. Approach to generalized weakness and peripheral neuromuscular disease. *Emerg Med Clin North Am*. 1997;15:605–623.
419. Lin SH, Huang CL. Mechanism of thyrotoxic periodic paralysis. *J Am Soc Nephrol*. 2012;23:985–988.
420. Depoix JP, Julliard JM, Aubry P. Propofol-remifentanil target-controlled anesthesia in a patient with hyperkalemic familial periodic paralysis. *Anesth Analg*. 2004;99:302.
421. Aouad R, Atanassoff PG. Epidural anesthesia in a patient with hyperkalemic periodic paralysis undergoing orthopedic surgery. *Can J Anaesth*. 2004;51:92.
422. Ashwood EM, Russell WJ, Burrow DD. Hyperkalaemic periodic paralysis and anaesthesia. *Anaesthesia*. 1992;47:579–584.
423. Aarons JJ, Moon RE, Camporesi EM. General anesthesia and hyperkalemic periodic paralysis. *Anesthesiology*. 1989;71:303–304.
424. Cone AM, Sansome AJ. Propofol in hyperkalaemic periodic paralysis. *Anaesthesia*. 1992;47:1097.
425. Weller JF, Elliott RA, Pronovost PJ. Spinal anesthesia for a patient with familial hyperkalemic periodic paralysis. *Anesthesiology*. 2002;97:259–260.
426. Barker MC. Combined spinal/general anesthesia with postoperative femoral nerve block for total knee replacement in a patient with familial hyperkalemic periodic paralysis: a case report. *AANA J*. 2010;78:191–194.
427. Silen JN, Discavage WJ. Anesthetic management of hypokalemic periodic paralysis. *Anesthesiology*. 1975;43:489–490.
428. Melnick B, Chang JL, Larson CE, Bedger RC. Hypokalemic familial periodic paralysis. *Anesthesiology*. 1983;58:263–265.
429. Rooney RT, Shanahan EC, Sun T, Nally B. Atracurium and hypokalemic familial periodic paralysis. *Anesth Analg*. 1988;67:782–783.
430. Hofer C, Zalunardo MP, Zollinger A. Total intravenous anaesthesia in a patient with familial hypokalaemic periodic paralysis. *Anesthesia*. 2001;56:1082–1085.
431. Chitra S, Korula G. Anaesthetic management of a patient with hypokalemic periodic paralysis- a case report. *Indian J Anaesth*. 2009;53:226–229.
432. Visconti CM, Ptacek LJ, Dudley D. Anesthetic management of familial hypokalemic periodic paralysis during parturition. *Anesth Analg*. 1999;88:1081–1082.
433. Parness J, Bandschapp O, Girard T. The myotonias and susceptibility to malignant hyperthermia. *Anesth Analg*. 2009;109:1054–1064.
434. Lambert C, Blanloel Y, Horber RK, Berard L, Reyford H, Pinaud M. Malignant hyperthermia in a patient with hypokalemic periodic paralysis. *Anesth Analg*. 1994;79:1012–1014.
435. Rajabally YA, El Lahawi M. Hypokalemic periodic paralysis associated with malignant hyperthermia. *Muscle Nerve*. 2002;25:453–455.
436. Marchant CL, Ellis FR, Halsall PJ, Hopkins PM, Robinson RL. Mutation analysis of two patients with hypokalemic periodic paralysis and suspected malignant hyperthermia. *Muscle Nerve*. 2004;30:114–117.
437. Neuman GG, Kopman AF. Dyskalemic periodic paralysis and myotonia. *Anesth Analg*. 1993;76:426–428.

BECKY SCHROEDER, JONATHAN MARK, and ATILIO BARBEITO

KEY POINTS

- Monitoring of the electrocardiogram (ECG) provides continuous monitoring of heart rate, identification of arrhythmias and conduction abnormalities, and detection of myocardial ischemia.
- Accurate and reliable ECG monitoring requires attention to lead placement and selection, choice of filter, and gain that will influence the displayed ECG tracing.
- An anterolateral precordial lead (V_3 , V_4 , or V_5) should be selected for the most sensitive detection of myocardial ischemia.
- Demand-mediated subendocardial ischemia resulting in ST-segment depression is the most commonly observed form of perioperative ischemia. ST-segment depression is most commonly observed in an anterolateral precordial lead regardless of the coronary territory responsible.
- Supply-mediated transmural ischemia resulting in ST-segment elevation is uncommonly observed intraoperatively except during cardiac operations. In contrast to ST-segment depression, ST-segment elevation is indicative of the myocardial territory and coronary artery involved.
- Most automated noninvasive arterial blood pressure measuring devices use an oscillometric measurement technique and rarely cause complications. Caution should be exercised in patients who cannot complain of arm pain, those with irregular rhythms that force repeated cuff inflation, and those receiving anticoagulant therapy.
- The Allen test for palmar arch collateral arterial flow is not a reliable method to predict complications from radial artery cannulation. Despite the absence of anatomic collateral flow at the elbow, brachial artery catheterization for perioperative blood pressure monitoring is a safe alternative to radial or femoral arterial catheterization.
- The accuracy of a directly recorded arterial pressure waveform is determined by the natural frequency and damping coefficient of the pressure monitoring system. Optimal dynamic response of the system will be achieved when the natural frequency is high, thereby allowing accurate pressure recording across a wide range of damping coefficients.
- The preferred position for alignment (or “leveling”) of external pressure transducers for measuring arterial or central venous pressure (CVP), which eliminates confounding hydrostatic pressure artifacts, lies approximately 5 cm posterior to the sternomanubrial junction. The more conventional location for the reference level used for hemodynamic monitoring including central venous and pulmonary artery pressures, is the mid-thoracic level, which corresponds most closely to the mid-left atrial position and is located halfway between the anterior sternum and the bed surface in the supine patient.
- Because of wave reflection and other physical phenomena, the arterial blood pressure recorded from peripheral sites has a wider pulse pressure than when measured more centrally.
- Dynamic measures of cardiac preload, such as stroke volume and pulse pressure variation, are better predictors of intravascular volume responsiveness than static indicators, such as CVP and pulmonary capillary wedge pressure.
- Selecting the best site, catheter, and method for safe and effective central venous cannulation requires that the physician consider the purpose of catheterization, the patient’s underlying medical condition, the intended operation, and the skill and experience of the physician performing the procedure. Right internal jugular vein cannulation is preferred due to its consistent, predictable anatomic location and its relative ease of access intraoperatively.
- Mechanical complications from central venous catheters can be decreased by the use of ultrasound vessel localization, venous pressure measurement before large catheter insertion, and radiographic confirmation that the catheter tip lies outside the pericardium and parallel to the walls of the superior vena cava.
- CVP is the result of a complex and diverse interplay among many different physiologic variables, the main ones being venous return and cardiac function. No simple relationship exists between CVP and circulating blood volume. Despite this, important pathophysiologic information can be obtained by careful assessment of the CVP waveform morphology.
- Catheter misuse and data misinterpretation are among the most common complications of central venous and pulmonary artery catheters.
- Pulmonary artery wedge pressure is a delayed and damped reflection of left atrial pressure. The wedge pressure provides a close estimate for pulmonary capillary pressure in many cases, but it may underestimate capillary pressure when postcapillary pulmonary vascular resistance is increased, as in patients with sepsis.

- Use of central venous, pulmonary artery diastolic, or pulmonary artery wedge pressures as estimates of left ventricular preload is subject to many confounding factors, including changes in diastolic ventricular compliance and juxtacardiac pressure.
- Pulmonary artery catheter monitoring has not been shown to improve patient outcomes. Reasons cited for these results include misinterpretation of catheter-derived data and failure of hemodynamic therapies that are guided by specific hemodynamic indices.
- Thermodilution cardiac output monitoring, the most widely used clinical technique, is subject to measurement errors introduced by rapid intravenous fluid administration, intracardiac shunts, and tricuspid valve regurgitation.
- Mixed venous hemoglobin oxygen saturation is a measure of the adequacy of cardiac output relative to body oxygen requirements. This measurement is also dependent on the arterial hemoglobin oxygen saturation and hemoglobin concentration.

Introduction to Cardiovascular Monitoring: Focused Physical Examination

Electronic devices currently provide the vast majority of information used in monitoring a patient's cardiovascular status. However, the physician's senses, augmented by clinical context, continue to provide global insight into the patient's condition and remain critical in evaluating, and interpreting data derived from other sources.¹ Manual palpation of an arterial pulse will differentiate true asystole from monitoring artifact more efficiently than troubleshooting any monitor. Regardless of the manner used, though, it is important to understand the strengths and limitations of monitoring techniques.

Heart Rate and Pulse Rate Monitoring

The ability to estimate the heart rate quickly with a "finger on the pulse" is as important as this expression is common despite near-universal use of electronic devices for continuous monitoring. The electrocardiogram (ECG) is the most common heart rate monitoring method used in the operating room, even though any device measuring the period of the cardiac cycle will suffice. Accurate detection of the R wave and measurement of the interval from the peak of one QRS complex to the peak of the next on an ECG (R-R interval) serve as the basis from which digitally displayed values are derived and periodically updated (e.g., at 5- to 15-second intervals) (Fig. 36.1).²

The distinction between heart rate and pulse rate lies in the difference between electrical depolarization with systolic contraction of the heart (heart rate) and a detectable peripheral arterial pulsation (pulse rate). Pulse deficit describes the extent to which the pulse rate is less than the heart rate and may arise in conditions such as atrial fibrillation in which stroke volume is periodically compromised by a very short R-R interval to such an extent that no arterial pulse is detectable for that systolic ejection. Electrical-mechanical dissociation and pulseless electrical activity are extreme examples of pulse deficit in which cardiac contraction is completely unable to generate a palpable peripheral pulse. The heart rate is reported from the ECG trace and the pulse rate from the pulse oximeter plethysmograph

or arterial blood pressure monitor. Considering both in monitoring and clinical evaluation improves accuracy and reduces measurement errors and false alarms.³

Electrocardiography Monitoring

The value and importance of intraoperative monitoring of the ECG is evidenced by its requirement as a basic circulatory monitoring standard by the American Society of Anesthesiologists (ASA):⁴ "Every patient receiving anesthesia shall have the ECG continuously displayed from the beginning of anesthesia until preparing to leave the anesthetizing location." Similar recommendations have been recently updated by the American Heart Association (AHA) to guide indications, duration, and implementation of ECG monitoring in hospitalized patients outside of the operating room.⁵

The three primary reasons for ECG monitoring are continuous monitoring of heart rate, identification of arrhythmias and conduction abnormalities, and detection of myocardial ischemia. Furthermore, with many patients coming to surgery with pacemakers or implantable cardiac defibrillators in place, the ECG monitor enables the anesthesiologist to follow the proper function of these devices during the perioperative period. (Perioperative management of these devices is described in Chapter 38.) In order for bedside ECG monitoring to be accurate and effective, the clinician must attend to proper lead placement and selection, filter mode, and gain adjustment.

ELECTROCARDIOGRAM LEAD PLACEMENT AND SELECTION

Standard Lead Systems

Current operating room and intensive care monitoring systems have five leads that allow monitoring of the standard limb leads (I, II, III), the augmented limb leads (aVR, aVL, aVF), and a single precordial lead (V₁, V₂, V₃, V₄, V₅, or V₆). Typically, two of these 12 standard leads are simultaneously displayed on the bedside monitor. Historically, the augmented limb leads and precordial leads were described as *unipolar*, whereas the standard limb leads were described as *bipolar*. A recent scientific statement from the AHA and others⁶ discourages this distinction because in effect, all the lead configurations are effectively bipolar in their recording of surface electrical potentials.



Fig. 36.1 Digital heart rate (HR) displays may fail to warn of dangerous bradyarrhythmias. Direct observation of the electrocardiogram (ECG) and the arterial blood pressure traces reveals complete heart block and a 4-second period of asystole, whereas the digital display reports an HR of 49 beats/min. Note that the ECG filter (arrow) corrects the baseline drift so that the trace remains on the recording screen. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

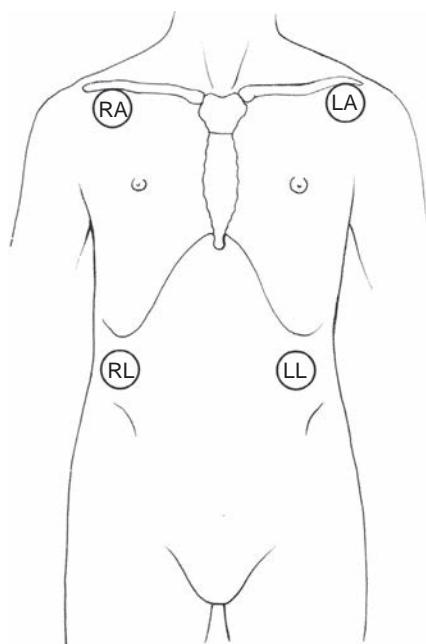


Fig. 36.2 Standard ECG limb lead placement for patient monitoring. LA, Left arm; LL, left leg; RA, right arm; RL, right leg. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

Based on AHA guidelines, ECG monitoring leads have a standard color-coding system: right arm (white), left arm (black), right leg (green), left leg (red), and precordial lead (brown). Of note, this color scheme is not the same used internationally or the one recommended by the International Electrotechnical Commission. Unlike recording a standard 12-lead ECG, where the limb leads are attached to electrodes placed on the wrists and ankles or arms and legs, when monitoring patients in the operating room or intensive care unit (ICU), the limb leads are typically placed on the torso, with the right and left arm leads placed just below the clavicles and the leg leads placed above the hips (Fig. 36.2). Of note, placement of the right leg lead (green lead) can be anywhere on the body because it is a ground electrode, and its location will not alter the display of any of the selected standard leads.⁷

Placement of the limb electrodes on the torso has been utilized since 1966, when Mason and Likar introduced a variation on positioning the standard limb electrodes of the 12-lead ECG during exercise stress testing to minimize

artifacts in the limb leads caused by movement.⁸ Although the limb lead QRS complexes are slightly different in amplitude and axis, and the precordial leads may vary slightly from the standard 12-lead ECG recording, studies have shown that the ST-segment measurements during exercise stress testing were generally similar when the Mason-Likar 12-lead ECG system is used, as compared with the standard 12-lead ECG.⁸⁻¹¹ Consequently, torso-positioned limb leads have become standard for monitoring in the operating room and ICU because of convenience and the potential to obviate motion artifact.

In some cases, surgical incisions, patient positioning, or other procedural aspects may mandate adjusting these limb lead electrode locations. However, for reliable recording of standard limb leads, the electrodes must be outside the cardiac borders, in the transverse plane above and below the heart, and in the sagittal plane to the left and right of the heart (Fig. 36.3). In practice, limb lead placement closer to the heart may lead to unintended distortion of the ECG tracings.¹⁰

Placement of the precordial lead (brown) electrode requires more attention than the limb leads, since this lead is often misplaced and its position is critical for the reliable and sensitive detection of myocardial ischemia. The V₅ precordial lead is the one most commonly chosen for monitoring patients at risk for myocardial ischemia, since historically it has been shown to be the most sensitive single lead for detecting ischemia during exercise stress testing^{12,13} and during anesthesia.^{14,15} Importantly, the V₅ precordial lead can be monitored during cardiac operations without interfering with the surgical prep and median sternotomy incision. For patients undergoing other operations, particularly high-risk patients undergoing vascular procedures, leads V₄ or V₃ may be chosen because there is good evidence that these leads are even more sensitive for detecting prolonged postoperative myocardial ischemia.¹⁶

Standard locations for the six precordial lead electrodes are shown in Fig. 36.4. Given that there is considerable evidence that precordial lead placement is inaccurate even during diagnostic 12-lead ECG recordings,⁶ it is likely that this is also commonplace during ECG monitoring in the operating room and ICU. Accurate lead placement is facilitated by locating the manubrial-sternal junction, its immediately inferior rib interspace (the second), and then palpating down to identify the fourth and fifth interspaces for accurate precordial lead location. Note that lead V₄ lies

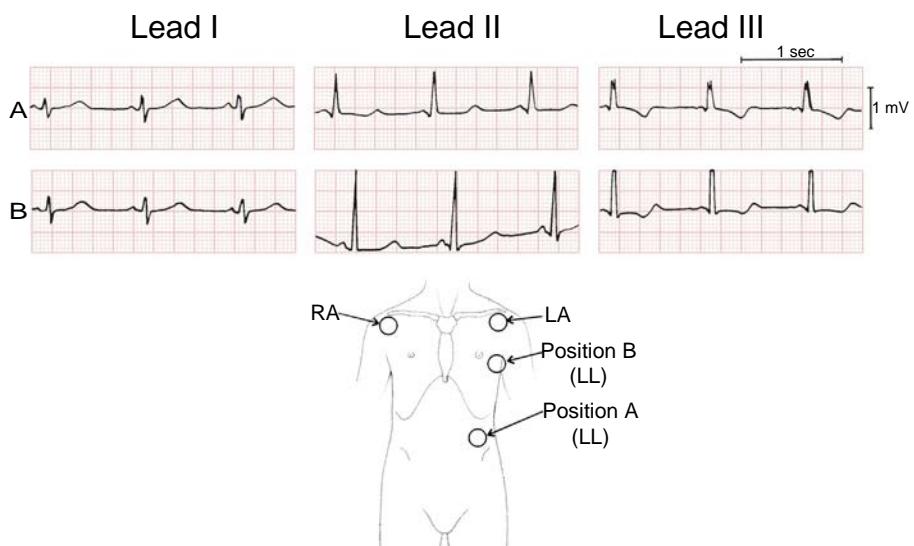


Fig. 36.3 Importance of ECG limb lead placement. ECG recording of leads I, II, and III from position A, with the left leg (LL) lead in the standard location below the heart near the left iliac crest compared with position B, with the LL lead placed over the precordium (near the V_5 position). Standard ECG limb lead positioning should be outside the cardiac borders, as shown here in position A. If the LL lead electrode is placed inappropriately in position B, the recording of leads II and III will be modified. Note, however, that the recording of lead I is not affected by the misplaced LL lead, since lead I measures the difference between left arm (LA) and right arm (RA) electrodes. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone;1998.)

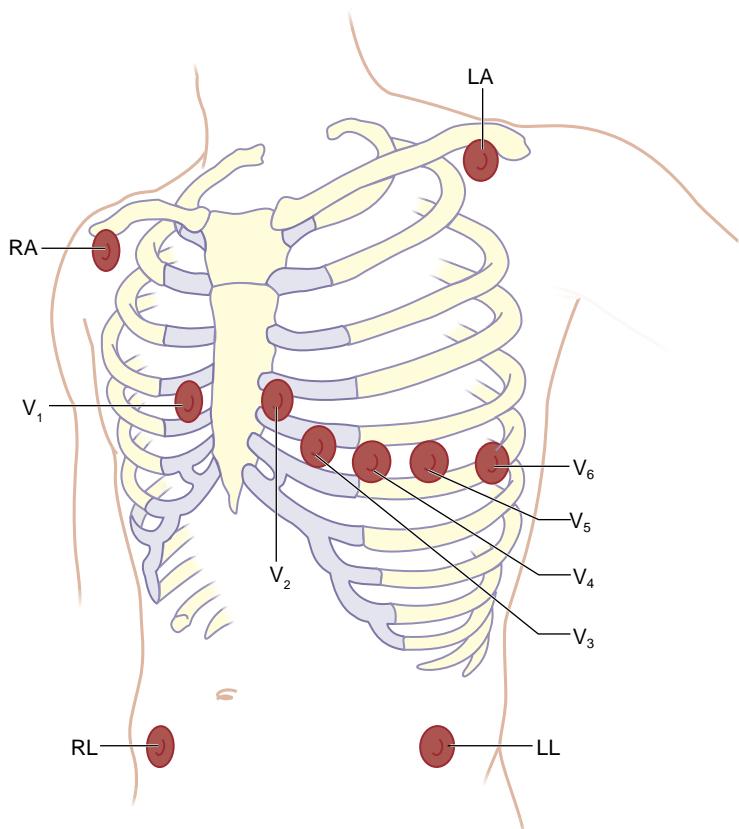


Fig. 36.4 Proper anatomic location of the six standard precordial ECG leads. Precise positioning of the lateral precordial leads is ensured by identifying the fifth intercostal space in the mid-clavicular line for lead V_4 , moving laterally to the anterior axillary line for V_5 , and further laterally to the mid-axillary line for V_6 . LA, Left arm; LL, left leg; RA, right arm; RL, right leg.

in the fifth interspace at the mid-clavicular line, and leads V_5 and V_6 are located directly lateral to V_4 in the anterior and mid-axillary lines, respectively.

Given anatomic considerations and the strong evidence that the mid-precordial leads (V_3 , V_4 , V_5) are best for

detection of ischemia, it is important that the precordial lead not be placed haphazardly or too laterally. In some cases (e.g., patients undergoing left thoracotomy), none of these precordial lead placement sites are possible. In this instance, it is reasonable to choose another standard lead

position, such as V_1 , but it is important that the clinician recognize that ECG monitoring for ischemia will not be as sensitive.

Alternative Lead Systems

Electrocardiographic evidence for right ventricular (RV) ischemia and infarction is best identified by right-sided precordial leads, particularly lead V_{4R} , a mirror image of the V_4 lead, positioned in the fourth intercostal space at the mid-clavicular line. Although never chosen for routine ischemia monitoring, this lead has proven valuable for detecting RV ischemia and infarction, and might be chosen to monitor patients at risk for inferior left ventricular (LV) ischemia, which is commonly accompanied by RV involvement.^{6,17}

Three-lead ECG monitoring systems, while less common today than five-lead systems, remain available particularly in non-operating room procedural settings and for patient transport. A three-lead system is also the standard ECG monitoring system incorporated in external defibrillator devices. The three leads (right arm, left arm, left leg) can be placed in similar locations to their five-lead system counterparts, and this allows reliable monitoring of heart rate, detection of R waves for synchronized direct current cardioversion, and monitoring for potentially life-threatening arrhythmias such as ventricular fibrillation. These systems are more limited than five-lead systems (or standard 12-lead ECG recordings) for diagnosing more complex arrhythmias and detection of myocardial ischemia. Modifications of these standard limb leads allow better sensitivity for ischemia monitoring by placing the positive (left arm) electrode in the standard precordial V_5 position and selecting an appropriate limb lead (usually lead I) to create this modified lead recording. These three-lead variations useful for ischemia monitoring are created by placing the right arm lead in the following locations: CS_5 (central subclavicular), CM_5 (central manubrial), CB_5 (central back), and CC_5 (central chest) (Fig. 36.5). Each of these lead recordings will be a modification of the standard precordial V_5 lead, and owing to differences in R-wave amplitude and ST-segment morphology, may lead to over- or underestimation of ST-segment changes.¹⁸

Another modified three-lead system is a surrogate for precordial lead V_1 . This lead (MCL_1) is recorded by placing the left arm lead in standard position, the left leg lead at the V_1 position, and selecting lead III (see Fig. 36.5). This modified lead system is useful for monitoring in the ICU or other circumstances where detection of P-wave morphology and arrhythmias is of paramount importance.

Following cardiac surgical procedures, recording the ECG signal from an epicardial atrial pacing wire may also be useful for detecting P waves that may not be as evident from skin surface ECG recordings (Fig. 36.6). This alternative lead recording is usually performed in the ICU using a 12-lead ECG system and attaching one of the atrial pacing wires to a precordial lead wire.

ELECTROCARDIOGRAM FILTER SELECTION

The ECG signal is subject to artifacts (noise) both in the low-frequency and high-frequency ranges. Consequently, all ECG monitors use bandpass filters to narrow the signal bandwidth, preserving the signal of interest while reducing

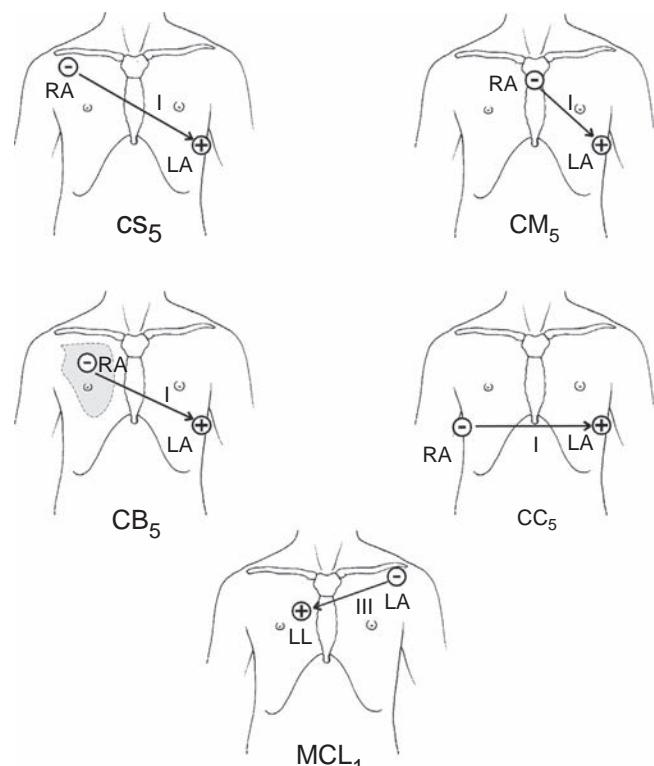


Fig. 36.5 When only a three-electrode lead set is available, modified bipolar limb leads may be recorded as surrogates for standard precordial leads. Alternatives to precordial lead V_5 are recorded by selecting lead I on the bedside monitor and placing the positive exploring left arm (LA) electrode in the V_5 position. The nomenclature describing these leads derives from the location of the positive exploring electrode located in the V_5 position and the negative right arm (RA) electrode position being located as follows: (CS_5) central subclavicular, (CM_5) central manubrial, (CB_5) central back (shown overlying the right scapula), and (CC_5) central chest. In contrast, note that the (MCL_1) lead (modified central lead 1) is recorded by selecting lead III on the bedside monitor and placing the positive exploring left leg (LL) electrode in the V_1 position with the negative LA lead in a modified position beneath the left clavicle. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone;1998.)

artifacts and improving signal quality. As the name suggests, a bandpass filter allows signal frequencies within a certain range to pass or be displayed, while attenuating or functionally eliminating signal frequencies both at a low range and a high range.

Low-frequency artifact is typically caused by respiration or patient movement that causes the ECG tracing to wander above and below the baseline (Fig. 36.7). Often this will appear as the ECG tracing being cut off or only partially displayed on the bedside monitor channel. Therefore, low-frequency filters (also called high-pass filters) are used in ECG monitoring. The heart rate forms a rough lower bound for the frequency content of the ECG signal and is measured in Hertz (Hz, cycles per second). Since heart rates slower than 40 beats per minute (bpm) (0.67 Hz) are uncommon, traditional low-frequency analog filters are used to cut off signals at frequencies below 0.5 Hz. However, such filters may introduce considerable distortion into the ECG, particularly with respect to the level of the ST segment, resulting from phase nonlinearities that occur in areas of the ECG signal where frequency content and wave amplitude abruptly change, as occurs where the end of the QRS complex meets the ST segment. The 1975 AHA recommendations included

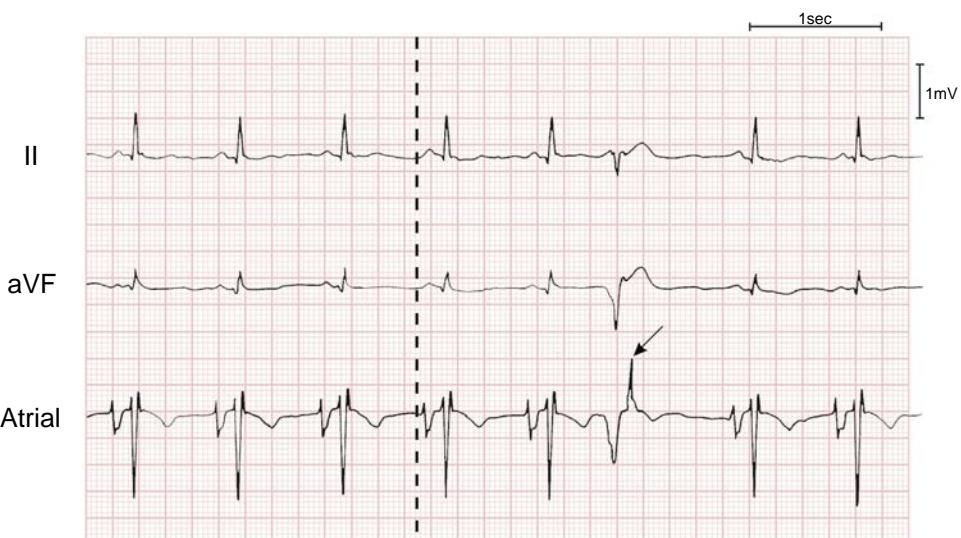


Fig. 36.6 Simultaneous recording of surface ECG leads II and aVF and an atrial epicardial lead (atrial) recorded from a pacing wire attached to the surface of the right atrium. Onset of atrial electrical activity is denoted by the P wave in the surface leads and marked by the dashed vertical line. Note that the amplitude of the atrial electrical signal is greatest in the atrial lead recording. In addition, the sixth beat is a ventricular premature beat, and the resulting retrograde atrial depolarization is clearly evident in the atrial lead (arrow) but not seen as easily in standard surface ECG leads II or aVF. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone;1998.)

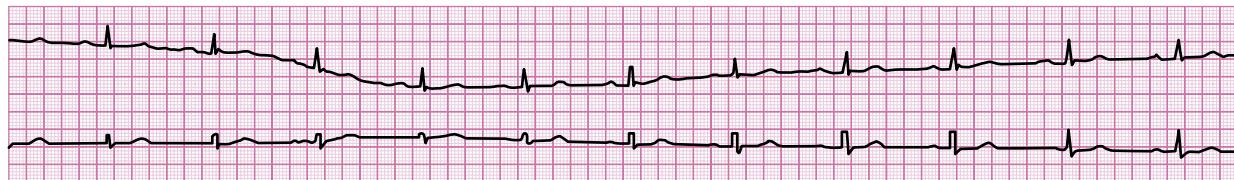


Fig. 36.7 ECG recording of lead II (top) and lead V₅ (bottom) at standard speed (25 mm/s) and gain (10 mm/mV) with a diagnostic bandpass filter. The respiratory artifact is evident from the varying or wandering baseline most noticeable in lead II. This artifact will be eliminated by using the monitor bandpass filter.

a 0.05-Hz low-frequency cutoff for diagnostic ECGs. This recommendation preserves the fidelity of repolarization, but baseline drift can still be a problem. Current modern digital filtering provides more sophisticated methods for a higher cutoff for low-frequency filtration without those phase distortions observed with analog filtering. Thus, to reduce artifactual distortion of the ST segment, current AHA recommendations suggest the low-frequency cutoff should be either 0.05 Hz for monitors with analog filters or 0.67 Hz or below for monitors and ECG recording devices with linear digital filters with zero phase distortion.⁶

High-frequency ECG artifacts are typically caused by muscle fasciculations, tremors, and most importantly, the ever present 60 cycle (Hz) electromagnetic interference from other electrical equipment in the monitoring environment. These artifacts can be eliminated with high-frequency filters (also termed low-pass filters), but like low-frequency filters, the high-frequency filters may distort the ECG signal in undesirable ways. The higher frequencies in the ECG signal include features such as rapid upstroke velocity (QRS complex), peak amplitude (R wave), and waves of short duration. Most importantly, pacing spikes, which by definition are high frequency and low amplitude, are often eliminated by high-frequency filters and make bedside identification of pacemaker function impossible. A high-frequency cutoff of 100 Hz was considered adequate by the AHA in 1975 to

maintain diagnostic accuracy during visual inspection of an ECG, although it has long been recognized that higher-frequency components of the QRS complex may have clinical significance in patients with various forms of heart disease. According to current AHA recommendations, to measure routine duration and amplitudes accurately in adults, adolescents, and children, an upper frequency cutoff of at least 150 Hz is required, and an upper frequency cutoff of 250 Hz is more appropriate for infants.⁶

Current ECG monitors allow the clinician a choice among several filtering modes or bandwidths. The actual filter frequencies tend to vary among manufacturers, but in general there are three different filters that may be selected, termed diagnostic mode, monitoring mode, and filter mode. The **diagnostic mode** typically has a bandpass of 0.05 to 150 Hz, and this filter should always be selected for the most undistorted and accurate display of the ST segment and the identification of pacing spikes. The **monitor mode** typically has a bandpass of 0.5 to 40 Hz, and while both low-frequency (respiratory drift) and high-frequency (60 Hz) noise is reduced or attenuated, the ST segments are often distorted and typically show an exaggerated deviation that is artifactually introduced by the filter (Figs. 36.8A and B).¹⁹ The **filter mode** bandpass is 0.5 to 20 Hz and may incorporate a notch filter aimed at further attenuating and eliminating 60 Hz interference from nearby electrical equipment.

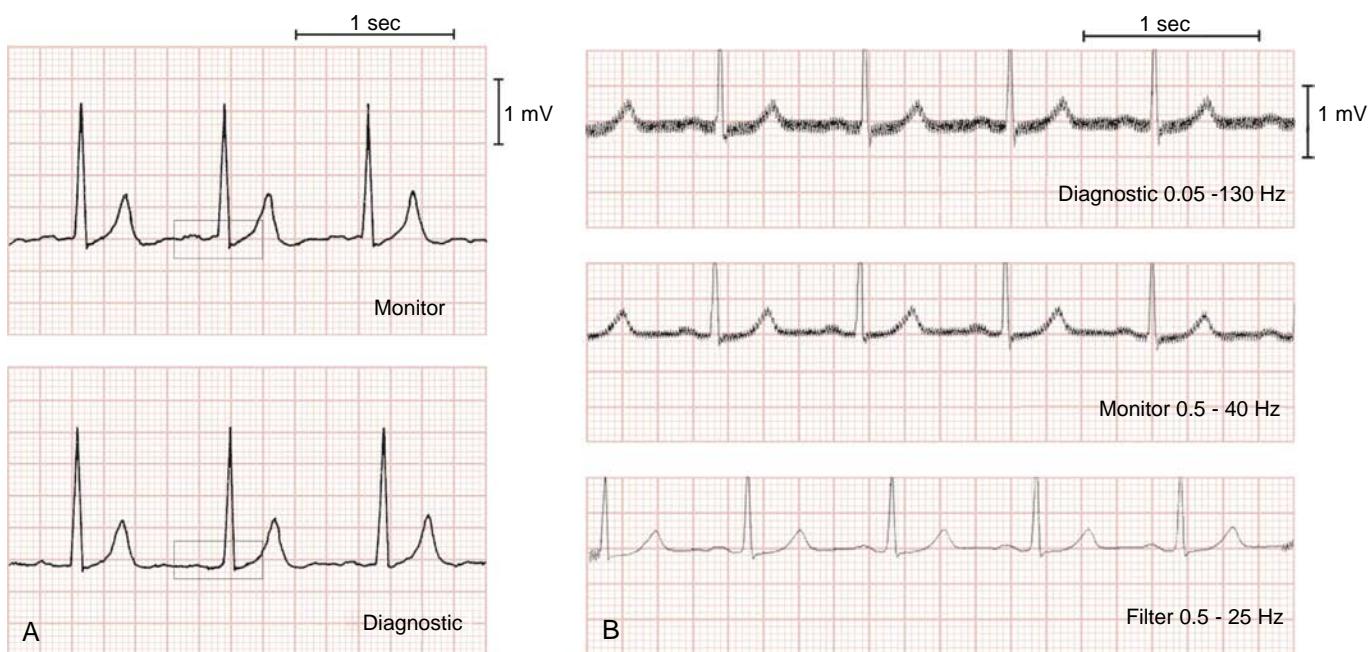


Fig. 36.8 Effects of filter selection on the ST segment. Application of the monitor mode filter (8A, top panel) produces artifactual J-point depression and upsloping ST-segment depression (box). These abnormalities are not seen when the diagnostic mode filter (8A, bottom panel) is used to record the ECG. Filter selection also effects ECG electrical interference originating from the wall power source (8B). Compared to the diagnostic mode filter (bandpass 0.05-130 Hz), the narrower bandpass of the monitor mode (0.5-40 Hz) reduces this high-frequency artifact, and the filter mode (0.5-25 Hz) that incorporates an additional notch filter at 60 Hz eliminates this electrical artifact entirely. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone;1998.)

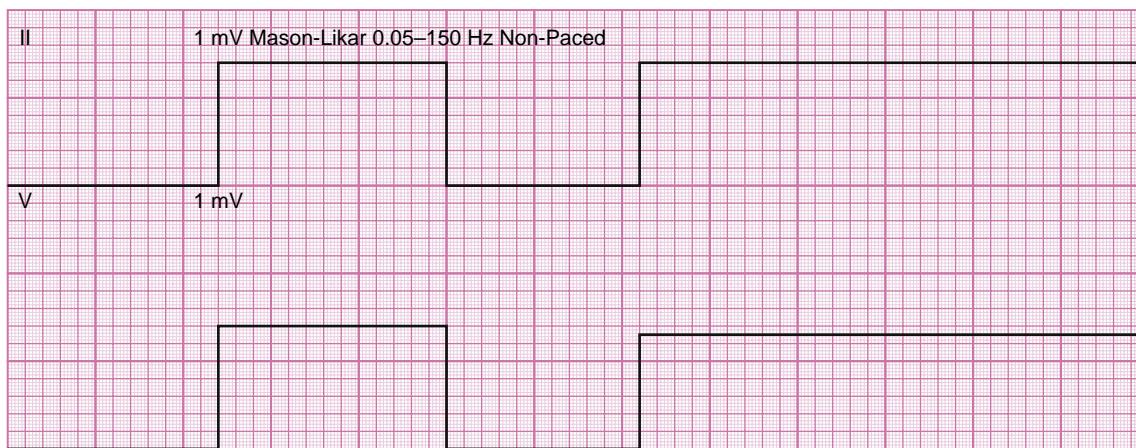


Fig. 36.9 ECG gain is indicated by a 1 mV rectangular calibration signal on a paper recording or by a 1 mV vertical marker at the edge of the bedside monitor ECG waveform. In this example, the ECG is shown at standard gain, 10 mm/mV.

ELECTROCARDIOGRAM GAIN SELECTION

In addition to lead and filter selection, bedside monitors also allow adjustment and selection of the ECG signal gain. A standard ECG is recorded at a gain of 10 mm/mV and is indicated by a 1 mV rectangular calibration signal on a paper recording (Fig. 36.9) or by a 1 mV vertical marker at the edge of the bedside monitor ECG waveform. Bedside monitors may be set to an autogain mode, where the available display space is filled by the ECG tracing and the corresponding increase or decrease from standard gain is indicated by the vertical marker. Alternatively, the clinician may adjust the ECG signal gain manually. This is done

when the monitor detection of heart rate is inaccurate. For example, one might reduce the ECG signal gain when the monitor is inappropriately counting a tall T wave as an R wave and displaying an artifactual heart rate that is twice the true rate. Conversely, one would increase the ECG gain when there are very small R waves and the monitor cannot record and display the heart rate.

Gain adjustment is important because all features of the ECG are equally amplified or reduced when the gain is changed from the 10 mm/mV standard. As a consequence, ST-segment deviations can be obscured when gain is reduced and thereby impair clinical observation of important ST-segment changes. Alternatively, if the gain is

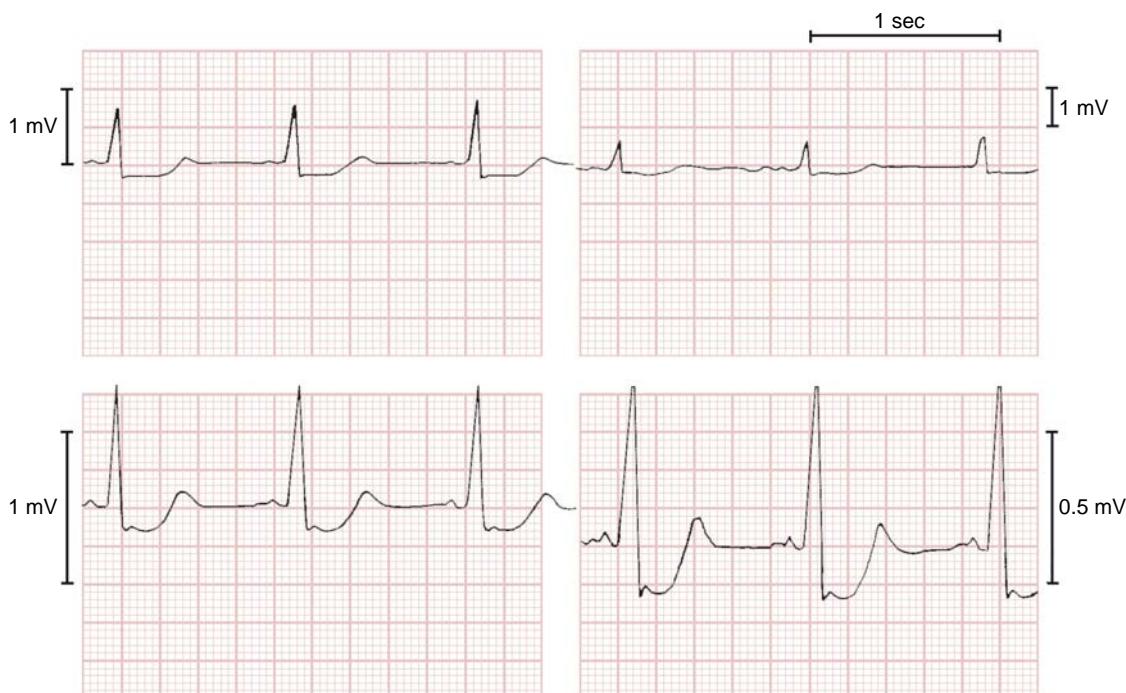


Fig. 36.10 Effect of gain adjustment on the magnitude of ST-segment shift. The magnitude of ST-segment depression and R-wave amplitude vary in direct proportion to overall signal gain denoted by the vertical calibration signals adjacent to the traces (10 mm/mV, upper left panel; 5 mm/mV, upper right panel; 20 mm/mV, lower left panel; 20 mm/0.5 mV or 40 mm/mV, lower right panel). Note that at four times standard gain (lower right panel), the ST depression increases to 6 mm but R-wave amplitude only increases to 21 mm because the R-wave peak is “cut off” at the upper limits of the recording display. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone;1998.)

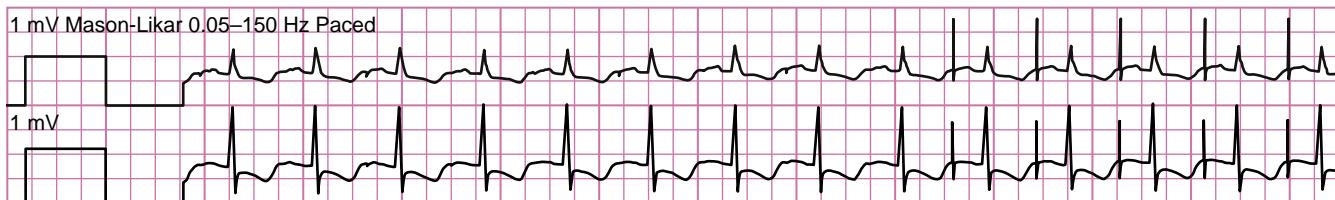


Fig. 36.11 Leads II (top) and V₅ (bottom) are recorded during atrial pacing (86 beats/min) at standard speed (25 mm/ms) and gain (10 mm/mV). Atrial pacing spikes are small and difficult to discern, particularly in lead V₅. Prior to the 10th beat, the *Pacing Mode* is selected and the monitor marks the atrial

increased, ST deviations will also be amplified proportionally. While common clinical communication of ST-segment shifts is always described in terms of millimeters (mm) of depression or elevation, interpretation of bedside monitor ECG tracings must always be tempered by consideration of the display gain (Fig. 36.10).

ELECTROCARDIOGRAM PACING MODE

While older ECG monitors recorded analog (continuous) signals, current devices convert the analog ECG signal to digital form by sampling the signal at very high rates up to 15,000 times per second.⁶ This oversampling of the ECG signal was originally introduced to allow identification and recording of pacemaker stimulus outputs (pacing spikes), which are generally shorter than 0.5 ms, but current systems do not always detect these small-amplitude high-frequency signals reliably. As a result, most bedside ECG monitors now include a **pacing mode** selection, which when activated, employs an algorithm to detect and highlight these pacing spikes, making detection of pacemaker

function easier. When this monitoring mode is selected, clinicians should recognize that the displayed ECG tracing shows regular markers, often in a different color than the ECG tracing, that indicate and highlight presence of a pacemaker stimulus output. These are not amplified pacemaker signals, but rather monitor-generated markers of their detection. While very helpful to the clinician at the bedside, pacemaker mode monitoring may not reliably detect pacemaker spikes in all patients. In other instances, the intrinsic features of the pacemaker stimulus in different leads might allow their detection in some leads but not others (Fig. 36.11).

ELECTROCARDIOGRAM DISPLAYS AND RECORDINGS

Monitoring the ECG during anesthesia and in the ICU includes both observation of the bedside monitor display and periodic recording of the ECG “rhythm strip” for documentation or more careful analysis. The most common bedside recording system provides a 2-inch strip that records two



Fig. 36.12 Electrosurgical unit interference with heart rate measurement from the ECG. (Top panel) The ECG signal from lead V is distorted by the electrosurgical unit. As a result, the digital value for heart rate (HR) is erroneous (146 beats/min), although the pulse rate (PR) is measured accurately by the monitor from the arterial blood pressure waveform (58 beats/min). (Lower panel) Correct (and identical) digital values for both HR and PR are displayed by the monitor. ART, Arterial blood pressure. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone;1998.)

ECG leads (see Fig. 36.11), but other recording systems may provide larger formats for multi-lead or multi-waveform recording. Monitoring systems may also have “full disclosure” capability whereby monitored ECG (and other) waveforms are stored for up to 24 hours and can be retrieved and printed for review. This last system is particularly useful for the retrospective identification, interpretation, and documentation of arrhythmias or other cardiovascular changes that may have escaped detection in real time by clinicians at the bedside.

The ECG tracing on the bedside monitor can be displayed at varying sweep speeds, but most typically is displayed at 25 mm/s, the same speed as a standard 12-lead ECG tracing. As described previously, the ECG gain can be adjusted and the displayed gain should be indicated by a vertical marker overlying the ECG tracing, the standard being 10 mm/mV.

Paper recordings of the ECG should have standard millimeter grids, such that with a standard sweep speed of 25 mm/s, each 1 mm is a 40 ms interval, and a darker line appearing every 5 mm indicates a 200 ms interval (see Fig. 36.11). As noted, the recorded gain is indicated by a 1 mV rectangular calibration signal, the standard being 10 mm/mV.

ELECTROCARDIOGRAM ARTIFACTS

As is the case for all bedside monitoring,²⁰ artifacts commonly distort the monitored ECG tracing and must be identified to prevent misinterpretation or inappropriate treatment. In the operating room, the most common cause of ECG artifact is the electrosurgical unit (ESU). Since some of the frequencies generated by the ESU fall within the QRS frequency range, and the amplitude of these signals can be very high (1 kV or 1 million times the typical QRS amplitude of 1 mV),²¹ even the best current advanced filtering techniques cannot eliminate this artifact that often totally masks the ECG signal (Fig. 36.12). This not only precludes identification of any ECG waveform features, but it can also prevent ECG monitoring of heart rate. The almost universal availability of additional simultaneously displayed waveforms, such as the pulse oximetry plethysmogram or an arterial blood pressure waveform, allow safe patient monitoring during these brief periods of ESU deployment (Fig. 36.12).

Other common ECG artifacts have been identified, and include common sources such as the 60 Hz interference from other medical devices near the patient (see Fig. 36.8B) and less common sources such as the cardiopulmonary

BOX 36.1 Equipment or Component-Related Electrocardiographic Artifacts

- Monitor/components
 - Manufacturing problems (50/60-Hz filter)
 - Defective monitor insulation
- Orthopedic shaver
- Intraoperative MRI
- Sinus endoscope
- Pressure-controlled irrigation pumps
- Flexible bronchoscopes
- ESWL
- Digital urine output-core temperature monitors
- Intravenous fluid warmer/warming sets
- Cardiopulmonary bypass machine
- Ventilator—HFOV
- Electrostimulators
 - Spinal cord, peripheral nerve, thalamic, vagal nerve, transcutaneous nerve, other
- Evoked potential monitoring units
- Hemodialysis machines
- Cellular telephones

ESWL, Extracorporeal shock-wave lithotripsy; HFOV, high-frequency oscillatory ventilation; MRI, magnetic resonance imaging.

Adapted from Patel SI, Souter MJ. Equipment-related electrocardiographic artifacts: causes, characteristics, consequences, and correction. *Anesthesiology*. 2008;108(1):138–148.

bypass machine.²² Patel and Souter provide a comprehensive list of reported sources of ECG artifact (Box 36.1).²³

ELECTROCARDIOGRAM MONITORING FOR MYOCARDIAL ISCHEMIA

The ST segment, representing myocardial repolarization, is the ECG component most sensitive to acute myocardial ischemia. ST elevation, with or without tall positive (hyperacute) T waves, indicates transmural ischemia and is most often the result of acute coronary artery occlusion either by coronary thrombosis or vasospasm (Prinzmetal-variant angina). Reciprocal ST-segment depression may appear in the contralateral leads. Ischemia confined to the subendocardial area is usually denoted by ST-segment depression. Subendocardial, ST-depression-type ischemia typically occurs during episodes of symptomatic or asymptomatic (*silent*) stable angina pectoris, and is characteristic of ischemia occurring during exercise, tachycardia, or pharmacologic stress testing in patients with significant but stable coronary artery disease.

Automated Real-Time ST-Segment Monitoring

Real-time ST-segment analysis first appeared in cardiac monitoring in the mid-1980s and is currently standard in most ECG monitors. On some monitors, the ST-segment analysis is set up to turn on automatically, but while ST-segment analysis is commonplace in the operating room, it is underutilized in other monitoring settings. A recent study has shown that even among coronary care units, less than 50% routinely use ST-segment monitoring for the detection of myocardial ischemia in patients admitted with acute coronary syndromes.²⁴ Chief among the reasons for the underuse of ST-segment analysis are the frequent number of false alarms and the lack of education on how to use the technology. In addition, no evidence exists as to whether

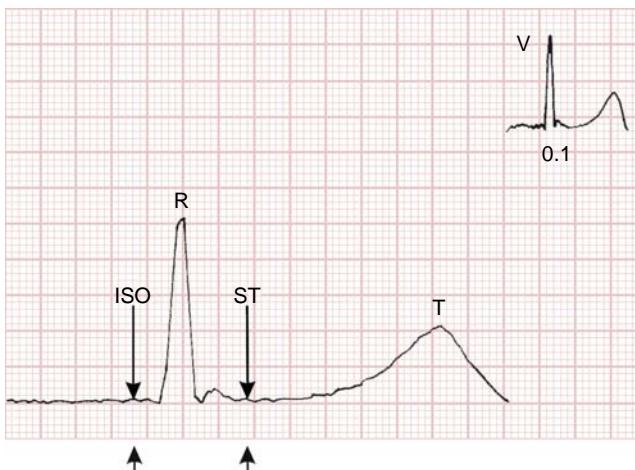


Fig. 36.13 Enlarged display of ECG lead V₅, showing the isoelectric (ISO) and ST-segment (ST) measurement points during continuous computer-aided ST-segment monitoring. The ECG R and T waves are also identified. This V lead ECG complex is shown at standard gain (10 mm/mV) in the upper right corner of the panel. The computer measures and displays 0.1 mm (0.01 mV) of ST-segment elevation in this lead. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone;1998.)

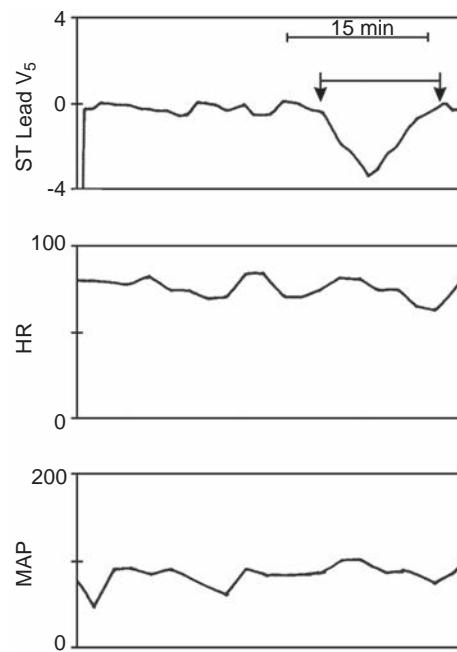


Fig. 36.14 One-hour trend displays for computer-aided continuous ST-segment monitoring in lead V₅, heart rate (HR, beats/min), and mean arterial pressure (MAP, mm Hg). A 15-minute episode of ST-segment depression (arrows) occurs without significant accompanying changes in HR or MAP. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone;1998.)

the addition of computerized ST-segment ischemia monitoring improves patient outcomes after surgery.

Computerized ST-segment analysis is achieved by the monitor measuring the ST segment at 60 or 80 ms after the J point (termed as J+60 or J+80 ms) and comparing it with the isoelectric point measured during the PR interval (Fig. 36.13). One millimeter of ST-segment deviation is equivalent to a 0.1 mV difference. The changes in ST-segment level over time in each lead can be displayed as ST-segment trends, just like trend displays of other hemodynamic variables (Fig. 36.14).

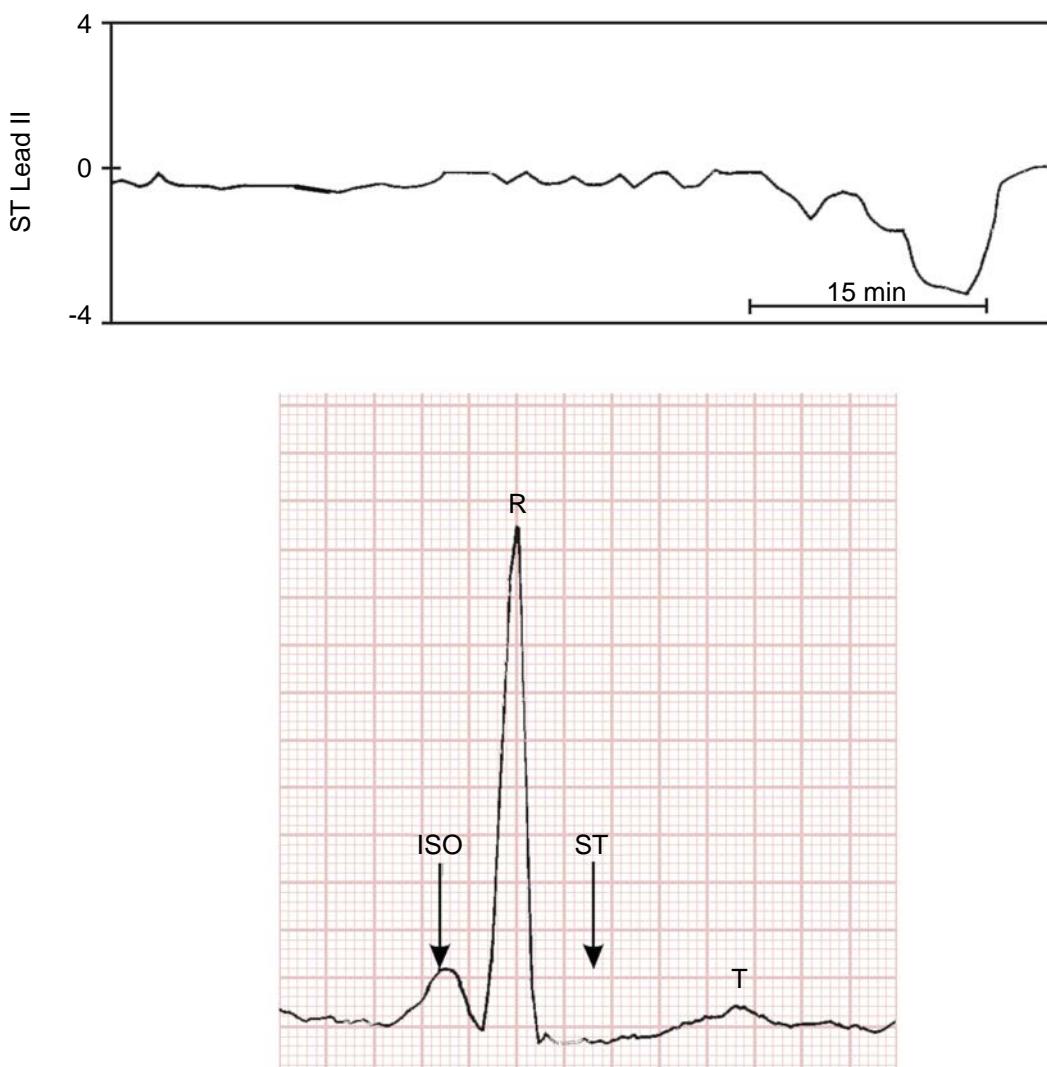


Fig. 36.15 Erroneous identification of the isoelectric (ISO) point measurement during computer-aided continuous ST-segment monitoring. A 1-hour trend recording of ST-segment deviations in lead II, displayed as millimeters of ST displacement, shows approximately 15 minutes of ST-segment depression, which reaches 3 mm in magnitude during this episode (top panel). The enlarged display of ECG lead II showing the ISO and ST-segment (ST) measurement points during the episode of ST-segment depression reveals that the ISO point is identified inappropriately at the peak of the P wave, thereby producing artifactual ST-segment depression (bottom panel). (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone;1998.)

When the computer misidentifies the appropriate isoelectric or ST monitoring point, the clinician can manually adjust the J-point or the ST-segment measurement point (Fig. 36.15).

One major advantage of continuous ST-segment monitoring is that the electrodes stay in place and do not vary as they may with serial 12-lead ECG recordings. However, for improved diagnostic accuracy of ST-segment monitoring, the following points should be recognized:

1. Changes in body position may cause ST-segment changes and lead to false ST-segment alarms. However, changes in the QRS complex almost always accompany these positional ST-segment changes and therefore can be easily distinguished from true ST-segment deviations (Fig. 36.16). Changes in position of the heart in the mediastinum have also shown to affect the ST segment. Mark and associates observed that placement of a sternal retractor during cardiac surgery was associated with a reduction in V_5 R-wave amplitude (Fig. 36.17).²⁵

Simultaneously, V_5 S-wave amplitude and absolute ST-segment deviation were reduced. These investigators concluded that inclusion of an R-wave gain factor might improve perioperative ECG ischemia monitoring.

2. Many patients have preexisting ECG abnormalities that confound interpretation of ST-segment changes. Early repolarization (a normal variant), intraventricular conduction delays, LV hypertrophy, digitalis, pericarditis, and other conditions may cause baseline ST-segment abnormalities. In these conditions, standard ECG criteria for diagnosing myocardial ischemia are less specific.
3. Most cardiac monitors with ST-segment monitoring software provide displays of ST-segment trends in a single lead or the sum of absolute ST-segment deviations from multiple leads (Fig. 36.18). Although such graphic trends are convenient for the quick identification of potential ischemic events, analysis of the ECG waveform on the monitor screen or by recording the ECG tracing is of paramount importance for verification.

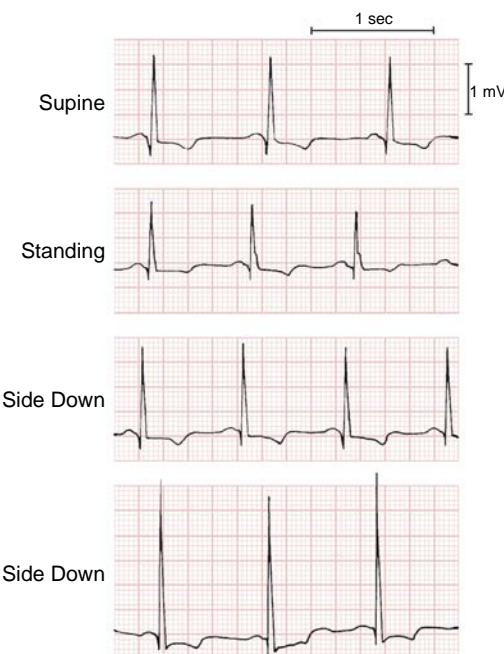


Fig. 36.16 Effect of changing body position on the ECG in a patient with preexisting ST-segment depression. Lead CC_5 , a surrogate for lead V_5 , is recorded with the patient in four different positions: supine, standing, right (R) side down, and left (L) side down. The magnitude of ST-segment depression changes in direct proportion to the R-wave amplitude. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone;1998.)

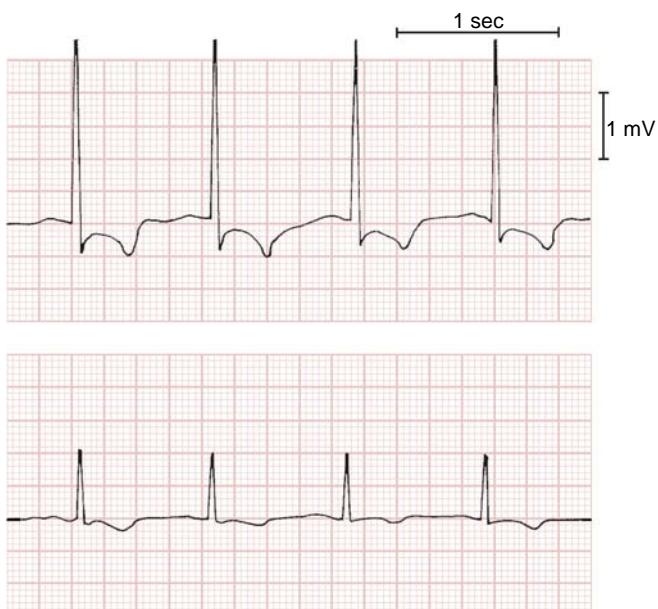


Fig. 36.17 Effect of surgical retraction on the ECG. Baseline lead V_5 recording shows 2 mm ST-segment depression and 27 mm R-wave amplitude (top panel). Placement of a sternal retractor during cardiac surgery displaces the precordial lead electrode relative to the heart, resulting in a marked reduction in R-wave amplitude to 10 mm and a proportional reduction in the magnitude of ST-segment displacement (bottom panel). (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone;1998.)

Electrocardiogram Criteria for Acute Myocardial Ischemia

The ECG criteria most accepted for detecting myocardial ischemia during continuous ECG monitoring are those established and validated during exercise stress testing.²⁶ During stress

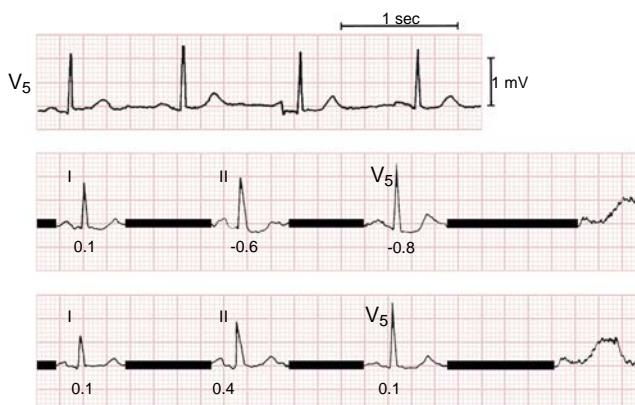


Fig. 36.18 Computer-aided continuous ST-segment monitoring. A baseline recording of lead V_5 shows isoelectric ST segments (top panel). Shortly after induction of anesthesia, the ST-segment monitoring display shows the three monitored leads I, II, and V_5 and the absolute amount of ST-segment elevation (0.1 mm in lead I) or depression (-0.6 mm in lead II, -0.8 mm in lead V_5) in each lead (middle panel). A trend line is displayed on the right side of the panel and demonstrates that the sum of ST-segment deviations in these three monitored leads has increased and reached a plateau over the previous few minutes. Another ST-segment display recorded 5 minutes later shows resolution of these subtle ST changes (bottom panel). Note that the appearance of lead V_5 in this last display closely resembles the baseline recording and that the trend line has returned to pre-induction baseline level. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone;1998.)



Fig. 36.19 Subendocardial ischemia produces ST-segment depression. As heart rate increases progressively from 63 beats/min (top panel) to 75 beats/min (middle panel) and finally to 86 beats/min (bottom panel) in this patient with left main coronary artery disease, the ST segment becomes more depressed and more downsloping, owing to an increase in myocardial oxygen demand. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone;1998.)

testing and with acute subendocardial ischemia, the electrical forces responsible for the ST segment are deviated toward the inner layer of the heart, causing ST-segment depression or demand-mediated ischemia (Fig. 36.19). With acute transmural epicardial ischemia, the electrical forces in the ischemic area are deviated toward the outer layer of the heart, causing ST-segment elevation or supply-mediated ischemia in

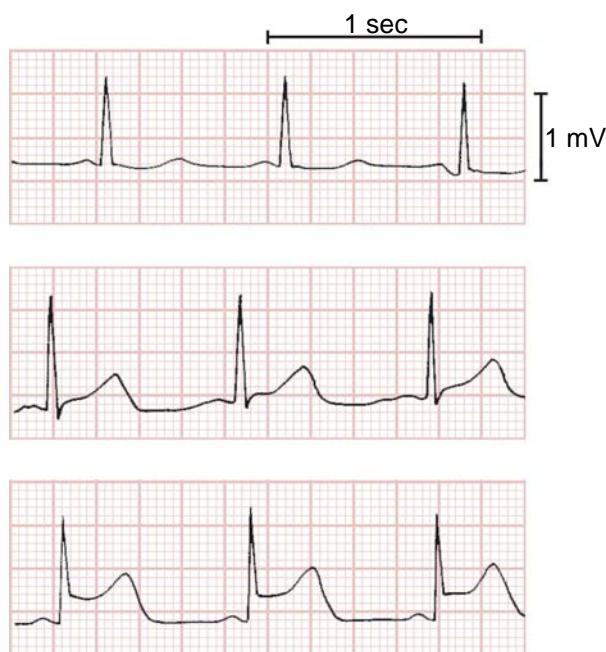


Fig. 36.20 Transmural ischemia produces ST-segment elevation. Occlusion of a patent saphenous vein graft during repeat coronary artery bypass surgery causes an abrupt reduction of coronary blood supply and results in progressive ST-segment elevation (middle and bottom panels). (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone;1998.)

the overlying leads (Fig. 36.20). Note that most commonly, intraoperative or perioperative ischemia is demand-mediated subendocardial ischemia, which is manifest as ST-segment depression.²⁷ Although the anterolateral precordial leads are most sensitive for detecting these changes, they are **non-localizing** as to the coronary distribution responsible. In contrast, supply-mediated transmural ischemia, while much less common perioperatively, causes ST-segment elevation in leads overlying the involved coronary bed and thus are able to **localize** the responsible coronary territory (e.g., ST elevations in inferior leads II, III, aVF suggest occlusion of the right or posterior descending coronary artery).

With demand-mediated ischemia, as heart rate increases, J-point depression and upsloping ST-segment depression occurs. As the severity of ischemia progresses, the ST segment typically becomes horizontal (flattens) and the extent of ST-segment depression may increase and the ST segment may become downsloping (see Fig. 36.19). Standard criteria for stress-induced ischemia are 1 mm (0.1 mV) or more of horizontal or downsloping ST-segment depression measured 60 to 80 ms after the J point. As noted earlier, patients with preexisting ST-segment abnormalities make ST-segment interpretation more difficult.

During the perioperative period, ECG monitoring most commonly identifies stress-induced, ST-depression, demand-mediated ischemia, or other causes of supply-demand imbalance such as prolonged or severe hypotension. Such ECG changes do not provide information about the location of the ischemic myocardial area. In contrast, ST-segment elevation indicating transmural or supply-mediated ischemia, observed particularly during cardiac surgery, provides useful information about the myocardial segment and coronary perfusion territory

responsible for the ischemic episode. Because the majority of modern patient-monitoring systems do not simultaneously monitor all 12 ECG leads, selecting which chest leads to monitor is of great importance, particularly in noncardiac surgery. During exercise stress testing, investigators have identified leads V₄ and V₅ as the most sensitive leads to detect exercise-induced ischemia (90%-100% sensitivity).²⁸ London and colleagues studied high-risk patients undergoing noncardiac surgery and showed that the greatest sensitivity for ischemia was obtained with lead V₅ (75%), followed by lead V₄ (61%).¹⁵ Combining leads V₄ and V₅ increased the sensitivity to 90%, whereas with the standard lead II and V₅ combination, the sensitivity was only 80%. They also suggested that if three leads (II, V₄, and V₅) could be simultaneously examined, the sensitivity would increase to 98%. More recently, Landesberg and associates monitored continuous 12-lead ST-segment changes greater than 0.2 mV from baseline in a single lead or more than 0.1 mV in two contiguous leads at J+60 ms, lasting longer than 10 minutes in patients undergoing major vascular surgery.¹⁶ They showed that leads V₃ and V₄ were more sensitive than V₅ in detecting perioperative ischemia (87%, 79%, and 66%, respectively). As a result of these and other investigations, it appears most appropriate to monitor lead V₃, V₄, or V₅ for optimal detection of perioperative ST-segment depression, choosing the specific lead location based on whether the lead placement might interfere with the surgical prep and procedure.

Blood Pressure Monitoring

Like heart rate, blood pressure has long been a fundamental cardiovascular vital sign included in the mandated standards for basic anesthetic monitoring.²⁹ Measuring blood pressure is primarily performed with either indirect cuff devices or direct arterial cannulation with pressure transduction. These techniques measure different physical signals and differ in their degree of invasiveness, but both are subject to numerous confounding factors that often result in significant discrepancies among simultaneous measurements.³⁰

INDIRECT MEASUREMENT OF ARTERIAL BLOOD PRESSURE

Manual Intermittent Techniques

Most indirect methods of blood pressure measurement utilize a sphygmomanometer, first described by Riva-Rocci in 1896.³¹ The systolic pressure was identified using an inflatable elastic cuff around the arm and a mercury manometer to measure cuff pressure, while the radial arterial pulse was palpated as the cuff pressure was increased or rapidly decreased. The technique was later modified to detect both systolic and diastolic pressure with description of auscultatory method of blood pressure measurement by Korotkoff in 1905.³² Korotkoff sounds are a complex series of audible frequencies produced by turbulent flow beyond the partially occluding cuff. Put simply, the systolic pressure is associated with first sound heard (beginning of turbulent flow through the vessel) and diastolic pressure at the point

when the sounds disappear (when vessel flow becomes laminar).³³ Mean blood pressure cannot be measured using this technique.

A fundamental principle of the auscultatory method is its reliance on blood flow to generate Korotkoff sounds. Physiologic conditions that interfere with sound detection (e.g., severe edema, obesity, abnormal compliance of overlying tissue) or blood flow (shock, intense vasoconstriction) will frustrate manual blood pressure measurement.³³⁻³⁷ Furthermore, the cuff must also be snugly fitted, with a bladder that measures 40% of arm circumference and 80% of length of the upper arm, and centered over the artery. A cuff that is too large will often yield acceptable results when used for *manual* measurements, but a small cuff will usually yield falsely high readings.³⁶

Automated Intermittent Techniques

Automated noninvasive blood pressure (NIBP) devices are the most commonly used means of measuring blood pressure in the operating room. Small oscillations in pressure amplitude are measured in an air-filled cuff that slowly deflates from a pressure well in excess of that needed to collapse the underlying artery. The point of maximal oscillation marks the mean arterial blood pressure (MAP), with systolic and diastolic being calculated by various proprietary algorithms specific to individual device manufacturers.^{33,35,36} In general, a cuff that is too large will underestimate the blood pressure while a small cuff will overestimate.^{36,38} Of the three possible measurements, systolic has the poorest agreement with invasive blood pressure values.^{38,39}

Although automated NIBP measurements have generally been shown to approximate directly measured arterial pressures, there are also important shortcomings to keep in mind.^{36,38} For reasons involving the ethics of validation against invasive measurements, standards for device performance established by the Association for the Advancement of Medical Instrumentation (AAMI) and the British Hypertension Society are defined by auscultation.⁴⁰ New devices must demonstrate average differences $\leq \pm 5$ mm Hg and standard deviations ≤ 8 mm Hg, which means that deviations of up to 20 mm Hg are still considered “acceptable performance.”⁴¹

Clinical studies comparing NIBP with direct arterial pressure measurements reflect the problematic nature of NIBP monitoring. Direct comparisons of oscillometric devices to invasive monitoring have shown that mean blood pressure measurements generally show the greatest degree of agreement with invasive blood pressure readings while systolic measurements are the most divergent.^{39,42-44} Agreement is especially problematic in critically ill or older patients.^{38,42-44}

Oscillometric NIBP values tend to underestimate MAP values during periods of hypertension and overestimate during hypotension, potentially biasing clinical decisions in unstable patients.⁴⁵ And they often underestimate the systolic while overestimating the diastolic measurements.⁴⁶ A well-fitted arm cuff does appear to be helpful in identifying hypotension in unstable patients and differentiating responses to therapy in such situations, but below a MAP of 65 mm Hg, it is not useful for titration of therapy, and a more frequent interval of measurement is probably required to be considered reliable.^{38,42,47,48} Dysrhythmia may also

BOX 36.2 Complications of Noninvasive Blood Pressure (NIBP) Measurement

- Pain
- Petechiae and ecchymoses
- Limb edema
- Venous stasis and thrombophlebitis
- Peripheral neuropathy
- Compartment syndrome

result in significant error in blood pressure measurement, especially in systolic and diastolic estimation, although averaging three measurements seems to minimize the clinical impact.^{49,50}

While the upper arm is the most common cuff location, various factors may force choice of an alternative site. In obese patients, there is little agreement between any alternate location and invasively measured pressures while ankle, calf, and thigh cuffs have never been validated at all.⁵¹ Interestingly, the forearm may be a preferable site to upper arm in obese patients, although such cuffs display a reversed pattern of bias; overestimation of the systolic and underestimation of the diastolic pressure.⁴⁸

It is important to remember the auscultatory method measures the systolic and diastolic pressures while oscillometric devices measure the mean and calculate the systolic and diastolic, albeit in different and non-interchangeable ways. Furthermore, directly-measured arterial pressure measurements utilize another technique altogether. In some authors' opinions, “current protocols for validating blood pressure monitors give no guarantee of accuracy in clinical practice.”^{40,52} Expecting them to yield identical values is unrealistic, especially in complex and unstable clinical situations. The sources of error vary significantly for each of these measurement techniques and should closely guide evaluation and therapeutic intervention, especially when there is discrepancy between the measured values or between measurements and clinical conditions.

Complications of Noninvasive Blood Pressure Measurement

Although automated NIBP measurement is generally safe, there have been reports of rare but severe complications (Box 36.2).⁵³ Compartment syndrome is possible after prolonged periods of frequent cycling and is most likely related to trauma or impaired distal limb perfusion. Caution should be exercised in cases of peripheral neuropathy, arterial or venous insufficiency, severe coagulopathies, or recent use of thrombolytic therapy.

Automated Continuous Techniques

Continuous methods for NIBP monitoring are being developed with various degrees of success. The most current version is based on the volume clamp technique and involves photoplethysmography and closed loop continuous control of a pressure cuff around a finger. This creates a stable arterial pressure waveform via quantification of an infrared beam applied distal to the finger cuff. Many of these require initial calibration with a standard NIBP

BOX 36.3 Indications for Arterial Cannulation

- Continuous, real-time blood pressure monitoring
- Anticipated pharmacologic or mechanical cardiovascular manipulation
- Repeated blood sampling
- Failure of indirect arterial blood pressure measurement
- Supplementary diagnostic information from the arterial waveform

cuff, and all are significantly affected by changes in vascular tone and perfusion in the finger, as well as movement, vascular disease, and a host of other factors.⁵⁴ While none of these devices technically meet AAMI standards when compared with invasive pressures, clinical studies have shown their correlation to be reasonable in a variety of operative cases.^{35,55-58}

Other devices use technologies related to pulse transit time or arterial tonometry.^{59,60} All of these techniques, however, have limitations, including need for calibration, sensitivity to motion artifact, and limited applicability in critically ill patients.^{36,61,62} It remains unclear whether any noninvasive technique will reduce the need for direct arterial pressure monitoring during anesthesia or critical care, but with continued development and technical refinement, they remain promising.

DIRECT MEASUREMENT OF ARTERIAL BLOOD PRESSURE

Arterial cannulation with continuous pressure transduction remains the accepted reference standard for blood pressure monitoring despite its risk, cost, and need for technical expertise for placement and management (Box 36.3). Its superiority over noninvasive techniques for early detection of intraoperative hypotension was confirmed by The Australian Incident Monitoring Study of 1993.^{42,63} More recently, though, the use of waveform analysis in physiologic monitoring has become more popular. This was initially proposed more than a half century ago by Eather and associates, who advocated monitoring of “arterial pressure and pressure pulse contours” in anesthetized patients.⁶⁴ Arterial pressure waveform characteristics used in current clinical practice include the dicrotic notch as a trigger for intra-aortic balloon counterpulsation as well as respiratory-induced variation in an array of directly-measured and derived pressure measurements to indicate preload reserve and volume responsiveness.⁶⁵⁻⁶⁸ Rates of intraoperative direct arterial blood pressure measurement vary significantly across clinical environments even for similar procedures.⁶⁹

Percutaneous Radial Artery Cannulation

The radial artery is the most common site for invasive blood pressure monitoring because it is technically easy to cannulate and complications are rare.^{70,71} Slogoff et al. described 1700 cardiovascular surgical patients who underwent radial artery cannulation without ischemic complications despite evidence of arterial occlusion after decannulation in more than 25% of patients.⁷² Furthermore, most investigations of hand perfusion following

radial artery harvest have reported no significant decrease relative to the contralateral hand in either the early or late postoperative periods.⁷³⁻⁷⁸

Before radial artery cannulation, some clinicians assess collateral blood flow to the hand by performing a modified Allen test, originally described in 1929 to assess arterial stenosis in patients suffering from thromboangiitis obliterans.⁷⁹ The radial and ulnar arteries are both compressed while the patient makes a tight fist to exsanguinate the palm and then slowly reopens it. As occlusion of the ulnar artery is released, the color of the open palm is observed. Normally, the color will return to the palm within several seconds; severely reduced collateral flow is present when the palm remains pale for more than 6 to 10 seconds. Unfortunately, the predictive value of this test is poor. There are numerous reports of ischemic sequelae in the face of a normal Allen test, and conversely, reports of uncomplicated radial catheter use and even harvest for bypass grafting in the presence of an abnormal result.^{72,73,80,81} In recent years, the radial artery has become more popular for coronary catheterization and stenting access, even in individuals with abnormal Allen tests.⁸² Overall, the diagnostic accuracy of the modified Allen test with a 5-second threshold is only 80% with 76% sensitivity and 82% specificity. It appears that the test is unable to provide a cutoff point below which perfusion can be deemed vulnerable.⁸³ Use of pulse oximetry, plethysmography, or Doppler ultrasound as adjuncts does not seem to improve its accuracy. Oximetry detects blood flows at extremely low flows, leading to poor specificity, while there are no established ultrasound criteria by which to evaluate radial or ulnar blood flow.^{73,84,85} In general, it seems that while a normal modified Allen test may be useful in identifying patients unacceptable for radial artery use for bypass graft or coronary angiography, there is no evidence that it predicts clinical outcomes following cannulation for blood pressure monitoring.⁷³

Techniques for radial artery cannulation have been unchanged for decades with the notable exception of the use of ultrasound in guiding catheter placement. Evidence supports its use, especially as a rescue method following a failed attempt.⁸⁶ Although evidence in the critical care setting suggests that ultrasound techniques improve first-pass cannulation success rates, it is not clear that this translates to improved clinical outcomes, nor that the impact on time required to perform the procedure or other factors warrants routine intraoperative use.⁸⁷⁻⁹⁰ Ultrasound guidance in catheterization of other vessels other than the radial artery or in special populations, such as those on mechanical support without pulsatile flow, is more likely to be of substantial benefit.⁹¹

Alternative Arterial Pressure Monitoring Sites

If the radial arteries are unsuitable or unavailable, there are multiple alternatives. The *ulnar artery* has been used safely even following failed attempts to access the ipsilateral radial artery.^{72,92} Similarly, the *brachial artery*, while lacking collateral branches to protect the hand, has a long track record of safe use. Several investigators have reported large series of brachial artery catheters in patients undergoing cardiac surgery with very few vascular, neurologic, or thrombotic sequelae.^{93,94} The *axillary artery* has the advantages of patient comfort and mobility, and complications appear to be similar in incidence to those for radial and femoral

BOX 36.4 Complications of Direct Arterial Pressure Monitoring

- Distal ischemia, pseudoaneurysm, arteriovenous fistula
- Hemorrhage
- Arterial embolization
- Infection
- Peripheral neuropathy
- Misinterpretation of data
- Misuse of equipment

arteries.⁷¹ A slightly longer catheter is preferred for the brachial or axillary sites due to their relatively deeper and more mobile anatomic locations. Clinicians should be aware, however, that the risk of cerebral embolization is significantly increased when more central vessels are utilized.

The *femoral artery* is the largest vessel in common use for blood pressure monitoring but its safety profile seems comparable to other sites.⁷¹ Catheterization of the femoral artery is best achieved with a guidewire technique and the point of vessel entry must be distal to the inguinal ligament to minimize the risk of arterial injury, hidden hematoma formation, or even uncontrolled hemorrhage into the pelvis or retroperitoneum.⁹⁵

Less commonly used alternatives include the *dorsalis pedis*, *posterior tibial*, and *superficial temporal arteries*, with the pedal vessels being more popular in pediatric patients. Lower extremity vessels tend to demonstrate greater with disagreement noninvasively acquired data, with diastolic and mean measurements being the most affected.⁹⁶

Complications of Direct Arterial Pressure Monitoring

Although large clinical investigations confirm the low incidence of long-term complications after radial arterial pressure monitoring, factors that may increase such risks include vasospastic arterial disease, previous arterial injury, thrombocytosis, protracted shock, high-dose vasopressor administration, prolonged cannulation, and infection.^{70-73,97,98}

Rare but serious complications have been reported after arterial cannulation at all locations (Box 36.4). In most cases, catheter placement was technically difficult or there were contributory factors such as shock or coagulopathy. In a large observational study of 2000 untoward clinical events resulting from any kind of vascular access, only 13 were related to peripheral arterial cannulation, fewer than those associated with central venous (18) or even peripheral venous cannulation (33). The events involved equipment problems, inadvertent drug administration, or disruption/kinking of the catheter itself. In only 1 case did transient vasospasm follow radial artery cannulation. An additional 10 cases were noted to involve problems with incorrect device calibration or erroneous data interpretation.^{63,99} Data from the anesthesia closed claims reports have shown that claims related to arterial pressure monitoring constitute only 8% of all claims related to any vascular access (2% of total claims). Of this small number, almost 54% were related to radial artery use (ischemic injury, median or radial nerve injury, or retained wire fragment), less than 8% were associated with use of the brachial

artery, and the remainder involved severe thrombotic or hemorrhagic complications following femoral artery monitoring.¹⁰⁰ While patient physiology is important, equipment misuse, poor placement technique or catheter care, as well as improper data interpretation play important roles in most complications related to arterial pressure monitoring.

Technical Aspects of Direct Blood Pressure Measurement

There are a variety of factors, including extension tubing, stopcocks, flush devices, recorders, amplifiers, and transducers that may confound the process by which pressure waveforms are reproduced for measurement and display.¹⁰¹

Most invasive blood pressure monitoring systems are underdamped second-order dynamic systems that demonstrate simple harmonic motion dependent on *elasticity*, *mass*, and *friction*.¹⁰¹⁻¹⁰³ These three properties determine the system operating characteristics (i.e., *frequency response* or *dynamic response*) which in turn are characterized by *natural frequency* and *damping coefficient*. The natural frequency of a system determines how rapidly the system oscillates after a perturbation, while the damping coefficient reflects how rapidly it returns to its prior resting state. Both parameters may be estimated or measured at the bedside and dramatically influence the appearance of the displayed pressure waveform.

Natural Frequency, Damping Coefficient, and Dynamic Response of Pressure Monitoring Systems

The displayed pressure waveform is a periodic complex wave produced via Fourier analysis of a summation of multiple propagated and reflected pressure waves. As such, it is a mathematical re-creation of the original complex pressure wave created and propagated by stroke volume ejection.^{104,105} The original pressure wave is characterized by its fundamental frequency, a characteristic manifested clinically as the pulse rate and expressed as cycles/second (Hertz).

The sine waves that sum to produce the final complex wave have frequencies that are multiples or harmonics of the fundamental frequency (i.e., pulse rate). A very crude arterial waveform depicting a systolic upstroke and peak, dicrotic notch, and so forth can be reconstructed with reasonable accuracy from only two sine waves, the fundamental frequency and the second harmonic (Fig. 36.21). As a general rule, though, 6 to 10 harmonics are required to provide distortion-free reproductions of most arterial pressure waveforms.^{104,106} Consequently, accurate blood pressure measurement in a patient with a pulse rate of 120 beats/min (2 cycles/s or 2 Hz) requires a monitoring system dynamic response of 12 to 20 Hz (i.e., 6 to 10 waveforms X 2 Hz). The faster the heart rate and the steeper the systolic pressure upstroke, the greater the demands on the monitoring system.

Natural frequency and damping coefficient are intrinsic characteristics of all monitoring systems. If the system's natural frequency is too low, the system will resonate, and pressure waveforms recorded on the monitor will be exaggerated or amplified versions of true intraarterial pressure. An underdamped system may combine elements of the measurement system itself with the measured sine waves

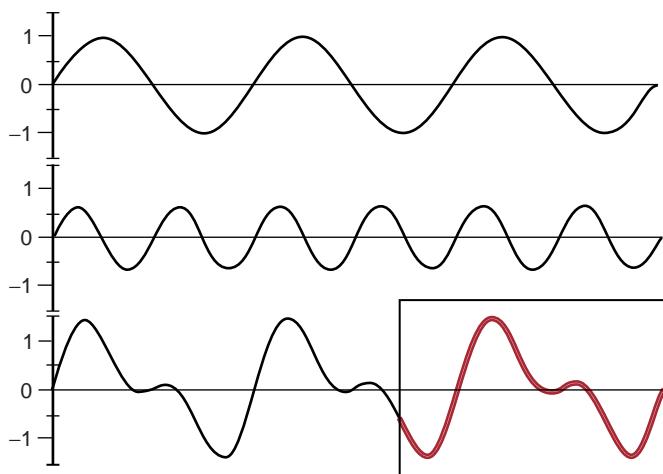


Fig. 36.21 Arterial blood pressure waveform produced by summation of sine waves. The fundamental wave (top) added to 63% of the second harmonic wave (middle) results in a pressure wave (bottom) resembling a typical arterial blood pressure waveform (box). (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

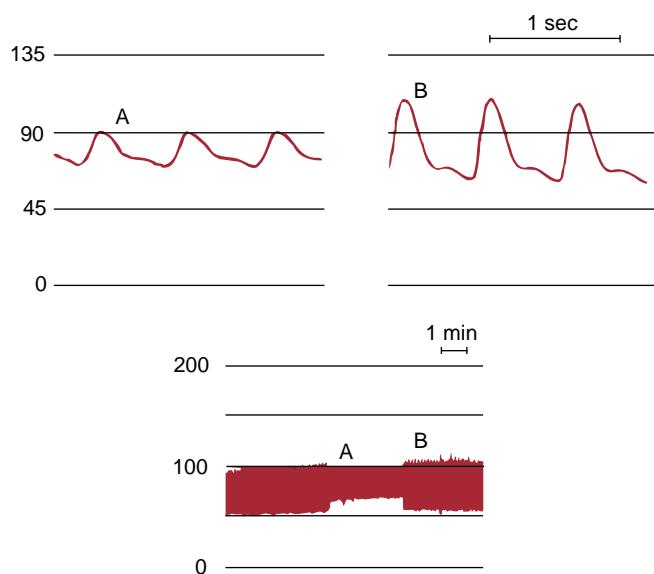


Fig. 36.23 Overdamped arterial pressure waveform. The over-damped pressure waveform (A) shows a diminished pulse pressure compared with the normal waveform (B). The slow-speed recording (bottom) demonstrates a 3-minute period of damped arterial pressure. Note that despite the damped system, mean arterial pressure remains unchanged. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

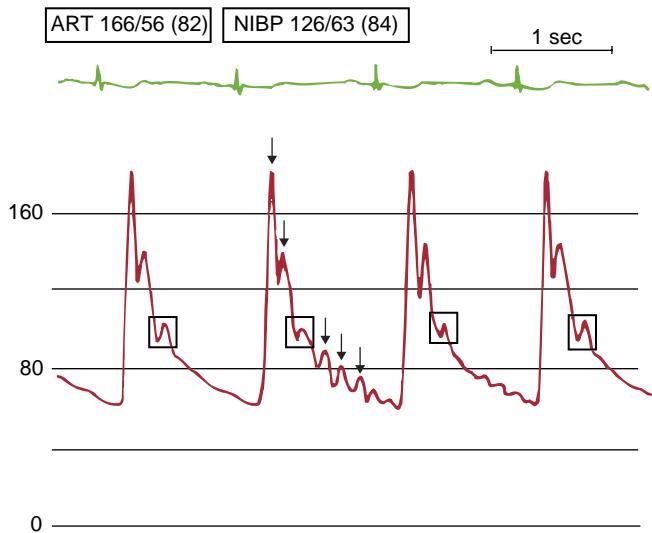


Fig. 36.22 Underdamped arterial pressure waveform. Systolic pressure overshoot and additional small, nonphysiologic pressure waves (arrows) distort the waveform and make it hard to discern the dicrotic notch (boxes). Digital values displayed for direct arterial blood pressure (ART 166/56, mean 82 mm Hg) and noninvasive blood pressure (NIBP 126/63, mean 84 mm Hg) show the characteristic relationship between the two measurement techniques in the presence of an underdamped system. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

and display systolic pressure overshoot (Fig. 36.22). In contrast, an overdamped waveform exhibits a slurred upstroke, absent dicrotic notch, and loss of fine detail. In such cases, the pulse pressure will be falsely narrow but MAP may remain reasonably accurate (Fig. 36.23).

The interplay between natural frequency and damping coefficients is complex, but in general, the lower the natural frequency of the system, the narrower the range of acceptable damping coefficients. It follows logically that for any specific system, the highest possible natural frequency yields the optimal result.¹⁰⁵ In theory, this is best achieved by using short lengths of stiff pressure tubing and limiting

additions or connections to the system such as stopcocks. While adding an air bubble to the monitoring system will increase damping, it simultaneously lowers natural frequency and may actually increase the intrinsic system resonance and worsen systolic pressure overshoot (Fig. 36.24).

The fast-flush test provides a convenient bedside method for determining system dynamic response and assessing signal distortion.^{101,103,105} The nature and duration of the flush artifact following a brief opening of the fast-flush valve are noted visually with shorter oscillation cycles indicating a higher natural frequency and the damping coefficient being related to the resulting pattern of peak amplitudes (Fig. 36.25).^{101,105} Thus, an adequate fast-flush test pattern has short oscillation cycles (<30 ms) and a pattern of amplitudes that rapidly return to rest. The clinical impact of resonance and under- or over-damping is common, occurring in up to 30% of surgical patients and 44.5% of patients admitted to the ICU. Interestingly, it appears to be more significant for systolic blood pressure measurement than mean or diastolic, and is associated with preexisting arteriopathy, lung disease, hypertension, and smaller-gauge arterial catheters.¹⁰⁷ Distortion of the arterial waveform is common in clinical practice, particularly systolic pressure overshoot secondary to underdamped systems.^{101,108}

Pressure Monitoring System Components

Arterial pressure monitoring systems have a number of components, including the intraarterial catheter itself, stopcocks for blood sampling and transducer zeroing, in-line blood sampling ports, a pressure transducer, continuous-flush device, and electronic cable. Innovation to the basic system such as needleless ports and closed aspiration systems, while intended to improve safety, may also degrade the dynamic response of the monitoring system and further exacerbate systolic arterial pressure overshoot.

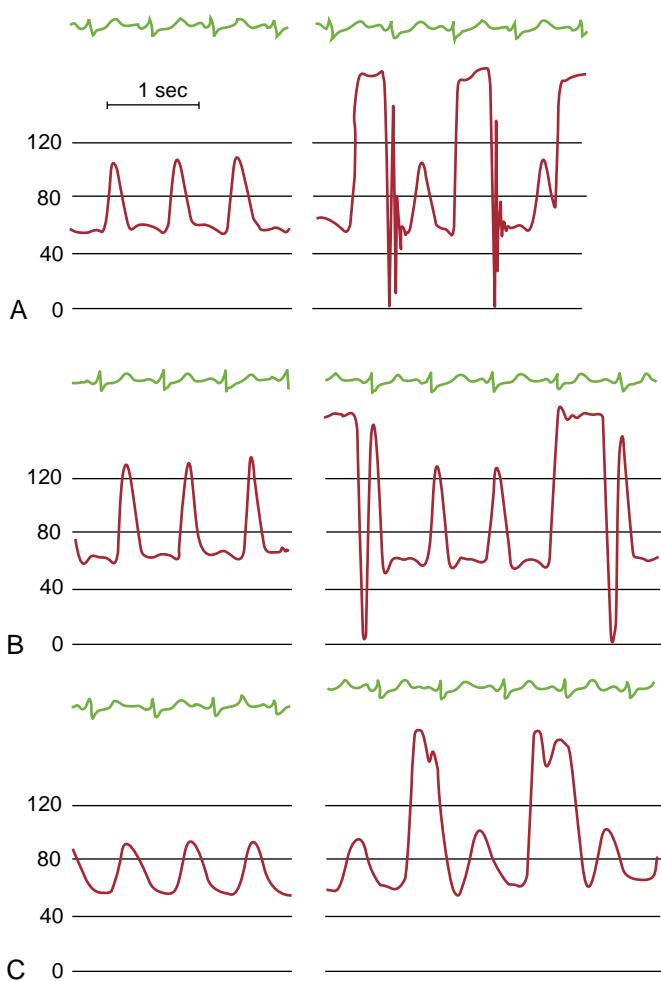


Fig. 36.24 Effect of small air bubbles within arterial pressure monitoring systems. Arterial pressure waveforms are displayed, along with superimposed fast-flush square-wave artifacts. (A) Original monitoring system has an adequate dynamic response (natural frequency 17 Hz, damping coefficient 0.2). (B) A small 0.1-mL air bubble added to the monitoring system produces a paradoxical increase in arterial blood pressure. Note decreased natural frequency of the system. (C) A larger 0.5-mL air bubble further degrades dynamic response and produces spurious arterial hypotension. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

The flush device provides a continuous, slow (1–3 mL/h) infusion of saline to purge the monitoring system and prevent thrombus formation within the system. Dextrose solutions should not be used, since flush contamination of sampled blood may cause serious errors in blood glucose measurement.¹⁰⁹ The flush device not only ensures continuous slow flushing of the system but also includes a spring-loaded valve for periodic, high-pressure flushing following sample collection or to restore the system's dynamic response to baseline.¹¹⁰

Transducer Setup: Zeroing and Leveling

Prior to use, pressure transducers must be zeroed, calibrated, and leveled to the appropriate position, a maneuver accomplished by exposing the transducer to atmospheric pressure and performing the zero procedure as defined by each device manufacturer. It is important to recognize that the *zero pressure locus* should be positioned appropriately given the specific clinical context, that it is positioned

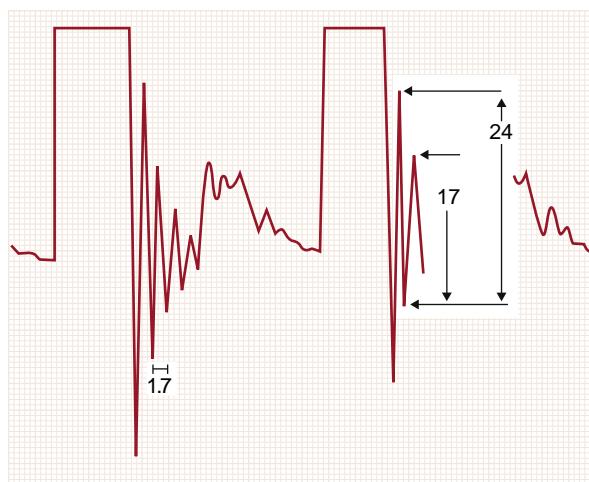


Fig. 36.25 Clinical measurement of natural frequency and damping coefficient. Two square-wave fast-flush artifacts interrupt an arterial pressure waveform recorded on standard 1-mm grid paper at a speed of 25 mm/s. Natural frequency is determined by measuring the period of one cycle of adjacent oscillation peaks (1.7 mm). Damping coefficient is determined by measuring the heights of adjacent oscillation peaks (17 and 24 mm). From these measurements, a natural frequency of 14.7 Hz and an amplitude ratio of 0.71 may be calculated. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

relative to the patient, that the zero reference point is local atmospheric pressure, and that the zero should be checked and re-zeroed periodically.¹⁰⁵ Occasionally, a faulty transducer, cable, or monitor will cause the zero baseline to drift, introducing significant error until the zero reference is reestablished.^{111,112} Because current disposable pressure transducers meet accuracy standards established by the AAMI and the American National Standards Institute, formal bedside transducer calibration is no longer routinely performed. However, it remains good practice to routinely compare pressures obtained via a newly placed arterial catheter with a blood pressure obtained via other means.^{111,112}

Choosing the appropriate level at which to establish the zero point must be done with respect to the patient and the clinical context. Note that transducer zeroing and leveling are distinct and separate. Zeroing establishes the zero reference point as ambient atmospheric pressure, while leveling aligns this reference point relative to the patient's body, determining where the value "0" will be. This is even more important when monitoring values for which the physiologic range is small, such as central venous or intracranial pressure. In such cases, small zeroing or leveling errors may translate to large relative errors in measurement.

In most cases, arterial pressure transducers should be placed to best estimate aortic root pressure. In general, the best position for this is approximately 5 cm posterior to the sternal border.^{113,114} However, a more conventional location for the reference level used for all hemodynamic monitoring, including central venous and pulmonary artery pressures (PAPs), is the mid-thoracic level, which corresponds most closely to the mid-left atrial position and is located halfway between the anterior sternum and the bed surface in the supine patient.^{115,116} The most critical point, regardless of where the clinician chooses to assign the reference level, is that it is consistently maintained throughout the monitoring period.

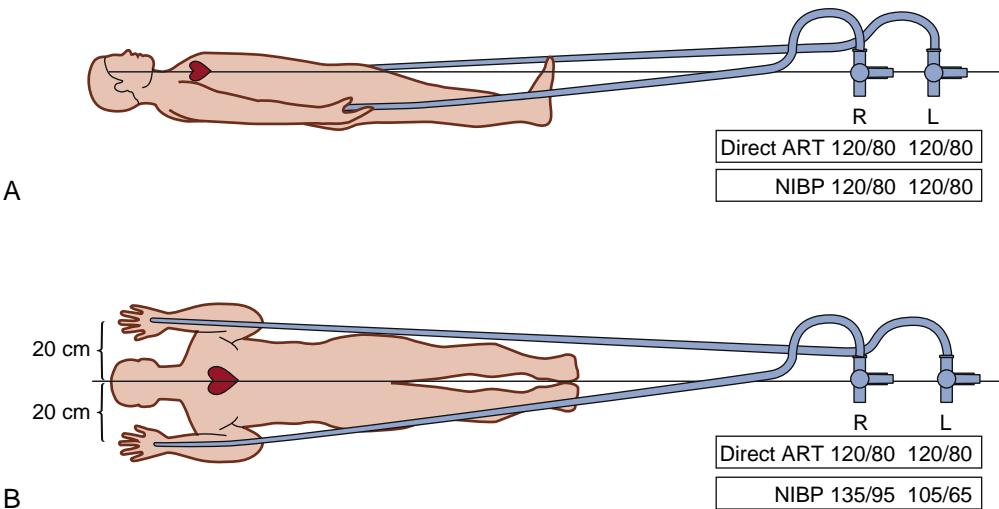


Fig. 36.26 Effect of patient position on the relation between direct arterial blood pressure (ART) and indirect noninvasive blood pressure (NIBP) measurements. (A) In the supine patient, pressures measured from the right (R) or left (L) arms by either technique will be the same. (B) In the right lateral decubitus position, ART pressures recorded directly from the right and left radial arteries will remain unchanged so long as the respective pressure transducers remain at heart level. However, NIBP will be higher in the dependent right arm and lower in the nondependent left arm. Differences in NIBP are determined by the positions of the arms above and below the level of the heart and are equal to the hydrostatic pressure differences between the level of the heart and the respective arm. A 20-cm difference in height produces a 15-mm Hg difference in pressure. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

In specific circumstances, though, clinicians may choose to place the transducer at a level different from the standard. For example, during a sitting neurosurgical procedure, it may be more informative to place it at the level of the patient's ear to approximate the level of the Circle of Willis. In such cases, the blood pressure at the level of the brain is being measured and displayed rather than that of the aortic root, which will be significantly higher. Fixing the transducer to a pole rather than the bed risks introducing error when the bed height or position is changed.

For proper interpretation of blood pressure measurements from a patient in the lateral decubitus position, differentiating zeroing and leveling pressure transducers and appreciating the differences between noninvasive and invasive blood pressure measurement is an informative exercise. In this position, while the aortic root remains stationary, one arm is necessarily higher than the other. However, as long as the pressure transducer remains *fixed at the level of the heart*, the measured pressure remains completely unaffected by the position of the arms, or location of the arterial catheter. Conversely, non-invasive cuff blood pressure measurements will differ in the two arms, being higher in the dependent (down) arm and lower in the non-dependent (up) arm (Fig. 36.26). This relationship must be taken into account when using the cuff to calibrate an invasively measured pressure.

Normal Arterial Pressure Waveforms

The systemic arterial pressure waveform results from ejection of blood from the left ventricle during systole followed by peripheral runoff during diastole. The systolic waveform immediately follows the ECG R wave and consists of a steep pressure upstroke, peak, and ensuing decline. The downslope of the arterial pressure waveform is interrupted by the dicrotic notch, continues its decline during diastole after the ECG T wave, and reaches its nadir at end-diastole

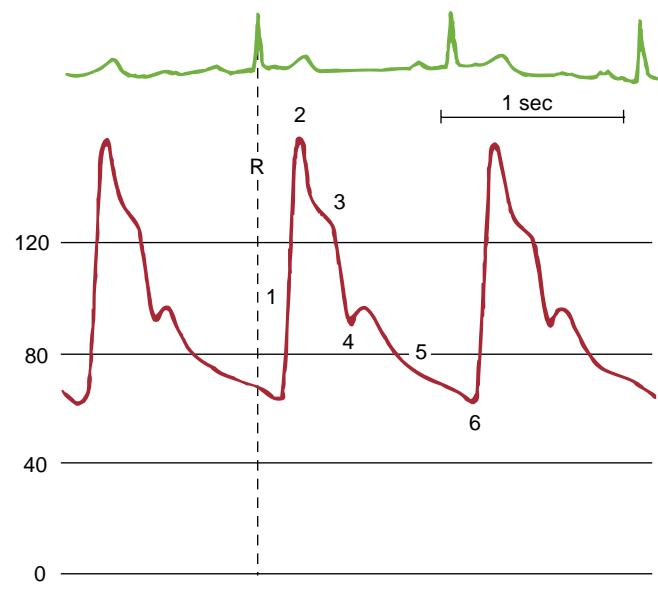


Fig. 36.27 Normal arterial blood pressure waveform and its relation to the electrocardiographic R wave. (1) Systolic upstroke, (2) systolic peak pressure, (3) systolic decline, (4) dicrotic notch, (5) diastolic runoff, and (6) end-diastolic pressure. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

(Fig. 36.27). The dicrotic notch of a central aortic pressure waveform is sharply defined and thought to result from aortic valve closure.¹¹⁷ In contrast, more peripheral arterial waveforms generally display a slightly delayed and mildly blunted dicrotic notch that is more dependent on properties of the arterial wall. Note that the systolic upstroke starts 120 to 180 ms after beginning of the R wave, reflecting the time required for LV depolarization, isovolumic contraction, opening of the aortic valve, LV ejection, and propagation of the pressure wave through the aorta to the pressure transducer (see Fig. 36.27).

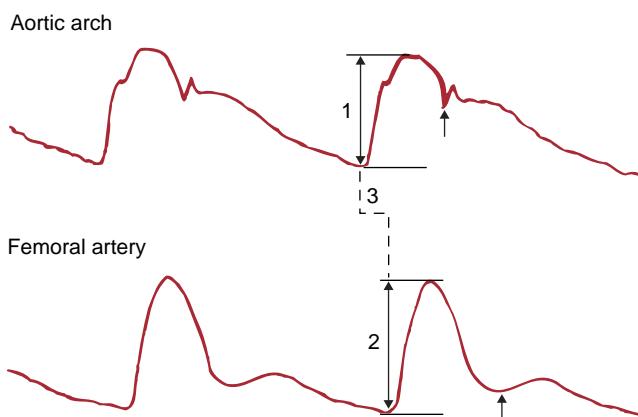


Fig. 36.28 Distal pulse wave amplification of the arterial pressure waveform. Compared with pressure in the aortic arch, the more peripherally recorded femoral artery pressure waveform demonstrates a wider pulse pressure (compare 1 and 2), a delayed start to the systolic upstroke (3), a delayed, slurred dicrotic notch (compare arrows), and a more prominent diastolic wave. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

The bedside monitor displays values for the systolic peak and end-diastolic nadir pressures. In simplest terms, MAP reflects the area beneath the arterial pressure curve divided by the beat period, averaged over multiple cardiac cycles, but is dependent on device-specific algorithms. MAP is sometimes estimated as diastolic pressure plus one third of the pulse pressure but this shortcut is only valid at slower heart rates, because the duration of diastole decreases as the heart rate increases.¹¹⁸

The morphology of the arterial waveform and the precise values of systolic and diastolic blood pressure vary throughout the arterial system even under normal conditions in healthy individuals in a variety of ways. Distal pulse amplification is one such example. Pressure waveforms recorded simultaneously from different sites have different morphologies due to the physical characteristics of the vascular tree, namely, impedance and harmonic resonance (Fig. 36.28).^{62,119} As the pressure wave travels from the central aorta to the periphery, the arterial upstroke becomes steeper, the systolic peak rises, the dicrotic notch appears later, the diastolic wave becomes more prominent, and end-diastolic pressure falls. As a result, peripheral arterial waveforms have higher systolic, lower diastolic, and wider pulse pressures compared with central aortic waveforms. Interestingly, the displayed MAP is only slightly increased.

Reflection of pressure waves within the arterial tree significantly affects the arterial pressure waveform as it travels peripherally.¹¹⁹ As blood flows from the aorta to the radial artery, MAP decreases only slightly because there is little resistance to flow in the major conducting arteries. At the arteriolar level, though, resistance to flow shrinks pressure pulsations in smaller downstream vessels but augments upstream arterial pressure pulses due to reflected pressure waves.¹²⁰ It is the summation of these antegrade and reflected waves that determines the shape of the displayed waveform. For example, reduced arterial compliance causes extremely rapid return of reflected pressure waves, resulting in arterial pressure waveforms with increased pulse pressure, a late systolic pressure peak, attenuated diastolic pressure waves, and at times, an early systolic hump distorting the smooth upstroke (Fig. 36.29).

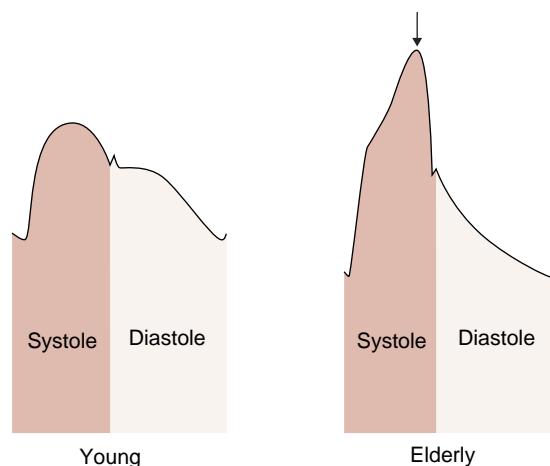


Fig. 36.29 Impact of pressure wave reflection on arterial pressure waveforms. In older individuals with reduced arterial compliance, early return of peripherally reflected waves increases pulse pressure, produces a late systolic pressure peak (arrow), attenuates the diastolic pressure wave, and at times, distorts the smooth upstroke with an early systolic hump.

Arterial Blood Pressure Gradients

Numerous pathophysiologic conditions cause exaggerated arterial pressure gradients between monitoring sites, be they real, iatrogenic, or artifactual. Frank and coworkers found that 21% of patients undergoing peripheral vascular surgery had a blood pressure difference between the two arms that exceeded 20 mm Hg.¹²¹ Atherosclerosis, arterial dissection, stenosis, or embolism may exclude certain locations as reliable sites for invasive monitoring. In addition, certain patient positions, surgical retraction, or clamp placement may compromise perfusion in regional or local areas, precluding specific sites from use for invasive monitoring.^{122,123}

Pathologic changes in peripheral vascular resistance may also produce generalized arterial pressure gradients that can affect the choice of site for arterial pressure monitoring. In patients receiving vasopressor infusions for septic shock, the femoral arterial pressure may exceed the radial pressure by greater than 50 mm Hg.¹²⁴ Less severe gradients have been noted with general anesthesia, neuraxial blocks, and changes in patient temperature.⁶² During hypothermia, vasoconstriction causes systolic pressure in the radial artery to exceed that in the femoral artery, whereas during rewarming, vasodilation reverses the gradient.¹²⁵

Characteristic gradients between central and peripheral sites have also been described during cardiopulmonary bypass (Fig. 36.30). The mean radial artery pressure falls on initiation of bypass and remains lower than mean femoral artery pressure throughout the bypass period and into the initial postbypass period, often by more than 20 mm Hg.^{126,127} In most patients, this gradient resolves within the first hour, but occasionally remains well into the postoperative period.

Abnormal Arterial Pressure Waveforms

The morphologic features of individual arterial pressure waveforms can provide important diagnostic information (Table 36.1) (Fig. 36.31A–D). Aortic stenosis produces a

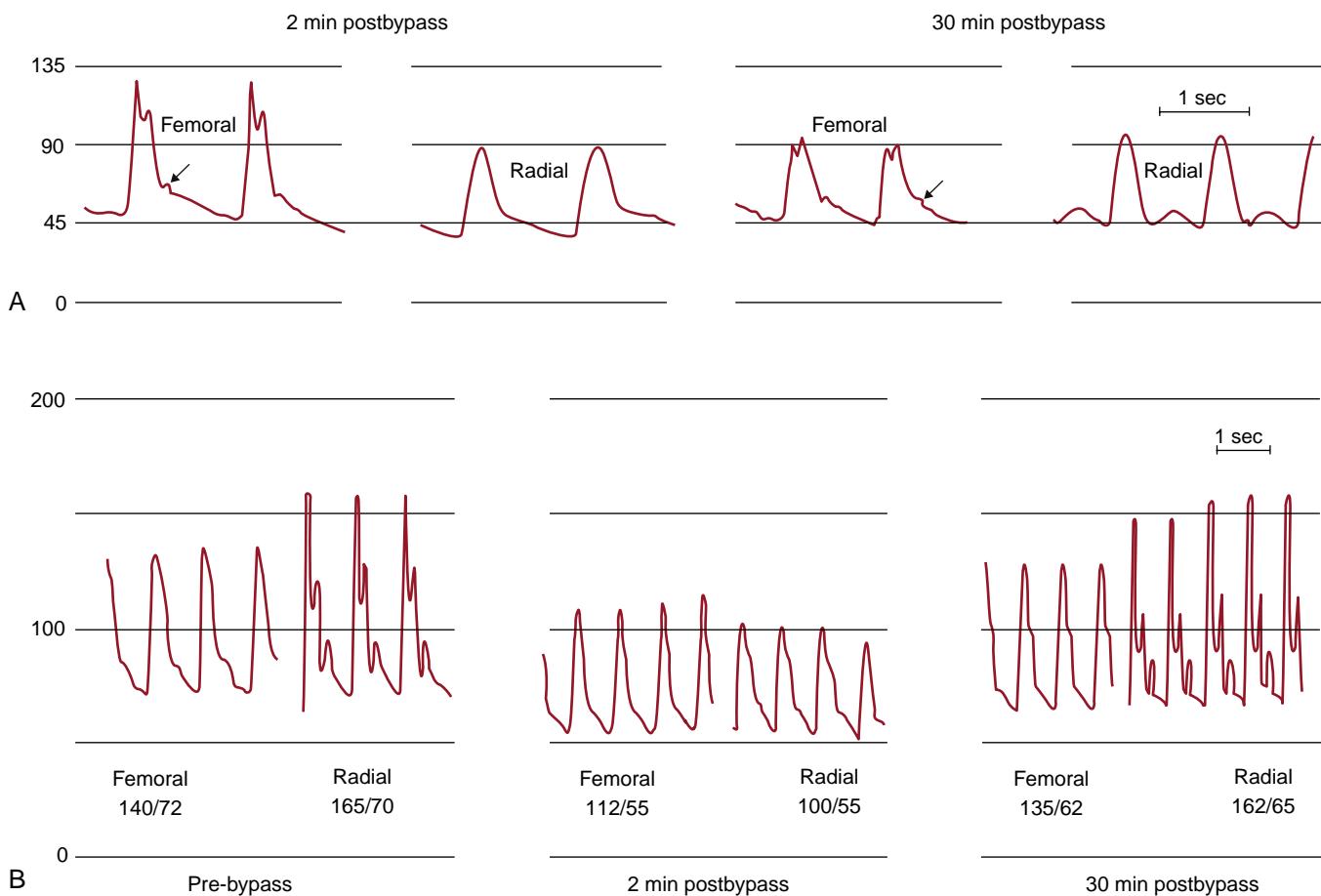


Fig. 36.30 Arterial pressure gradients following cardiopulmonary bypass. (A) Femoral and radial artery pressure traces recorded 2 minutes after bypass (2 min postbypass), when radial artery pressure underestimates the more centrally measured femoral artery pressure and 30 minutes later (30 min postbypass), when radial and femoral arterial pressures have equalized and radial pressure has resumed a more typical morphology. Note that dicrotic notch (arrows) is visible in the femoral pressure trace immediately after bypass, but is delayed in the radial pressure trace. (B) Femoral and radial artery pressure traces recorded before cardiopulmonary bypass (pre-bypass), 2 minutes following bypass (2 min postbypass), and 30 minutes following bypass (30 min postbypass). Note changing relationship between femoral and radial artery pressure measurements at these different times.

TABLE 36.1 Arterial Blood Pressure Waveform Abnormalities

Condition	Characteristics
Aortic stenosis	Pulsus parvus (narrow pulse pressure) Pulsus tardus (delayed upstroke)
Aortic regurgitation	Bisferiens pulse (double peak) Wide pulse pressure
Hypertrophic cardiomyopathy	Spike and dome (mid-systolic obstruction)
Systolic left ventricular failure	Pulsus alternans (alternating pulse pressure amplitude)
Cardiac tamponade	Pulsus paradoxus (exaggerated decrease in systolic blood pressure during spontaneous inspiration)

fixed obstruction to ejection resulting in reduced stroke volume and a slowed rate of ejection. As a result, the waveform is small in amplitude (*pulsus parvus*), has a slowly rising systolic upstroke (*pulsus tardus*), and a delayed peak in systole (see Fig. 36.31B). A distinct shoulder, termed the anacrotic notch, often distorts the pressure upstroke and the dicrotic

notch may not be discernible. These features may make the arterial pressure waveform appear overdamped.

In aortic regurgitation, the arterial pressure wave displays a sharp rise, wide pulse pressure, and low diastolic pressure owing to the diastolic runoff of blood both antegrade into the aortic root and retrograde into the left ventricle. The arterial pressure pulse may have two systolic peaks (*bisferiens pulse*), with the first peak resulting from antegrade ejection and the second from a wave reflected from the periphery (see Fig. 36.31C). In hypertrophic cardiomyopathy, the waveform assumes a peculiar bifid shape termed a “spike-and-dome” configuration. After an initial sharp blood pressure increase resulting from rapid, early systolic ejection, arterial pressure abruptly falls as mid-systolic LV outflow obstruction interrupts stroke volume ejection. This is finally followed by a second, late-systolic increase associated with arrival of reflected waves from the periphery (see Fig. 36.31D).

Changes in arterial waveform patterns over time are also valuable. *Pulsus alternans* is a pattern of alternating larger and smaller pressure waves that appear to vary with the respiratory cycle and is generally associated with severe LV systolic dysfunction or aortic stenosis (Fig. 36.32A).

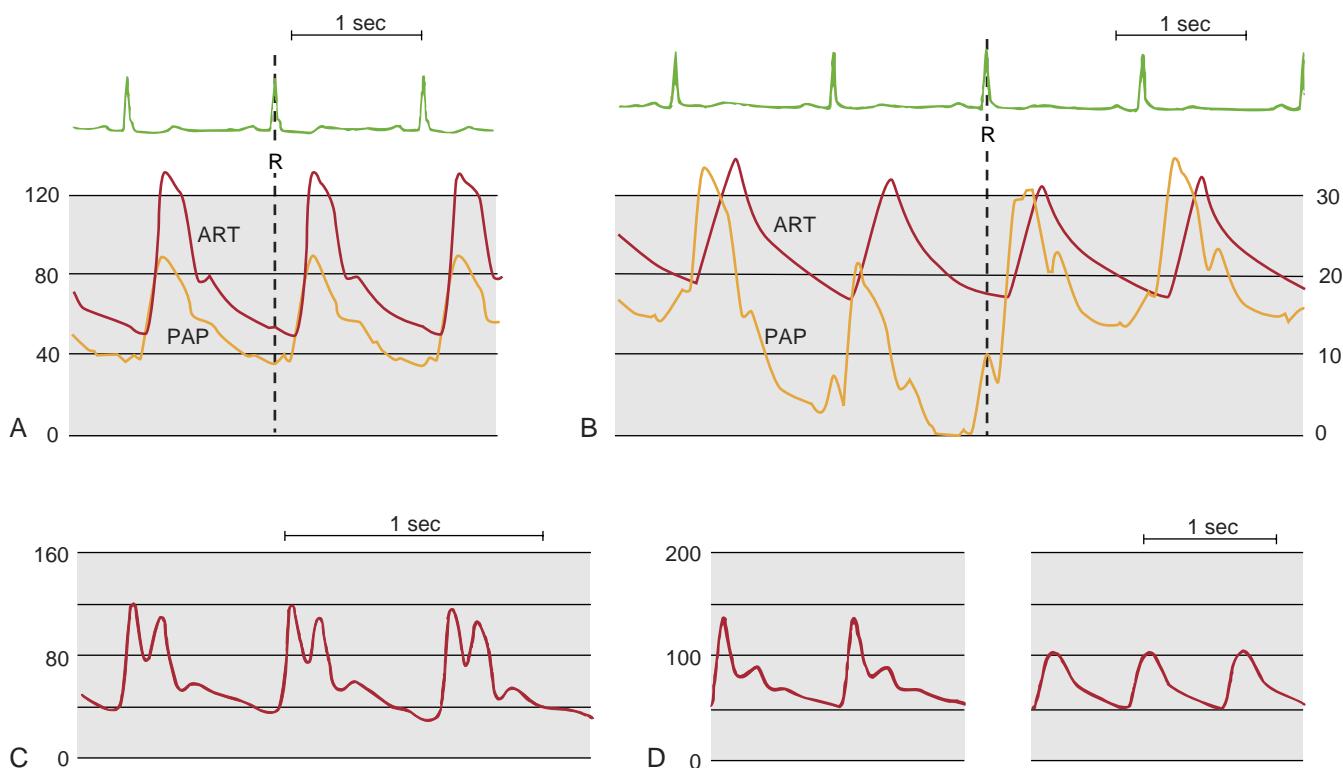


Fig. 36.31 Influence of pathologic conditions on arterial pressure (ART) waveform morphology. (A) Normal ART and pulmonary artery pressure (PAP) waveform morphologies demonstrating the similar timing of these waveforms relative to the electrocardiographic R wave. (B) In aortic stenosis, the ART waveform is distorted with a slurred upstroke and delayed systolic peak. These changes are particularly striking in comparison with the normal PAP waveform. Note the beat-to-beat respiratory variation in the PAP waveform. For A and B, the ART scale is on the left and the PAP scale is on the right. (C) Aortic regurgitation produces a bisferiens pulse and a wide pulse pressure. (D) Arterial pressure waveform in hypertrophic cardiomyopathy shows a peculiar spike-and-dome configuration. The waveform assumes a more normal morphology following surgical correction of this condition. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

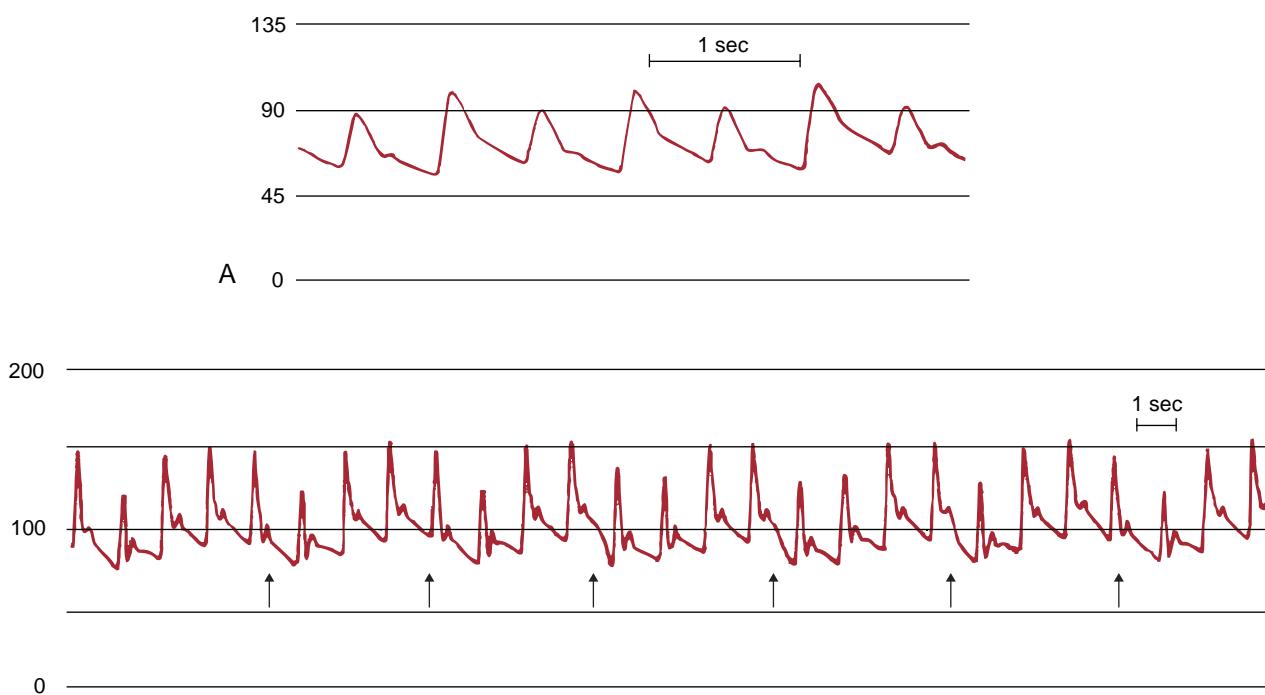


Fig. 36.32 Beat-to-beat variability in arterial pressure waveform morphologies. (A) Pulsus alternans. (B) Pulsus paradoxus. The marked decline in both systolic blood pressure and pulse pressure during spontaneous inspiration (arrows) is characteristic of cardiac tamponade. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

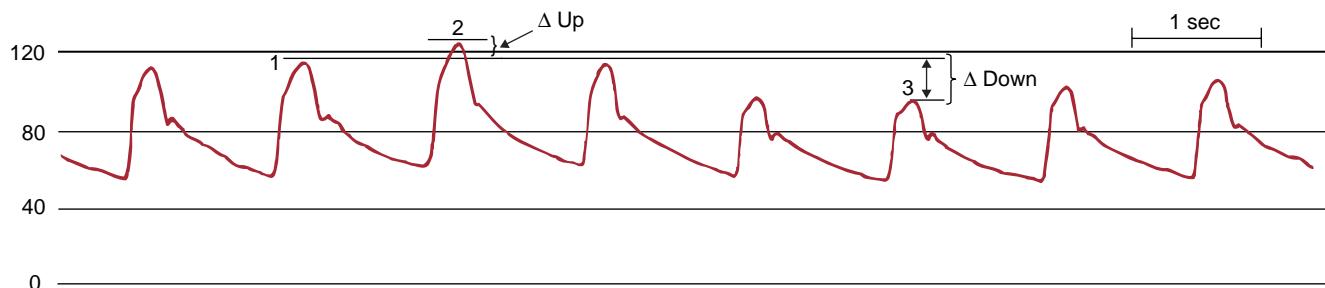


Fig. 36.33 Systolic pressure variation. Compared with systolic blood pressure recorded at end expiration (1) a small increase occurs during positive-pressure inspiration (2, Δ Up) followed by a decrease (3, Δ Down). Normally, systolic pressure variation does not exceed 10 mm Hg. In this instance, the large Δ Down indicates hypovolemia even though systolic arterial pressure and heart rate are relatively normal. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

Pulsus paradoxus is an exaggerated variation in arterial pressure (>10 – 12 mm Hg) during quiet breathing (see Fig. 36.32B).^{128,129} *Pulsus paradoxus* is not truly paradoxical, but rather an exaggeration of a normal variation in blood pressure that accompanies spontaneous ventilation. *Pulsus paradoxus* is a common and important sign in cardiac tamponade but may also be seen with pericardial constriction, severe airway obstruction, bronchospasm, dyspnea, or any condition that involves large swings in intrathoracic pressure. Importantly, though, in cases of cardiac tamponade, the *pulse pressure* and *left ventricular stroke volume* decrease during inspiration, in contrast to the pattern observed associated with large variations in intrathoracic pressure in which *pulse pressure* remains constant.¹³⁰

Arterial Pressure Monitoring and Waveform Analysis for Prediction of Volume Responsiveness

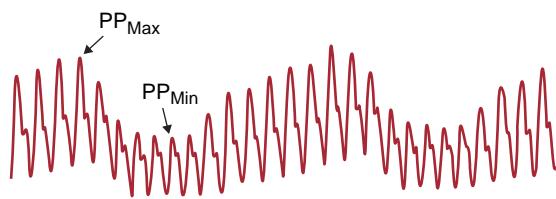
The starting point for volume resuscitation begins with optimizing cardiac preload, or more precisely, identifying the presence of residual preload reserve. The limitations and potential confounders of static indicators of preload such as central venous pressure (CVP) are well documented.¹³¹ A wide array of dynamic markers of preload reserve and volume responsiveness have been described and evaluated for their ability to discriminate patients for whom volume expansion would be beneficial from those for whom it would not. These are largely based on cyclic variations in arterial blood pressure resulting from respiratory-induced changes in intrathoracic pressure.

During the inspiratory phase of a positive pressure breath, the increase in intrathoracic pressure simultaneously decreases LV afterload while increasing total lung volume which displaces blood from the pulmonary venous reservoir forward into the left side of the heart and increases LV preload. The increase in LV preload and decrease in afterload produce an increase in LV stroke volume, an increase in cardiac output, and in the absence of changes in system resistance, an increase in systemic arterial pressure. In most patients the preload effects predominate, but in patients with severe LV systolic failure, the reduction in afterload facilitates ventricular ejection. At the same time, rising intrathoracic pressure impairs systemic venous return and RV preload, possibly increasing RV afterload by slightly increasing pulmonary vascular resistance. These effects combine to reduce RV ejection during the early phase of inspiration. During the expiratory phase, however, the situation is reversed. The smaller stroke volume

ejected from the RV during inspiration traverses the pulmonary vascular bed and enters the left heart, resulting in reduced LV filling, reduced LV stroke volume, and a fall in systemic arterial blood pressure. This cycle of increasing and decreasing stroke volume and systemic arterial blood pressure in response to inspiration and expiration is known as the *systolic pressure variation* (SPV).

SPV is often subdivided into inspiratory and expiratory components by measuring the increase (Δ Up) and decrease (Δ Down) in systolic pressure relative to the end-expiratory, apneic baseline pressure (Fig. 36.33). In a mechanically ventilated patient, normal SPV is 7 to 10 mm Hg, with Δ Up being 2 to 4 mm Hg and Δ Down being 5 to 6 mm Hg. Values greater than this are felt to indicate hypovolemia.^{66,67} Both in experimental animals and critically ill patients, hypovolemia causes a dramatic increase in SPV, particularly the Δ Down component. Patients who manifest increased SPV during positive pressure mechanical ventilation may be described clinically as having residual preload reserve or being “volume responsive.” While not synonymous with hypovolemia, preload reserve describes a physiologic state in which volume expansion or fluid challenge shifts the patient upward on the Frank-Starling curve resulting in increased stroke volume and increased cardiac output as long as systemic vascular resistance remains unchanged. Indeed, in a heterogeneous group of intensive care patients, Marik demonstrated that a large SPV (>15 mm Hg) was highly predictive of a low pulmonary artery wedge pressure (PAWP; <10 mm Hg), a surrogate for LV preload reserve.¹³²

Pulse pressure variation (PPV), another dynamic indicator of preload reserve, is now available as part of standard monitoring software packages whenever an invasive arterial catheter is in use. In general, normal PPV is less than 13% to 17% (Fig. 36.34).^{133–137} More sophisticated methods of pulse contour analysis allow real-time measurement of *stroke volume variation* (SVV), as well as calculation of a *stroke volume variation index*. When these measures exceed 10% to 13%, the patient is likely to have a positive response to volume expansion.^{136,138} Although all of these dynamic measures are thought to indicate preload reserve, they are not interchangeable. PPV has been shown to diverge from SVV in the setting of vasopressor use or when the autonomic nervous system intervenes to preserve perfusion pressure in the face of falling stroke volume. In such cases, PPV will remain low while SVV increases.^{139,140}



Note: The arterial blood pressure tracing is not drawn to scale

$$PP_{Max} = 150-70-80$$

$$PP_{Min} = 120-60-60$$

$$PPV = (PP_{Max} - PP_{Min}) / [(PP_{Max} + PP_{Min}) / 2]$$

$$PPV = 80-60 / [(80+60) / 2] = 29\%$$

Fig. 36.34 Pulse pressure variation. Pulse pressure variation (PPV) is calculated as the difference between maximal (PP_{Max}) and minimal (PP_{Min}) pulse pressure values during a single mechanical respiratory cycle, divided by the average of these two values. (Note that the arterial blood pressure trace is drawn for illustrative purposes and not to scale.)

Devices based on respiratory cycle-induced variation in the pulse plethysmogram have been developed as a similar but less invasive alternative for assessing preload reserve or volume responsiveness. Measures such as *photoplethysmography variation* (ΔPOP) or the *plethysmography variability index* appear to be useful when clinical and environmental conditions are optimal, but the transcutaneous oximetry signal is even more subject to confounding influences than the arterial blood pressure waveform.^{135,141,142} Tidal volume, core and peripheral temperature, ambient light, and cardiac dysrhythmias pose significant impediments to valid and reproducible data collection and interpretation. There is no consensus regarding meaningful threshold values, and validity seems especially poor in children, in settings where patients are ventilated and sedated but not paralyzed, or in the setting of an open abdomen.¹⁴² Furthermore, there are sophisticated auto-gaining features incorporated in most commercially available monitoring systems to optimize signal display. As such, the degree of variation visible to the naked eye may not correlate with true signal variation, resulting in erroneous clinical decisions and incorrect therapy.

Evidence is accumulating that dynamic measures are significantly superior to static indices of intravascular volume, especially in critically ill patients. Both PVV and SVV have been shown to be accurate following cardiac surgery in patients with normal and reduced ventricular function, while PPV was validated in assessing fluid responsiveness in patients with septic shock.^{143,144} Intraoperative use has also been examined with similar results.^{145,146} Indeed, the ability of clinicians to “eyeball” respiratory variation in the arterial blood pressure waveform as displayed on the monitor seems reasonably accurate. Subjective estimates of such pressure variation were incorrect only 4.4% of the time, a rate that would have resulted in only 1% of treatments being erroneous.¹³⁷

There is disagreement on precise threshold values that differentiate fluid responders from non-responders, and the variety of techniques, devices, and approaches have not been standardized.¹³⁵ In a recent systematic review, mean discriminatory thresholds defining volume responsiveness for PVV and SVV were found to be $12.5\% \pm 1.6\%$ and $11.6\% \pm 1.9\%$, respectively, with acceptable sensitivities and specificities (89%, 88% and 82%, 86%,

respectively).¹⁴⁷ However, simply differentiating patients who will respond from those who will not fails to take into account the nature of the clinical intervention at issue. Volume expansion does not result in a dichotomous outcome, and the asymmetric nature of the Frank-Starling curve dictates that the cost-benefit ratio of acting in one direction will be different from acting in the other. For any given change in preload, the change in stroke volume will be different depending on the direction of the preload change, with that differential being dependent on how close to the peak of the curve the patient begins. Consequently, the concept of the “gray zone” has been proposed that defines a range of values between which evidence-based decision making is not possible.¹⁴⁸ For PPV, this zone has been described as 9% to 13% such that those above 13% should receive volume expansion while those below 9% should not. Between those two values, the measurement is not able to provide meaningful guidance and the decision should be based on other criteria.^{136,149}

Continuous display of PPV is now routine on bedside monitors, a feature that has facilitated rapid adoption of dynamic preload reserve assessment.^{150,151} As such, while its use is clinically relevant, it is even more important to understand the shortcomings of all respiratory-induced dynamic indicators and the clinical conditions under which they were originally studied and validated. While PPV appears to be valid in the setting of liver failure, it is significantly affected by increased abdominal pressure; patient position, including steep Trendelenburg, prone, or lateral positions; and use of vasopressors.^{136,140,152-154} Variability in diastolic filling causing variable stroke volumes makes irregular heart rhythms highly problematic in the use of all dynamic preload reserve indicators.^{155,156} In addition, there is evidence that patients with pulmonary hypertension or reduced RV ejection fraction may not have reliable responses to changes in intrathoracic pressure, increasing the risk of over-hydration and worsening right heart failure.¹⁵⁷ Dynamic indices are of marginal value in the setting of either minimally invasive or open thoracic surgery, and their use in children is considered unreliable due to the increased compliance of the myocardium and the chest wall in younger patients.^{158,159} It has even been suggested that tachypnea, (especially in the setting of respiratory failure), or significant bradycardia may disrupt the relationship between respiratory-cycle-induced changes in intrathoracic pressure and cardiac chamber volumes, thus invalidating the theoretical basis for blood pressure variation analysis.¹³⁶

Most importantly, though, is the profound effect of protective lung ventilation on the predictive power of respiratory-induced SPV, PPV, or SVV to identify a patient with residual preload reserve.¹⁶⁰⁻¹⁶² Mechanical ventilation with tidal volume of 8 to 10 mL/kg, positive end-expiratory pressure ≥ 5 mm Hg, regular cardiac rhythm, normal intra-abdominal pressure, and a closed chest are necessary to duplicate the experimental conditions under which most of these indices have been investigated, and these conditions are largely inconsistent with ventilatory parameters chosen for lung protective ventilation. Clinical trials have found waveform analysis to be of limited utility in this setting.¹⁶⁰⁻¹⁶² However, measuring PPV or SVV during or immediately following a recruitment maneuver increased

its sensitivity and specificity in predicting fluid responsiveness, although a broader gray zone of up to 26% should be considered.^{163,164}

As noted above, respiratory-cycle-induced arterial pressure variations are dependent on changes in LV preload and, to a lesser degree, afterload. Indeed, decreased arterial compliance and the resultant increased pulse pressure that accompanies both normal and pathologic vascular aging results in an exaggerated PPV response to any change in stroke volume. As such, it is possible that PPV thresholds should be higher in such patients than in those with greater elastance in their vascular trees.^{165,166}

Central Venous Pressure Monitoring

Cannulation of a central vein and direct measurement of CVP are frequently performed in hemodynamically unstable patients and those undergoing major operations. A central venous catheter may be inserted to provide secure vascular access for administration of vasoactive drugs or fluids, CVP monitoring, transvenous cardiac pacing, temporary hemodialysis, pulmonary artery catheterization (PAC) for more comprehensive cardiac monitoring, or aspiration of entrained air in patients at risk for venous air emboli. A central venous catheter may also be inserted when no peripheral access can be obtained, or when repeated venous blood sampling is required (Box 36.5).

CENTRAL VENOUS CANNULATION

When required in the intraoperative period, the decision to perform central venous cannulation before or after induction of anesthesia is guided most often by individual patient and physician preferences or institutional practice.

CHOOSING THE CATHETER, SITE, AND METHOD FOR CENTRAL VENOUS CANNULATION

Central venous catheters come in a variety of lengths, gauges, compositions, and lumen numbers.^{167,168} This makes it critical for the physician to choose the best catheter for any given application. Multiport catheters, which allow monitoring of CVP and infusion of drugs and fluids simultaneously, are the most common,¹⁶⁹ but introducer sheaths with one or two integrated ports for multiple drug infusions are an alternative. Introducer sheaths allow insertion of a single-lumen catheter through the hemostasis valve for continuous CVP monitoring and rapid placement of a pacing wire or PAC for more intensive monitoring should the need arise.

Selecting the best site for safe and effective central venous cannulation ultimately requires consideration of the indication for catheterization (pressure monitoring versus drug or fluid administration), the patient's underlying medical condition, the clinical setting, and the skill and experience of the physician performing the procedure. In patients with severe bleeding diatheses, it is best to choose a puncture site where bleeding from the vein or adjacent artery is easily detected and controlled with local compression. In such a patient, an internal or external

BOX 36.5 Indications for Central Venous Cannulation

- Central venous pressure monitoring
- Pulmonary artery catheterization and monitoring
- Transvenous cardiac pacing
- Temporary hemodialysis
- Drug administration
 - Concentrated vasoactive drugs
 - Hyperalimentation
 - Chemotherapy
 - Agents irritating to peripheral veins
 - Prolonged antibiotic therapy (e.g., endocarditis)
- Rapid infusion of fluids (via large cannulas)
 - Trauma
 - Major surgery
- Aspiration of air emboli
- Inadequate peripheral intravenous access
- Sampling site for repeated blood testing

jugular approach would be preferable to a subclavian site. Likewise, patients with severe emphysema or others who would be severely compromised by a pneumothorax would be better candidates for internal jugular than subclavian cannulation, owing to the higher risk with the latter approach. If transvenous cardiac pacing is required in an emergency situation, catheterization of the right internal jugular vein is recommended, as it provides the most direct route to the right ventricle. Trauma patients, with their necks immobilized in a hard cervical collar, are best resuscitated using a femoral or subclavian approach; the latter may be placed even more safely if the risk of pneumothorax is obviated by prior placement of a thoracostomy tube. The physician must recognize that the length of catheter inserted to position the catheter tip properly in the superior vena cava will vary according to puncture site, being slightly (3–5 cm) greater when the left internal or external jugular veins are chosen, compared with the right internal jugular vein.¹⁷⁰ Finally, a physician's personal experience undoubtedly plays a significant role in determining the safest site for central venous cannulation, particularly when the procedure is performed under urgent or emergent circumstances.

A central vein may be cannulated using either a landmark technique or ultrasound guidance. Ultrasound technology is now widely available and is strongly recommended for central line placement.^{171–173} The reader is referred to other sources for detailed descriptions and tutorials on the various insertion techniques for different access sites.^{169,174–176} Regardless of the insertion technique used or the cannulation site chosen, certain general principles should be emphasized. Ideally, a protocol or checklist describing the basic procedural steps for central line insertion should be in place at every institution, and all staff members should feel empowered to speak up when they witness a protocol violation. Standardized equipment, routine use of an assistant, hand washing, and maximal barrier precautions all contribute to the sterility of the procedure.¹⁷² The use of real-time ultrasound guidance for vessel localization and venipuncture should be routine or at least strongly considered, especially when the internal jugular vein site is selected. Waveform manometry or pressure measurement

BOX 36.6 Complications of Central Venous Pressure Monitoring

Mechanical
Vascular injury
Arterial
Venous
Cardiac tamponade
Respiratory compromise
Airway compression from hematoma
Pneumothorax
Nerve injury
Arrhythmias
Thromboembolic
Venous thrombosis
Pulmonary embolism
Arterial thrombosis and embolism
Catheter or guidewire embolism
Infectious
Insertion site infection
Catheter infection
Bloodstream infection
Endocarditis
Misinterpretation of data
Misuse of equipment

should be used to confirm venous placement of the catheter before use. Finally, the position of the catheter tip should be verified as soon as clinically appropriate to avoid delayed complications.

COMPLICATIONS OF CENTRAL VENOUS PRESSURE MONITORING

Complications of central venous cannulation are becoming increasingly recognized as major sources of morbidity with more than 15% of patients experiencing some sort of related adverse event.^{177,178} Although serious immediate complications are infrequent when these procedures are performed by well-trained, experienced clinicians, use of CVP catheters continues to result in significant morbidity and mortality. Complications are often divided into mechanical, thromboembolic, and infectious etiologies (Box 36.6).

Mechanical Complications of Central Venous Catheterization

The incidence of complications depends on a number of factors including the catheter insertion site and the patient's medical condition. Large retrospective and observational studies provide the best estimates of incidence and frequency.

Vascular injuries from central venous catheterization have a range of clinical consequences. The most common minor complications are localized hematoma or injury to the venous valves.¹⁷⁹ More serious complications include perforation into the pleural space or mediastinum, resulting in hydrothorax, hemothorax, hydromediastinum, hemo-mediastinum, and or chylothorax.¹⁸⁰⁻¹⁸⁶

In general, *unintended arterial puncture* is the most common acute mechanical complication, ranging from 1.9 to 15%.¹⁸⁷ Many of these injuries result in localized hematoma formation, but in rare occasions even small-gauge-needle punctures may lead to serious complications such as

arterial thromboembolism.¹⁸⁸ Delayed vascular complications following central venous catheterization are uncommon but should be considered as consequences of this procedure. A number of these have been described in the literature, including aorto-atrial fistula, venobronchial fistula, carotid artery–internal jugular vein fistula, and pseudoaneurysm formation.¹⁸⁹⁻¹⁹²

The most important life-threatening vascular complication of central venous catheterization is **cardiac tamponade** resulting from perforation of the intrapericardial superior vena cava, right atrium, or right ventricle, and resulting hemopericardium or unintentional pericardial instillation of intravenous fluid.¹⁹³ Most reports document the avoidable nature of this catastrophic event and highlight that patients are predisposed to this complication when central venous catheter tips are malpositioned within the heart chambers or abutting the wall of the superior vena cava at a steep angle. This latter position can be recognized radiographically as a gentle curvature of the catheter tip within the superior vena cava.¹⁹⁴ These observations emphasize that objective confirmation of proper catheter tip location is mandatory, regardless of whether the catheter is inserted from a central or peripheral site.

Pneumothorax is often cited as the most common complication of subclavian vein cannulation, although it appears that unintended arterial puncture is actually more frequent.^{99,195} Mansfield et al. reported 821 patients who underwent attempted subclavian venous cannulation, with a 1.5% incidence of pneumothorax and a 3.7% incidence of arterial puncture when using the landmark technique.¹⁹⁵ Pneumothorax is even less frequent with the internal jugular approach. Shah et al. reported an incidence of pneumothorax of 0.5% in their series of nearly 6000 internal jugular catheterizations.¹⁸⁷ This is most likely a high estimate, as these patients had undergone sternotomy for cardiac surgery, a procedure that may have been responsible for the pneumothorax in many cases.

Nerve injury is another potential complication of central venous cannulation. Damage may occur to the brachial plexus, stellate ganglion, phrenic nerve, or vocal cords.¹⁹⁶⁻¹⁹⁸ In addition, chronic pain syndromes have been attributed to this procedure.¹⁹⁹

Thromboembolic Complications of Central Venous Catheterization

Catheter-related thrombosis varies according to the site of central venous catheterization, occurring in as many as 21.5% of patients with femoral venous catheters and 1.9% of those with subclavian venous catheters.²⁰⁰ Catheters that are positioned low in the right atrium may be more prone to thrombus formation, possibly due to mechanical irritation of the right atrial endocardium by the catheter.²⁰¹ Thrombi that form at the catheter tip or adhere to the endocardium have the potential to become a nidus for infection, cause superior vena cava syndrome, or embolize into the pulmonary circulation.²⁰²⁻²⁰⁴ Occasionally, surgical removal is required.²⁰⁵

In addition to thromboembolism, other reported embolic complications of central venous catheterization include embolism of portions of the catheter or guidewire, and air

embolism.^{206,207} Almost invariably, these are the result of misuse of equipment, highlighting the need for proper education and training of nurses and physicians responsible for the use of these devices.

Infectious Complications of Central Venous Catheterization

By far, the most common major late complication of central venous cannulation is *infection*. Major progress has been made in the control of central line-associated blood stream infections (CLABSI), likely due to a focus on evidence-based best practices for catheter insertion and maintenance.²⁰⁸ In fact, CLABSI rates have declined by about 50% between 2008 and 2016.²⁰⁹ The majority of CLABSIs are occurring in inpatient wards and outpatients receiving hemodialysis, but approximately one third of these cases still occur in the ICU, a cohort that likely includes most of the catheters placed intraoperatively.²⁰⁹⁻²¹¹

As previously noted, the starting point for prevention of infection is meticulous attention to aseptic technique.²¹² Multilumen catheters may carry a higher risk of infection than single-lumen catheters although the added clinical functionality of such catheters often mandates their use.^{178,213} Catheters are made from materials such as silicone, polyvinyl chloride, Teflon, and polyurethane. Furthermore, catheters of the same material may be manufactured differently, which influences their surfaces and the frequency of bacterial adherence to the surface.²¹⁴ Heparin-bonded central venous catheters have been shown to reduce the incidence of catheter-related thrombosis and infection in children and adults.^{215,216} The incorporation of antimicrobial treatments such as silver (this metal has broad antimicrobial activity and is nontoxic), combinations of the antiseptics chlorhexidine and silver sulfadiazine, or the antibiotics minocycline and rifampin onto the catheter surfaces have been shown to reduce rates of catheter colonization and in some cases blood stream infection.²¹⁶⁻²¹⁸ The added expense has prevented more widespread adoption of these catheters, although an analysis has suggested their cost-effectiveness in settings in which the rate of catheter-related infections remains high (more than 3.3 per 1000 catheter days).²¹⁹

A chlorhexidine gluconate-impregnated sponge dressing has been shown to reduce catheter colonization in infants and children, but does not reduce the rate of catheter-associated bloodstream infections.^{220,221} Current guidelines from the Centers for Disease Control and Prevention do not support routine catheter site changes or scheduled changes over a guidewire and provide other detailed recommendations for catheter management to reduce the risk of infectious complications.^{213,222}

Overall, there does not appear to be an ideal site for central venous cannulation with respect to prevention of complications given that, taken together, the risk of mechanical, thrombotic, and infectious complications is similar among the three insertion sites. This was illustrated by a recent prospective, randomized, multicenter trial in adult ICU patients, where catheterization of the subclavian vein is associated with the lowest risk of infectious complications and deep vein thrombosis, but the highest risk of mechanical complications.²²³

TABLE 36.2 Normal Cardiovascular Pressures

Pressures	Average (mm Hg)	Range (mm Hg)
RIGHT ATRIUM		
a wave	6	2-7
v wave	5	2-7
Mean	3	1-5
RIGHT VENTRICLE		
Peak systolic	25	15-30
End-diastolic	6	1-7
PULMONARY ARTERY		
Peak systolic	25	15-30
End-diastolic	9	4-12
Mean	15	9-19
PULMONARY ARTERY WEDGE		
Mean	9	4-12
LEFT ATRIUM		
a wave	10	4-16
v wave	12	6-21
Mean	8	2-12
LEFT VENTRICLE		
Peak systolic	130	90-140
End-diastolic	8	5-12
Central aorta		
Peak systolic	130	90-140
End-diastolic	70	60-90
Mean	90	70-105

Other Complications of Central Venous Catheterization

Although many complications of CVP monitoring relate to equipment misuse, the frequency of complications caused by data misinterpretation remains unknown. It is extremely likely, however, that clinicians misinterpret CVP measurements and have suboptimal understanding of CVP monitoring, just as has been demonstrated repeatedly for PAC monitoring (see discussion later). Safe and effective use of CVP monitoring requires a detailed understanding of cardiovascular physiology, normal CVP waveforms, and common pathologic abnormalities in these measurements.

PHYSIOLOGIC CONSIDERATIONS FOR CENTRAL VENOUS PRESSURE MONITORING

Cardiac filling pressures are measured directly from a number of sites in the vascular system. CVP monitoring is the least invasive method, followed by pulmonary artery and left atrial pressure monitoring. Proper interpretation of all cardiac filling pressures requires knowledge of normal values for these pressures, as well as pressures in the cardiac chambers, the great vessels, and other measured and derived hemodynamic variables (Table 36.2).

Two prerequisites must be met in order to correctly interpret the information provided by the CVP monitor: (a) the clinician must possess a thorough understanding of all the variables that affect right atrial pressure; and (b) measurements need to be made with extreme attention to detail.

CVP is determined by the interaction of the venous return function of the circulatory system and the cardiac function.²²⁴ An increase in cardiac function with an increase in venous return will result in an increase in cardiac output and *rise* in CVP. An increase in cardiac function *without* an increase in venous return will result in an increase in cardiac output and a *fall* in CVP. In other words, an isolated CVP measurement has very little meaning unless the information is interpreted in the context of some estimation of cardiac function.

Central Venous Pressure and Venous Return

What determines venous return to the heart? The relationship among the multiple variables that affect blood return to the right atrium is complex. In short, venous return is mostly determined by the gradient between the *mean circulatory filling pressure* (MCFP) and CVP.¹³¹ MCFP results from the elastic recoil pressure from distended small veins and venules and is the force that drives blood back to the right atrium.²²⁴ This pressure has been estimated to be between 8 and 10 mm Hg in healthy individuals at rest, but it cannot be measured in the clinical setting.²²⁵ MCFP rises when volume is administered intravenously, but also in many other circumstances such as when venous tone changes in response to venoconstrictors or endogenous catecholamines, or when there is a shift of blood volume from the splanchnic system into the systemic circulation.¹³¹ The CVP, typically 2 to 3 mm Hg in healthy individuals, is the downstream pressure. Two important corollaries emerge: right atrial pressure is key for maintaining cardiac output, and the body will compensate through the mechanisms described above and others to preserve venous return. This explains why a patient may lose 10% to 12% of his circulating blood volume without exhibiting changes in blood pressure or CVP. Secondly, the difference between MCFP and CVP is only 6 to 8 mm Hg, and hence small changes in CVP may have profound hemodynamic consequences.

Central Venous Pressure and Cardiac Function

The exact same amount of blood returning to the heart can result in very different CVP values at different cardiac function states. This may be explained by the classic diastolic pressure-volume relationship. This curve is one limb of a pressure-volume loop that describes the relation between pressure and volume for the left or right ventricle during an entire cardiac cycle. When a ventricle is operating along the flat portion of its diastolic filling curve it will exhibit only a small increase in filling pressure (CVP in the case of the right ventricle) after significant increases in filling volume or preload. The same increase in filling volume causes a significant increase in filling pressure when the ventricle is operating on the steep portion of its curve.²²⁶ An even more confusing situation arises when the diastolic pressure-volume relation of the ventricle changes, for example with the onset of myocardial ischemia. Rather than moving along the same diastolic pressure-volume curve, the ventricle now shifts to a different, steeper curve where, somewhat paradoxically,

an increase in filling pressure may accompany a decrease in filling volume.²²⁷ As in this example, not only can one not assume that a given measured change in cardiac filling pressure reflects a proportional change in ventricular preload, it cannot even be assumed that pressure and volume change in the same direction.²²⁷ In summary, changes in CVP may be the sole result of changes in inotropic state or compliance of the ventricle, independent of the total circulating volume or venous return to the heart.

To summarize, CVP is the result of a complex and diverse interplay among many different physiologic variables, many of which are impossible to measure in the operating room or ICU. It is therefore not surprising that studies assessing the value of CVP as a predictor of volume status or fluid responsiveness have failed to demonstrate a relationship. There is, in fact, no simple relationship between CVP and circulating blood volume.¹³¹

Further complicating the analysis are the effects of intrathoracic and intrapericardial pressures on filling pressures such as CVP.^{226,228} In general, all intravascular pressures measured in clinical practice are referenced to ambient atmospheric pressure. Thus, a cardiac filling pressure of 10 mm Hg is 10 mm Hg higher than ambient atmospheric pressure. Does this pressure value accurately represent the distending force across the cardiac chamber wall at end-diastole?

To answer this question, one needs to consider transmural pressure. The cardiac chambers are all contained within the pericardium and thorax. Changes in pressure in the structures surrounding the heart will influence pressures recorded within the heart. Transmural pressure is the difference between chamber pressure and juxtagardiac or pericardial pressure. This transmural pressure determines ventricular preload, end-diastolic volume, or fiber length. The same measured filling pressure, referenced to atmospheric pressure, can be associated with markedly different transmural pressures and chamber volumes, depending on whether juxtagardiac pressure is high or low. Although juxtagardiac pressure can be ignored under some circumstances, marked alterations in pleural and pericardial pressures occur commonly and must be considered when any cardiac filling pressure is interpreted. Transmural pressure is always the pressure of physiologic interest. Because juxtagardiac pressure is not measured routinely, one must always consider that the measured central vascular pressure, referenced to the ambient atmosphere, may be a poor estimate of transmural pressure.^{226,228}

During spontaneous breathing, inspiration causes a decrease in pleural and juxtagardiac pressures which is transmitted, in part, to the right atrium, and lowers CVP. This same decrease in pleural pressure will influence other measured central vascular pressures in a similar fashion. Note a subtle but critically important observation about the measurement of central vascular pressures. Although CVP measured relative to atmospheric pressure decreases during the inspiratory phase of spontaneous ventilation, transmural CVP, the difference between right atrial pressure and juxtagardiac pressure may actually increase slightly as more blood is drawn into the right atrium. The opposite pattern is observed during positive-pressure ventilation, in which inspiration increases intrathoracic pressure while raising the measured CVP, but decreases transmural CVP,

TABLE 36.3 Central Venous Pressure Waveform Components

Waveform Component	Phase of Cardiac Cycle	Mechanical Event
a wave	End-diastole	Atrial contraction
c wave	Early systole	Isovolumic ventricular contraction, tricuspid motion toward right atrium
v wave	Late systole	Systolic filling of atrium
h wave	Mid- to late diastole	Diastolic plateau
x descent	Mid-systole	Atrial relaxation, descent of the base, systolic collapse
y descent	Early diastole	Early ventricular filling, diastolic collapse

because the elevated intrathoracic pressure reduces venous return. As mentioned before, transmural pressures are rarely measured in clinical practice owing to difficulties in assessing juxtacardiac or intrathoracic pressure. Instead, end-expiratory values for cardiac filling pressures should be recorded in all patients, to provide the best estimate of transmural pressure. At the end of expiration, intrathoracic and juxtacardiac pressures approach atmospheric pressure regardless of ventilatory status and the CVP values will coincide. Proper pressure values can also be determined by visual inspection of the CVP waveform on a calibrated monitor screen or paper recording. This facilitates comparison of CVP values (and other cardiac filling pressures) obtained from the same patient under varying patterns of ventilation, a common situation in anesthesia and critical care.

The second prerequisite for interpretation of CVP values is correct measurement. Details about the correct zeroing and leveling of the transducer are discussed elsewhere in this text. (See Technical Aspects of Direct Blood Pressure Measurement.). Leveling of the transducer for accurate CVP measurements is best achieved by aligning the stopcock (not the transducer) to a point 5 cm below the sternal angle, as opposed to the more commonly used mid-axillary line at the fourth intercostal space. When this reference point is used, measurements can be done in both the supine position or with the patient sitting up (up to an angle of 60 degrees),^{116,229,230} and better represent the upper fluid level of the right atrium. Regardless of the position chosen, it is most important to be consistent throughout the monitoring period to maintain the same reference point.

Despite these limitations, there is still a great deal of information that may be gathered from careful interpretation of the CVP waveform. For this, it is essential to understand the components of the normal CVP waveform.

NORMAL CENTRAL VENOUS PRESSURE WAVEFORMS

Mechanical events during the cardiac cycle are responsible for the sequence of waves seen in a typical CVP trace. The CVP waveform consists of five phasic events, three peaks (a, c, v) and two descents (x, y) (Table 36.3, Fig.

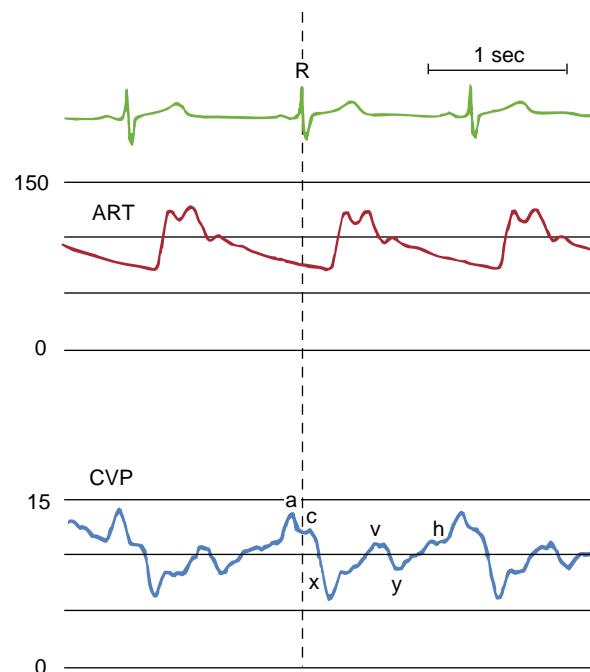


Fig. 36.35 Normal central venous pressure (CVP) waveform. The diastolic components (y descent, end-diastolic a wave) and the systolic components (c wave, x descent, end-systolic v wave) are all clearly delineated. A mid-diastolic plateau wave, the h wave, is also seen because heart rate is slow. Waveform identification is aided by timing the relation between individual waveform components and the electrocardiographic R wave. Waveform timing using the arterial (ART) pressure trace is more confusing, owing to the relative delay in the systolic arterial pressure upstroke. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

36.35).^{231,232} The most prominent wave is the **a wave** of atrial contraction, which occurs at end-diastole following the ECG P wave. Atrial contraction increases atrial pressure and provides the “atrial kick” to fill the right ventricle through the open tricuspid valve. Atrial pressure decreases following the a wave, as the atrium relaxes. This smooth decline in pressure is interrupted by the **c wave**. This wave is a transient increase in atrial pressure produced by isovolumic ventricular contraction, which closes the tricuspid valve and displaces it toward the atrium. The c wave always follows the ECG R wave because it is generated during onset of ventricular systole. (Note that the c wave observed in a jugular venous pressure trace might have a slightly more complex origin. This wave has been attributed to early systolic pressure transmission from the adjacent carotid artery and may be termed a carotid impact wave.²³³ Because the jugular venous pressure also reflects right atrial pressure, however, this c wave likely represents both arterial [carotid impact] and venous [tricuspid motion] origins.) Atrial pressure continues its decline during ventricular systole, owing to continued atrial relaxation and changes in atrial geometry produced by ventricular contraction and ejection that draw the tricuspid annulus toward the cardiac apex. This is the **x descent** or systolic collapse in atrial pressure. The x descent can be divided into two portions, x and x', corresponding to the segments before and after the c wave. The last atrial pressure peak is the **v wave**, and is caused by venous filling of the atrium during late

systole while the tricuspid valve remains closed. The v wave usually peaks just after the ECG T wave. Atrial pressure then decreases, inscribing the **y descent** or diastolic collapse, as the tricuspid valve opens and blood flows from atrium to ventricle. (A final component of the CVP waveform, the **h wave**, occasionally appears as a pressure plateau in mid- to late diastole. The h wave is not normally seen unless the heart rate is slow and venous pressure is elevated.)^{233,234} In summary, the normal venous waveform components may be remembered as follows: the a wave results from atrial contraction; the c wave from tricuspid valve closure and isovolumic RV contraction; the x descent is the systolic decrease in atrial pressure due to atrial relaxation and ventricular contraction; the v wave from ventricular ejection, which drives venous filling of the atrium; and the y descent is the diastolic decrease in atrial pressure due to flow across the open tricuspid valve.

In relation to the cardiac cycle and ventricular mechanical actions, the CVP waveform can be considered to have three systolic components (c wave, x descent, v wave) and two diastolic components (y descent, a wave). By recalling the mechanical actions that generate the pressure peaks and troughs, it is easy to identify these waveform components properly by aligning the CVP waveform and the ECG trace and using the ECG R wave to mark end-diastole and onset of systole. When the radial artery pressure trace is used for CVP waveform timing instead of the ECG, confusion may arise because the arterial pressure upstroke occurs nearly 200 ms after the ECG R wave (see Fig. 36.35). This normal physiologic delay reflects the times required for the spread of the electrical depolarization through the ventricle (≈ 60 ms), isovolumic LV contraction (≈ 60 ms), transmission of aortic pressure rise to the radial artery (≈ 50 ms), and transmission of the radial artery pressure rise through fluid-filled tubing to the transducer (≈ 10 ms).^{117,235}

The normal CVP peaks are designated systolic (c, v) or diastolic (a) according to the phase of the cardiac cycle in which the wave begins. However, one generally identifies these waves not by their onset or upstroke, but rather by the location of their peaks. For instance, the a wave generally begins and peaks in end-diastole, but the peak may appear delayed to coincide with the ECG R wave, especially in a patient with a short PR interval. In this instance, a and c waves merge, and this composite wave is termed an a-c wave. Designation of the CVP v wave as a systolic event may be even more confusing. Although the ascent of the v wave begins during late systole, the peak of the v wave occurs during isovolumic ventricular relaxation, immediately prior to atrioventricular valve opening and the y descent. Consequently, the most precise description would be that the v wave begins in late systole, but peaks during isovolumic ventricular relaxation, the earliest portion of diastole. For clinical purposes, it is simplest to consider the v wave to be a systolic wave.

Although three distinct CVP peaks (a, c, v) and two troughs (x, y) are discernible in the normal venous pressure trace, heart rate changes and conduction abnormalities alter this pattern. A short ECG PR interval causes fusion of a and c waves, and tachycardia reduces the length of diastole and the duration of the y descent, causing v and a

TABLE 36.4 Central Venous Pressure Waveform Abnormalities

Condition	Characteristics
Atrial fibrillation	Loss of a wave Prominent c wave
Atrioventricular dissociation	Cannon a wave
Tricuspid regurgitation	Tall systolic c-v-wave Loss of x descent
Tricuspid stenosis	Tall a wave Attenuation of y descent
Right ventricular ischemia	Tall a and v waves Steep x and y descents M or W configuration
Pericardial constriction	Tall a and v waves Steep x and y descents M or W configuration
Cardiac tamponade	Dominant x descent Attenuated y descent
Respiratory variation during spontaneous or positive-pressure ventilation	Measure pressures at end-expiration

waves to merge. In contrast, bradycardia causes each wave to become more distinct with separate x and x' descents visible and a more prominent h wave. Although there are circumstances in which other pathologic waves may be evident in the CVP trace, one should resist the temptation to assign physiologic significance to each small pressure peak, as many will arise as artifacts of fluid-filled tubing-transducer monitoring systems. It is more useful to search for the expected waveform components, including those waveforms that are characteristic of the pathologic conditions suspected.

ABNORMAL CENTRAL VENOUS PRESSURE WAVEFORMS

Various pathophysiologic conditions may be diagnosed or confirmed by examination of the CVP waveform (Table 36.4). One of the most common applications is the rapid diagnosis of cardiac arrhythmias.²³⁶ In **atrial fibrillation** (Fig. 36.36A), the a wave disappears and the c wave becomes more prominent because atrial volume is greater at end-diastole and onset of systole, owing to the absence of effective atrial contraction. Occasionally, atrial fibrillation or flutter waves may be seen in the CVP trace when the ventricular rate is slow. Isorhythmic **atrioventricular dissociation or accelerated junctional (nodal) rhythm** (see Fig. 36.36B) alters the normal sequence of atrial contraction prior to ventricular contraction. Instead, atrial contraction now occurs during ventricular systole when the tricuspid valve is closed, thereby inscribing a tall “cannon” a wave in the CVP waveform. Absence of normal atrioventricular synchrony during ventricular pacing (see Fig. 36.36C) can be identified in a similar fashion by searching for cannon waves in the venous pressure trace. In these instances, the CVP helps diagnose the cause of arterial hypotension; loss of the normal end-diastolic atrial kick may not be as evident in the ECG trace as it is in the CVP waveform.

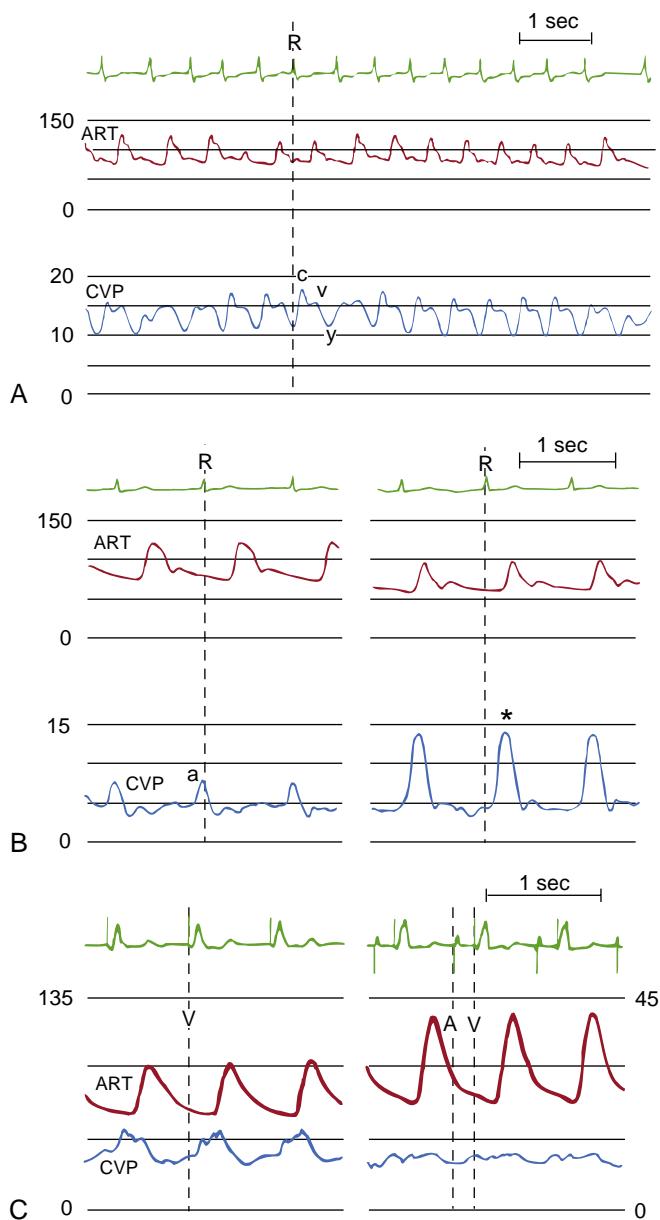


Fig. 36.36 Central venous pressure (CVP) changes caused by cardiac arrhythmias. (A) Atrial fibrillation. Note absence of the a wave, a prominent c wave, and a preserved v wave and y descent. This arrhythmia also causes variation in the electrocardiographic (ECG) R-R interval and left ventricular stroke volume, which can be seen in the ECG and arterial (ART) pressure traces. (B) Isorhythmic atrioventricular dissociation. In contrast to the normal end-diastolic a wave in the CVP trace (left panel), an early systolic cannon wave is inscribed (*, right panel). Reduced ventricular filling accompanying this arrhythmia causes a decreased arterial blood pressure. (C) Ventricular pacing. Systolic cannon waves are evident in the CVP trace during ventricular pacing (left panel). Atrioventricular sequential pacing restores the normal venous waveform and increases arterial blood pressure (right panel). ART scale left, CVP scale right. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

Right-sided valvular heart diseases alter the CVP waveform in different ways.²³⁷ **Tricuspid regurgitation** (Fig. 36.37A) produces abnormal systolic filling of the right atrium through the incompetent valve. A broad, tall systolic c-v-wave results, beginning in early systole and obliterating the systolic x descent in atrial pressure. The CVP trace is said to be ventricularized, resembling RV pressure.

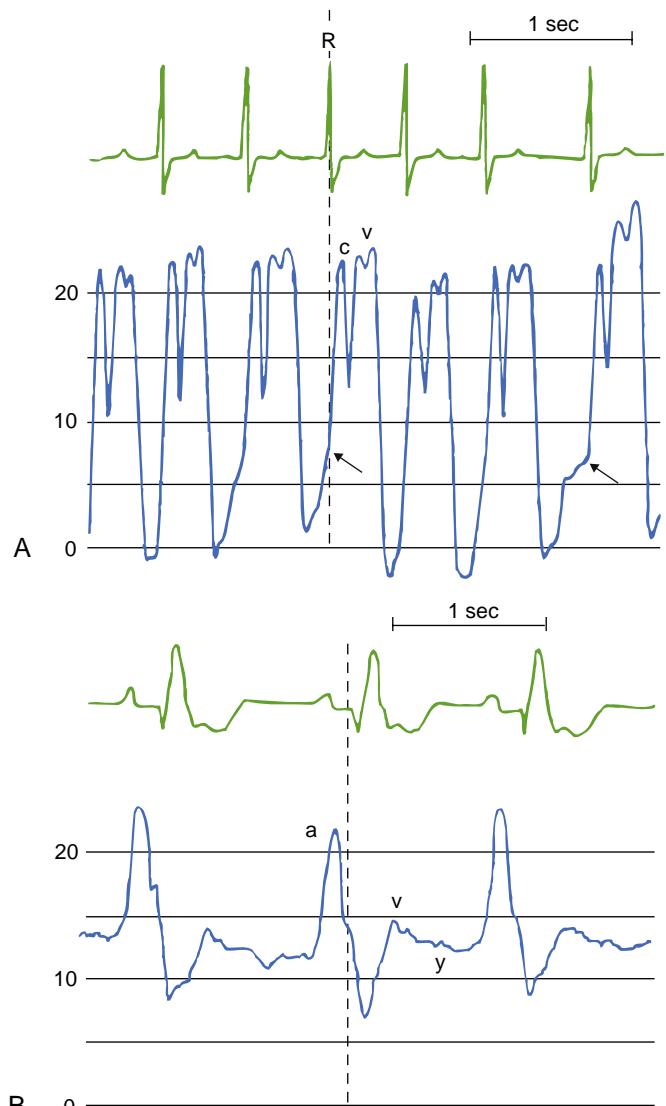


Fig. 36.37 Central venous pressure (CVP) changes in tricuspid valve disease. (A) Tricuspid regurgitation increases mean CVP, and the waveform displays a tall systolic c-v-wave that obliterates the x descent. In this example, the a wave is not seen because of atrial fibrillation. Right ventricular end-diastolic pressure is estimated best at the time of the electrocardiographic R wave (arrows) and is lower than mean CVP. (B) Tricuspid stenosis increases mean CVP, the diastolic y descent is attenuated, and the end-diastolic a wave is prominent. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

Note that this regurgitant wave differs in onset, duration, and magnitude from a normal v wave caused by end-systolic atrial filling from the venae cavae. In patients with tricuspid regurgitation, RV end-diastolic pressure is overestimated by the numeric display on the bedside monitor, which reports a single mean value for CVP. Instead, RV end-diastolic pressure is estimated best by measuring the CVP value at the time of the ECG R wave, prior to the regurgitant systolic wave (see Fig. 36.37A). Unlike tricuspid regurgitation, **tricuspid stenosis** produces a diastolic defect in atrial emptying and ventricular filling (see Fig. 36.37B). Mean CVP is elevated, and a pressure gradient exists throughout diastole between right atrium and ventricle. The a wave is unusually prominent and the

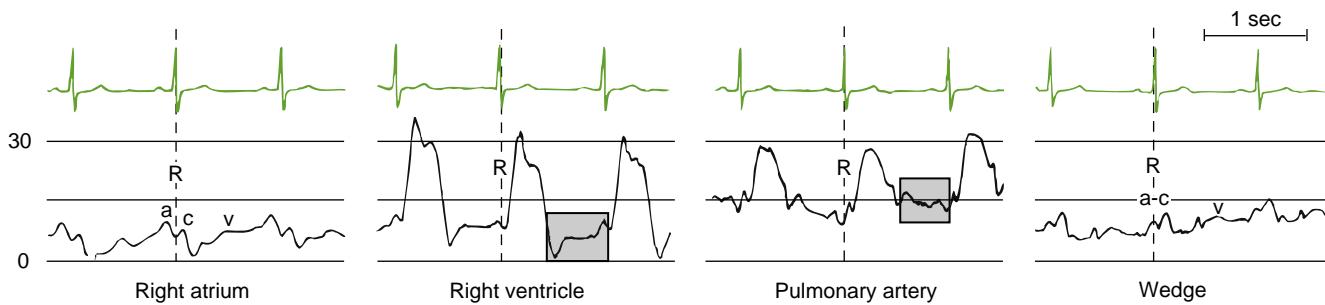


Fig. 36.38 Characteristic waveforms recorded during passage of the pulmonary artery catheter. The right atrial pressure resembles a central venous pressure waveform and displays a, c, and v waves. Right ventricular pressure shows a higher systolic pressure than seen in the right atrium, although the end-diastolic pressures are equal in these two chambers. Pulmonary artery pressure shows a diastolic step-up compared with ventricular pressure. Note also that right ventricular pressure increases during diastole, whereas pulmonary artery pressure decreases during diastole (shaded boxes). Pulmonary artery wedge pressure has a similar morphology to right atrial pressure, although the a-c and v waves appear later in the cardiac cycle relative to the electrocardiogram. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

y descent is attenuated, owing to the impaired diastolic egress of blood from the atrium. Other conditions that reduce RV compliance, such as RV ischemia, pulmonary hypertension, or pulmonic valve stenosis, may produce a prominent end-diastolic a wave in the CVP trace but do not attenuate the early diastolic y descent. CVP waveform morphology changes in other characteristic ways in the presence of pericardial diseases and RV infarction. These patterns are interpreted best in conjunction with PAP monitoring, which is discussed below.

Perhaps the most important traditional application of CVP monitoring is to provide an estimate of the adequacy of the circulating blood volume. Several randomized trials and systematic reviews have demonstrated a very poor relationship between CVP and circulating blood volume, as well as the inability of a static CVP value to predict the hemodynamic response to a fluid challenge.²³⁸⁻²⁴⁰ This is not surprising in light of the factors described above. Some have argued that the important clinical question with regard to volume responsiveness should be phrased in the negative, that is, whether a patient is *unlikely* to respond to fluids. The subset of patients that will derive all the deleterious effects of fluid administration (capillary leak and tissue edema) and no benefit (increased cardiac output) is in most instances the group of clinical interest. In this regard, the lack of an inspiratory fall in CVP in patients who have spontaneous inspiratory efforts (provided the inspiratory effort is adequate, i.e., >2 mm Hg fall in PAOP with inspiration) was able to predict no improvement in cardiac output following fluid administration.²⁴¹

Pulmonary Artery Catheter Monitoring

In 1970, Swan, Ganz, and colleagues introduced PAC into clinical practice for the hemodynamic assessment of patients with acute myocardial infarction.²⁴² This device allowed accurate bedside measurement of important cardiovascular physiologic variables, and its popularity soared. While the PAC provides measurements of several hemodynamic variables that clinicians find it hard to predict accurately from standard clinical signs and symptoms,²⁴³ it remains uncertain whether PAC monitoring leads to improved patient outcome.²⁴⁴

PULMONARY ARTERY CATHETER INSERTION

The standard PAC has a 7.0 to 9.0 Fr circumference, is 110 cm in length marked at 10-cm intervals, and contains four internal lumens. The distal port at the catheter tip is used for PAP monitoring, while the second is 30 cm more proximal and is used for CVP monitoring. The third lumen leads to a balloon near the tip which is used to float the catheter through the cardiac chambers, and the fourth houses wires for a temperature thermistor, the end of which lies just proximal to the balloon.²⁴⁵

PACs can be placed from any of the central venous cannulation sites described earlier, but the right internal jugular vein provides the most direct route to the right heart chambers. The balloon at the tip of the catheter is inflated with air, and the catheter is advanced into the right atrium, through the tricuspid valve, the right ventricle, the pulmonic valve, into the pulmonary artery, and finally into the wedge position. Characteristic waveforms from each of these locations confirm proper catheter passage and placement (Fig. 36.38).

After the PAWP is measured, the balloon is deflated, and the PAP waveform should reappear. Catheter position is confirmed with a chest radiograph. The tip of the PAC should be within 2 cm of the cardiac silhouette on a standard anteroposterior chest film.²⁴⁶

If an RV waveform is not observed after inserting the catheter 40 cm, coiling in the right atrium is likely. Similarly, if a pulmonary artery waveform is not observed after inserting the catheter to 50 cm, coiling in the right ventricle has probably occurred. The balloon should be deflated, the catheter withdrawn to 20 cm, and the PAC floating sequence repeated.

A few additional points might aid successful positioning of the PAC. The air-filled balloon tends to float to nondependent regions as it passes through the heart into the pulmonary vasculature. Consequently, positioning a patient head down will aid flotation across the tricuspid valve, and tilting the patient onto the right side and placing the head up will encourage flotation out of the right ventricle, as well as reduce the incidence of arrhythmias during insertion.^{247,248} Deep inspiration during spontaneous ventilation will increase venous return and RV output transiently, and may facilitate catheter flotation in a patient with low cardiac output. On occasion, a catheter may be floated to

BOX 36.7 Complications of Pulmonary Artery Catheter Monitoring

Catheterization

- Arrhythmias, ventricular fibrillation
- Right bundle branch block, complete heart block (if preexisting left bundle branch block)

Catheter residence

- Mechanical: catheter knots, entangling with or dislodgement of pacing wires
- Thromboembolism
- Pulmonary infarction
- Infection, endocarditis
- Endocardial damage, cardiac valve injury
- Pulmonary artery rupture
- Pulmonary artery pseudoaneurysm

Misinterpretation of data

- Misuse of equipment

proper position when stiffened by injecting 10 to 20 mL of ice cold solution through the distal lumen. Finally, maneuvering of the PAC can also be guided by transesophageal or transthoracic echocardiography, demonstrating the catheter passage through the right heart.^{249,250}

COMPLICATIONS OF PULMONARY ARTERY CATHETER MONITORING

Complications of PAC use may be divided into those resulting from catheter placement, those associated with the *in-vivo* presence of the catheter, and those resulting from catheter use and misuse. For the most part, problems encountered during catheter placement are the same for both PAC and CVP monitoring (see Box 36.6). However, catheterization of the right ventricle and pulmonary artery causes complications uniquely associated with PACs (Box 36.7).²⁵¹

When all adverse effects from PAC use are considered, including self-limited arrhythmias observed during catheter insertion, it appears that minor complications occur in more than 50% of catheterized patients.²⁵² However, major morbidity specifically attributable to PAC use is uncommon.²⁵³ In both an initial exhaustive review of the literature and in its 2003 update, the ASA Task Force on Pulmonary Artery Catheterization emphasized that the reported incidence of complications from PAC monitoring varies widely, although it seems that serious complications occur in 0.1% to 0.5% of PAC-monitored surgical patients.²⁵² In 1984, Shah et al. reported use of PACs in 6245 patients undergoing cardiac and noncardiac operations.¹⁸⁷ Quite remarkably, only 10 patients (0.16%) had serious complications resulting in morbidity and only 1 patient (0.016%) died as a result of PAC. Furthermore, a 1998 European report of PAC use in 5306 patients undergoing cardiac surgery confirms this low incidence of major morbidity, with injury of the right ventricle or PA occurring in only 4 patients (0.07%).²⁵⁴ Finally, only 1 of 2000 adverse events reported in the Australian Incident Monitoring Study of 1993 involved use of a PAC, in contrast to 64 adverse events involving access to the arterial or venous systems.⁹⁹ However, it is important to acknowledge that although these large studies indicate a low incidence of serious complications attributable to the

use of PACs, the frequency of complications in a particular clinical setting or patient group remains unknown.

A more insidious but possibly more common complication of PAC use is **misinterpretation of data**.^{255,256} Although the magnitude of the problem is not clear, studies show widespread knowledge deficits among practitioners who use PACs. In 1990, Iberti and associates reported the results of a 31-question multiple-choice examination given to 496 physicians. They found a poor overall level of knowledge of PACs, as evidenced by a mean score of only 67% correct answers. Although higher scores were demonstrated by individuals with more training and more experience inserting and using PACs, none of these factors ensured a high level of knowledge.²⁵⁷ These results have been duplicated in a variety of other specialty care groups.²⁵⁸ It is especially concerning that PAWP measurement was performed incorrectly by 30% to 50% of the clinicians in these studies and that educational programs failed to improve performance.^{259,260} Taken together, these observations highlight the fact that effective use of PACs requires a great deal of expertise and clinical experience, and even measuring the most fundamental PAC-derived variable, namely wedge pressure, is a complicated endeavor.²⁶¹

NORMAL PULMONARY ARTERY PRESSURES AND WAVEFORMS

As the balloon-tipped PAC is floated to its proper position in the pulmonary artery, characteristic pressure waveforms are recorded (see Fig. 36.38). In the superior vena cava or right atrium, a CVP waveform with characteristic a-, c-, and v waves and low mean pressure should be observed. RV pressure is characterized by a rapid systolic upstroke, a wide pulse pressure, and low diastolic pressure. Entry of the PAC into the pulmonary artery is heralded by a step-up in diastolic pressure and a change in waveform morphology.

On occasion, it may be difficult to distinguish RV pressure from PAP, particularly if only the numeric values for these pressures are examined. However, careful observation of the pressure waveforms, focusing on the diastolic pressure contours, allows differentiation. During diastole, the PAP will fall owing to continuous runoff flow to the lung, while the pressure in the right ventricle will increase due to filling from the right atrium (see Fig. 36.38).²⁶²

As noted above, the wedge pressure is an indirect measurement of pulmonary venous pressure and left atrial pressure and should therefore resemble these venous waveforms with characteristic a and v waves and x and y descents. However, owing to the pulmonary vascular bed interposed between the PAC tip and left atrium, wedge pressure is a delayed and damped representation of left atrial pressure.²⁶³

The terms PAWP and pulmonary artery occlusion pressure are used interchangeably and refer to the same measurement obtained from the tip of a PAC following balloon inflation and flotation to the wedged position. However, pulmonary capillary pressure must not be confused with wedge pressure or left atrial pressure, nor should the term *pulmonary capillary wedge pressure* be used at all. The hydrostatic pressure in the pulmonary capillaries that causes edema formation according to the Starling equation is different from left arterial pressure (LAP). This is the pressure that must exceed

LAP in order to maintain antegrade blood flow through the lungs. Although the magnitude of the difference between pulmonary capillary pressure and wedge pressure is generally small, it can increase markedly when resistance to flow in the pulmonary veins is elevated.²⁶⁴ In most situations, the major component of pulmonary vascular resistance occurs at the precapillary, pulmonary arteriolar level. However, rare conditions like pulmonary venoocclusive disease may cause a marked increase in postcapillary resistance to flow. Similar situations arise in conditions that disproportionately increase pulmonary venous resistance, such as central nervous system injury, acute lung injury, hypovolemic shock, endotoxemia, and norepinephrine infusion.^{265,266} Under these conditions, measurement of wedge pressure will underestimate pulmonary capillary pressure substantially and thereby underestimate the risk of hydrostatic pulmonary edema.

ABNORMAL PULMONARY ARTERY AND WEDGE PRESSURE WAVEFORMS

PAC monitoring is subject to the same technical artifacts inherent in all invasive pressure monitoring techniques as well as some additional problems unique to this method.²⁶⁷⁻²⁶⁹ Because the PAC is longer and passes through the cardiac chambers, it is more prone to distortions from clot or air bubbles, and motion-related artifacts are more problematic. Artifactual pressure spikes may be distinguished from the underlying physiologic pressure waveform by their unique morphology and timing.

At the onset of systole, tricuspid valve closure accompanied by RV contraction and ejection result in excessive **catheter motion** causing the most common PAC trace artifact.^{268,270} This pressure artifact may produce

an artificially low pressure, erroneously designated as the pulmonary artery diastolic (PAD) pressure (Fig. 36.39). Repositioning the PAC often solves the problem.

Another common artifact in PAC pressure measurement occurs when the balloon is overinflated and occludes the distal lumen orifice. This phenomenon is termed **over-wedging** and usually is caused by distal catheter migration and eccentric balloon inflation that forces the catheter tip against the vessel wall. The catheter now records a gradually rising, non-pulsatile pressure as the continuous flush system builds up pressure against the obstructed distal opening (Fig. 36.40). When observed, this should be corrected immediately by gentle catheter withdrawal to a more proximal location in the pulmonary artery.

As emphasized earlier, with each PAC balloon inflation and wedge measurement, the catheter tip migrates distally. When a wedge pressure tracing appears during partial balloon inflation, it suggests that the PAC is inappropriately located in a smaller, distal branch of the pulmonary artery. The catheter should be withdrawn slightly before over-wedging can occur and result in vascular injury or pulmonary infarction.

Pathophysiologic conditions involving the left-sided cardiac chambers or valves produce characteristic changes in the pulmonary artery and wedge pressure waveforms. One of the most easily recognized patterns is the tall v wave of **mitral regurgitation**. Unlike a normal wedge pressure v wave produced by late systolic pulmonary venous inflow, the prominent v wave of mitral regurgitation begins in early systole. Mitral regurgitation causes fusion of c and v waves and obliteration of the systolic x descent, as the isovolumic phase of LV systole is eliminated owing to the retrograde ejection of blood into the left atrium.²³⁷ Because the prominent v wave of mitral regurgitation is generated during

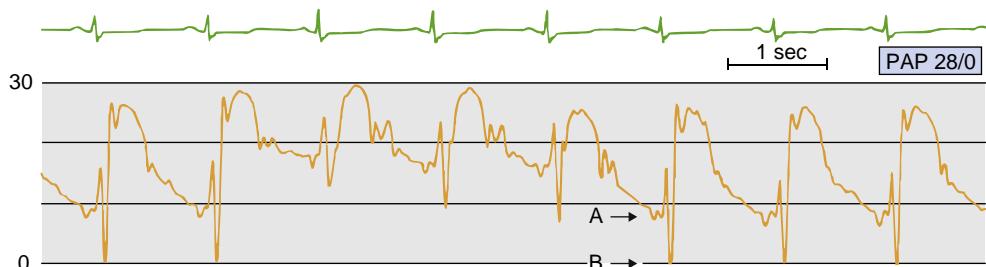


Fig. 36.39 Artifactual pressure peaks and troughs in the pulmonary artery pressure (PAP) waveform caused by catheter motion. The correct value for pulmonary artery end-diastolic pressure is 8 mm Hg (A), although the monitor digital display erroneously reports the PAP as 28/0 mm Hg (B). (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

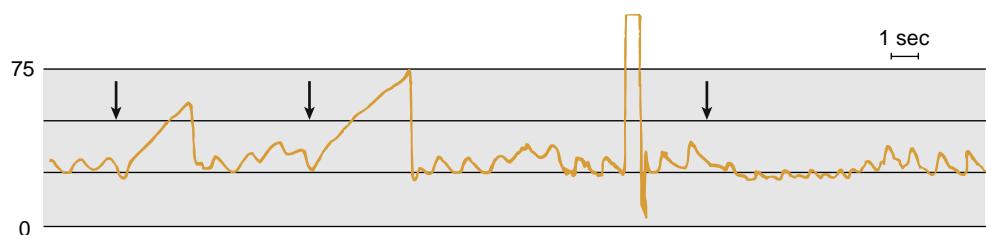


Fig. 36.40 Overwedging of the pulmonary artery (PA) catheter causes artifactual waveform recordings. The first two attempts to inflate the PA catheter balloon (first two arrows) produce a nonpulsatile increasing pressure caused by an occluded catheter tip. After the catheter is withdrawn slightly, balloon inflation allows proper wedge pressure measurement (third arrow). Before the third attempt at balloon inflation, the PA pressure lumen is flushed. This restores the appropriate pulsatile nature to the PA and wedge pressure waveforms on the right side of the trace. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

ventricular systole, the mean wedge pressure overestimates LV end-diastolic filling pressure, which is better estimated by the pressure value prior to onset of the regurgitant v wave (Fig. 36.41). However, it remains a good approximation for mean left atrial pressure and the subsequent risk of hydrostatic pulmonary edema.

It should be noted that although the height of the v wave in the wedge pressure trace will be affected by the volume of regurgitant blood entering the left atrium, it also depends on the left atrial volume and compliance (Fig. 36.42). This may explain why patients with acute mitral regurgitation tend to have tall wedge pressure v waves—they have smaller, stiffer left atria with poorer compliance compared to patients with longstanding disease. Therefore, the height of the wedge pressure v wave is neither a sensitive nor a specific indicator of mitral regurgitation severity.²⁷¹

In contrast to mitral regurgitation, which distorts the systolic portion of the wedge pressure waveform, **mitral stenosis** alters its diastolic aspect. In this condition, the

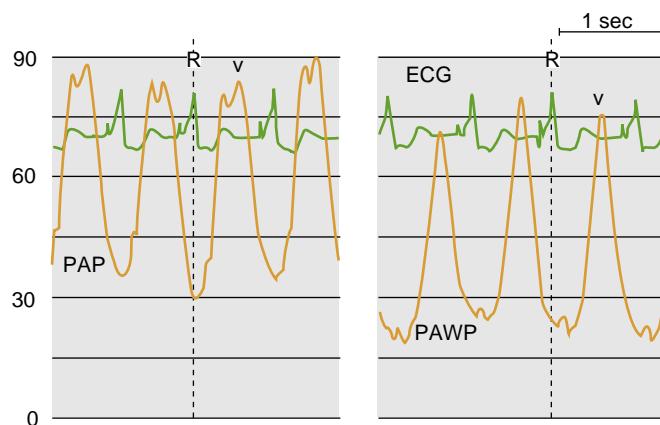


Fig. 36.41 Severe mitral regurgitation. A tall systolic v wave (v) is inscribed in the pulmonary artery wedge pressure (PAWP) trace and also distorts the pulmonary artery pressure (PAP) trace, giving it a bifid appearance. The electrocardiogram (ECG) is abnormal owing to ventricular pacing. Left ventricular end-diastolic pressure is estimated best by measuring PAWP at the time of the electrocardiographic R wave, before onset of the regurgitant v wave. Note that mean PAWP exceeds left ventricular end-diastolic pressure in this condition. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

holo-diastolic pressure gradient across the mitral valve results in an increased mean wedge pressure, a slurred early diastolic y descent, and a tall end-diastolic a wave. Similar hemodynamic abnormalities are seen in patients with left atrial myxoma or whenever there is obstruction to mitral flow. Diseases that increase LV stiffness (e.g., LV infarction, pericardial constriction, aortic stenosis, and systemic hypertension) produce changes in the wedge pressure that resemble in part those seen in mitral stenosis. In these conditions, mean wedge pressure is increased and the trace displays a prominent a wave, but the y descent remains steep because there is no obstruction to flow across the mitral valve during diastole. Because patients with advanced mitral stenosis often have coexisting atrial fibrillation, the a wave will not be present in many of these cases (Fig. 36.43).²⁷²

Myocardial ischemia may be detected by PAC in several ways. Ischemia itself impairs LV relaxation resulting in diastolic dysfunction, a pattern particularly characteristic of demand ischemia associated with tachycardia or induced by rapid atrial pacing.^{227,272,273} Impaired ventricular relaxation results in a stiffer, less compliant left ventricle, resulting in an increased LV end-diastolic pressure. This will result in a tall a wave on the wedge trace, as the left atrium contracts into a stiff, incompletely relaxed left ventricle (Fig. 36.44).²⁷⁴

Myocardial ischemia can also produce LV systolic dysfunction, typically as a result of supply ischemia, caused by a sudden reduction or cessation of coronary blood flow to a region of the myocardium.^{273,275} As ejection fraction falls significantly, LV end-diastolic volume and pressure rise, and elevated pulmonary diastolic and wedge pressures develop.²⁷⁶ Distortion of LV geometry or ischemia of the myocardium underlying the papillary muscles can lead to acute mitral regurgitation with its characteristic PAP trace changes described above (see Fig. 36.41).²⁷⁷

Whether the PAC should be used in high-risk patients as a supplemental monitor for detection of myocardial ischemia remains controversial. Although patients with LV ischemia are likely to have higher mean wedge pressures than those without ischemia, these differences are small, may be difficult to detect clinically, and no clear quantitative threshold values for diagnosis of ischemia have been identified.²⁷⁸

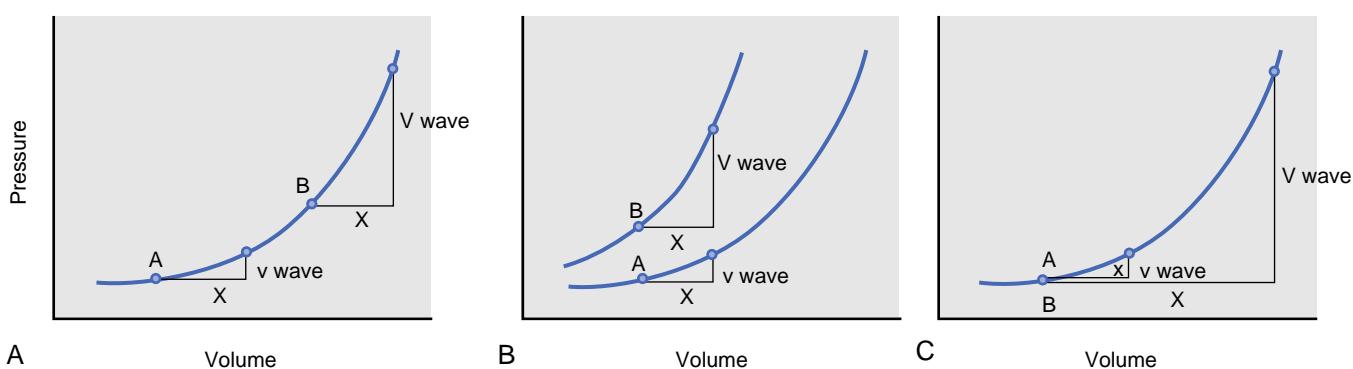


Fig. 36.42 V-wave height as an indicator of mitral regurgitation severity. Left atrial pressure-volume curves describe the three factors that determine v-wave height. (A) Influence of left atrial volume. For the same regurgitant volume (X), the left atrial v wave will be taller if baseline atrial volume is greater (point B versus point A). (B) Influence of left atrial compliance. For the same regurgitant volume (X), the left atrial v wave will be taller if baseline atrial compliance is reduced (point B versus point A). (C) Influence of regurgitant volume. Beginning at the same baseline left atrial volume (points A and B), if regurgitant volume increases (X versus x), the left atrial pressure v wave will increase (V versus v). (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

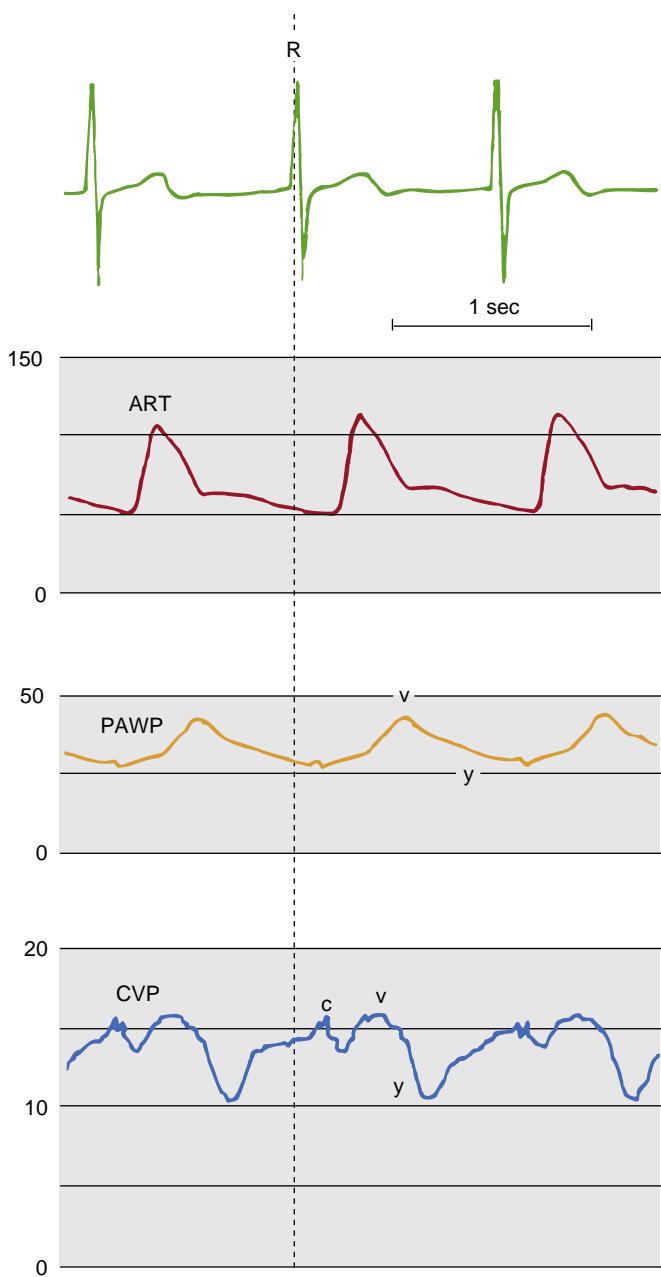


Fig. 36.43 Mitral stenosis. Mean pulmonary artery wedge pressure (PAWP) is increased (35 mm Hg), and the diastolic y descent is markedly attenuated. Compare the slope of the y descent in the PAWP trace with the y descent in the central venous pressure (CVP) trace. In addition, compare this PAWP y descent with the PAWP y descent in mitral regurgitation (see Figure 36.41); a waves are not seen in the PAWP or CVP traces, owing to atrial fibrillation. ART, Arterial blood pressure. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

Right ventricular ischemia produces characteristic PAC waveform patterns that may be helpful in diagnosis and management. Just as LV ischemia increases PAWP, RV ischemia increases CVP. In fact, this is one of the few situations in which CVP may be higher than wedge pressure. In addition, CVP waveforms may display a prominent a wave resulting from RV diastolic dysfunction, and a prominent v wave resulting from ischemia-induced tricuspid regurgitation.^{279,280} This particular CVP waveform is described

as having an M or W configuration, referring to the tall a and v waves and interposed steep x and y descents. Severe pulmonary artery hypertension may also result in RV ischemia and dysfunction as well as increased CVP, but this is distinguished from primary RV dysfunction in that the PAP and calculated pulmonary vascular resistance are normal in primary RV failure.

The CVP waveform in RV infarction is similar to that from a patient with restrictive cardiomyopathy or **pericardial constriction**, including elevated mean pressure, prominent a and v waves, and steep x and y descents.²⁸¹ The cardinal feature common to these conditions is impaired RV diastolic compliance, often termed “restrictive physiology.” In restrictive cardiomyopathy and RV infarction, diastolic dysfunction impairs ventricular relaxation and decreases chamber compliance, whereas in constrictive pericarditis cardiac filling is limited by the rigid, often calcified pericardial shell. Impaired venous return decreases end-diastolic volume, stroke volume, and cardiac output. Despite reduced cardiac volumes, cardiac filling pressures are markedly elevated and equal in all four chambers of the heart at end-diastole (Fig. 36.45). Although PAC monitoring reveals this pressure equalization, the characteristic M or W configuration is more apparent in the CVP trace, most likely because of the damping effect of the pulmonary vasculature on the left-sided filling pressures.²⁸²⁻²⁸⁴

Another hallmark of pericardial constriction is observed in the right and LV pressure traces. These demonstrate rapid but short-lived early diastolic ventricular filling, which produces a diastolic “dip-and-plateau” pattern or “square root sign.”^{129,285} In some cases, particularly when heart rate is slow, a similar waveform pattern may be noted in the CVP trace: a steep y descent (the diastolic dip) produced by rapid early diastolic flow from atrium to ventricle, followed by a mid-diastolic h wave (the plateau) from the interruption in flow imposed by the restrictive pericardial shell (see Fig. 36.45).

Like pericardial constriction, **cardiac tamponade** impairs cardiac filling, but in the case of tamponade, a compressive pericardial fluid collection produces this effect. This results in a marked increase in CVP and a reduced diastolic volume, stroke volume, and cardiac output. Despite many similar hemodynamic features, tamponade and constriction may be distinguished by the different CVP waveforms seen in these two conditions. In tamponade, the venous pressure waveform appears more monophasic and is dominated by the systolic x pressure descent. The diastolic y pressure descent is attenuated or absent, because early diastolic flow from right atrium to right ventricle is impaired by the surrounding compressive pericardial fluid collection (Fig. 36.46).^{282,286,287} Clearly, other clinical and hemodynamic clues help distinguish these diagnoses, such as the presence of *pulsus paradoxus*, an almost invariable finding in cardiac tamponade (see Fig. 36.32).²⁸⁸

Probably the single most important waveform abnormality or interpretive problem in PAC monitoring is discerning the correct pressure measurement in patients with large intrathoracic pressure swings like those receiving **positive pressure ventilation** or those with labored spontaneous breathing. During positive pressure ventilation, inspiration increases pulmonary artery and wedge pressures. By measuring these pressures at end-expiration, the confounding

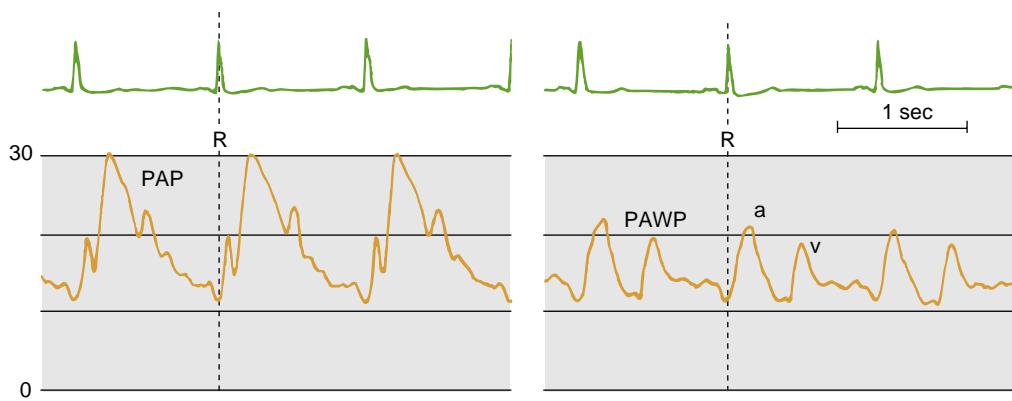


Fig. 36.44 Myocardial ischemia. Pulmonary artery pressure (PAP) is relatively normal and mean pulmonary artery wedge pressure (PAWP) is only slightly elevated (15 mm Hg). However, PAWP morphology is markedly abnormal with tall a waves (21 mm Hg) resulting from the diastolic dysfunction seen in this condition. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

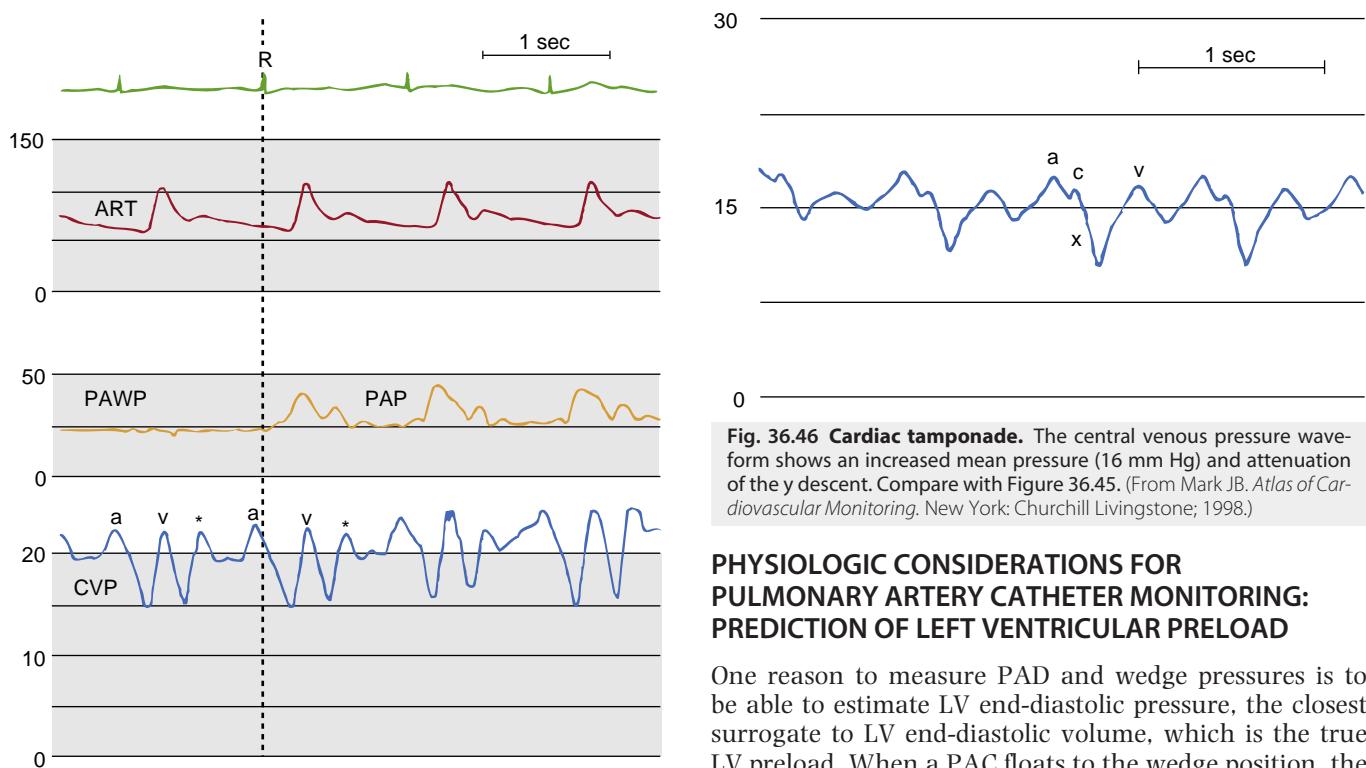


Fig. 36.45 Pericardial constriction. This condition causes elevation and equalization of diastolic filling pressures in the pulmonary artery pressure (PAP), pulmonary artery wedge pressure (PAWP), and central venous pressure (CVP) traces. The CVP waveform reveals tall a and v waves with steep x and y descents and a mid-diastolic plateau wave (*). ART, Arterial blood pressure. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

effect of this inspiratory increase in intrathoracic pressure is minimized (Fig. 36.47).²²⁸ Forceful inspiration during spontaneous ventilation has the opposite effect, but again, measurement of these pressures at end-expiration eliminates this confounding factor. Bedside monitors are designed with algorithms that aim to identify and report the numeric values for end-expiratory pressures but are often inaccurate.^{289,290} The most reliable method for measuring central vascular pressures at end-expiration is examination of the waveforms on a calibrated monitor screen or paper recording.^{290,291}

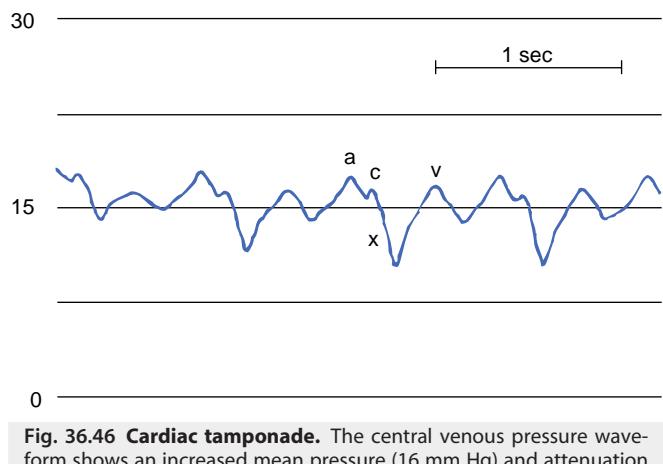


Fig. 36.46 Cardiac tamponade. The central venous pressure waveform shows an increased mean pressure (16 mm Hg) and attenuation of the y descent. Compare with Figure 36.45. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

PHYSIOLOGIC CONSIDERATIONS FOR PULMONARY ARTERY CATHETER MONITORING: PREDICTION OF LEFT VENTRICULAR PRELOAD

One reason to measure PAD and wedge pressures is to be able to estimate LV end-diastolic pressure, the closest surrogate to LV end-diastolic volume, which is the true LV preload. When a PAC floats to the wedge position, the inflated balloon isolates the distal pressure-monitoring orifice from upstream PAP. A continuous static column of blood now connects the wedged PAC tip to the junction of the pulmonary veins and left atrium. Thus, wedging the PAC, in effect, extends the catheter tip to measure the pressure at the point at which blood flow resumes on the venous side of the pulmonary circuit. Because resistance in the large pulmonary veins is negligible, PAWP provides an indirect measurement of both pulmonary venous pressure and left atrial pressure.^{292,293} For the column of blood connecting the tip of the wedged catheter and the draining pulmonary vein to be continuous, however, external compression by surrounding alveoli should be negligible (i.e., the catheter needs to reside in the so-called West zone 3 of the lung) (Fig. 36.48).²⁹³

PAD pressure is often used as an alternative to PAWP to estimate LV filling pressure. This is acceptable under normal circumstances because when pulmonary venous

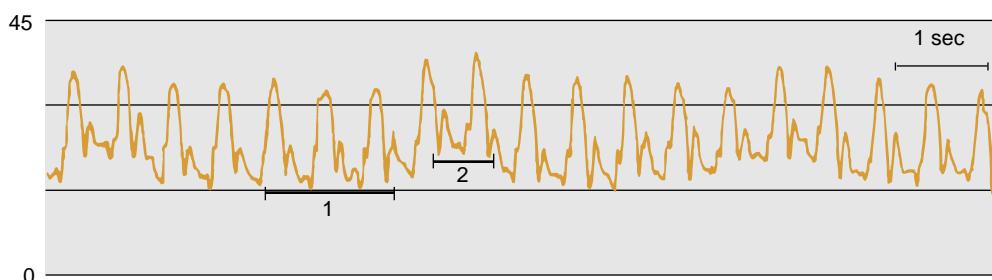


Fig. 36.47 Influence of positive-pressure mechanical ventilation on pulmonary artery pressure. Pulmonary artery pressure should be measured at end expiration (1, 15 mm Hg) in order to obviate the artifact caused by positive-pressure inspiration (2, 22 mm Hg). (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

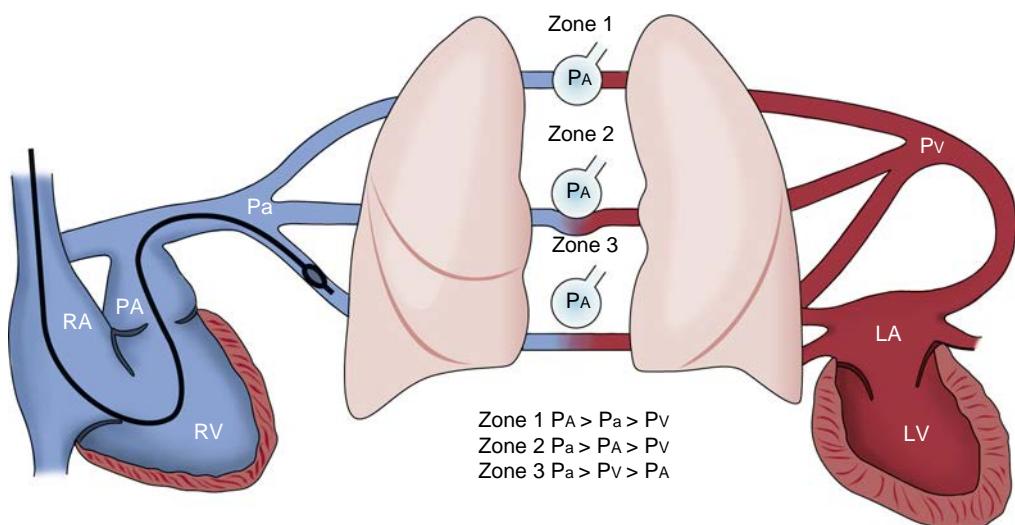


Fig. 36.48 The pulmonary artery catheter tip must be wedged in lung zone 3 to provide an accurate measure of pulmonary venous (Pv) or left atrial (LA) pressure. When alveolar pressure (P_a) rises above Pv in lung zone 2, or above pulmonary arterial pressure (Pa) in lung zone 1, wedge pressure will reflect alveolar pressure rather than intravascular pressure. RA, Right atrium; RV, right ventricle; PA, pulmonary artery; LV, left ventricle. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998, Fig. 6-10.)

resistance is low, the pressure in the pulmonary artery at end of diastole will equilibrate with downstream pressure in the pulmonary veins and left atrium.^{294,295} From a monitoring standpoint, PAD has the added advantage of being available for continuous monitoring whereas PAWP is only measured intermittently.

In many situations, LV end-diastolic pressure can be either underestimated or overestimated by the PAWP and/or PAD. These situations are summarized in Figure 36.49 and Tables 36.5 and 36.6. The interested reader is referred to several excellent references for further discussion of this topic.^{292,293,296}

However, even when PAD and wedge pressure accurately estimate LV end-diastolic pressure, many factors can influence the relationship between end-diastolic pressure and end-diastolic chamber volume, which is the true preload. Proper interpretation of filling pressures requires assessment of juxtagardiac pressure as well as ventricular compliance. When both are normal, a wedge pressure of 20 mm Hg is interpreted as hypervolemia, with an increased LV end-diastolic volume causing the increased PAWP. However, if juxtagardiac pressure is increased (e.g., due to cardiac tamponade, pericardial constriction, or positive pressure ventilation), or ventricular compliance is decreased (e.g., with myocardial ischemia, hypertrophy, or

cardiomyopathy), a wedge pressure of 20 mm Hg can coexist with a small, hypovolemic left ventricle (Fig. 36.50).

In addition, ventricular interdependence (caused by the shared septum of the left and right ventricles) and pericardial constraint couple changes in RV and LV function. For example, acute pulmonary arterial hypertension increases RV end-diastolic volume and pressure, and shifts the ventricular septum leftward, thus increasing LV end-diastolic pressure while simultaneously decreasing LV end-diastolic volume. Conversely, primary changes on the left side can adversely affect the right heart structures in similar ways. With all these considerations in mind, it should be of no surprise that various studies have repeatedly shown that both CVP and PAWP may not always correlate with cardiac preload and do not necessarily predict the cardiac output response to a fluid challenge.^{238,297} In contrast, in patients with systolic ventricular dysfunction, filling pressures were found more accurate than cardiac volume indices in predicting fluid responsiveness.²⁹⁸

PULMONARY ARTERY CATHETER-DERIVED HEMODYNAMIC VARIABLES

The cardiovascular system is often modeled as an electrical circuit, with the relationship between cardiac output, blood

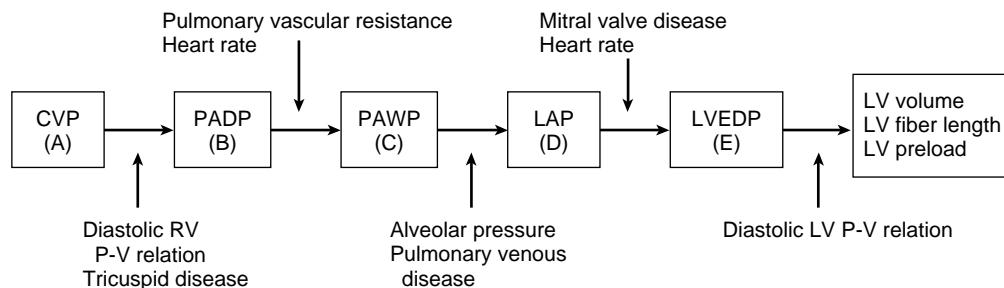
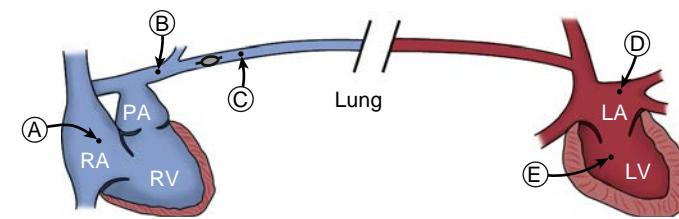


Fig. 36.49 Anatomic and physiologic factors that influence the relations between various measures of left ventricular (LV) filling and true LV preload. The further upstream the filling pressure is measured, the more confounding factors may influence the relation between this measurement and LV preload. CVP, Central venous pressure; LA, left atrium; LAP, left atrial pressure; LVEDP, left ventricular end-diastolic pressure; PA, pulmonary artery; PADP, pulmonary artery diastolic pressure; PAWP, pulmonary artery wedge pressure; P-V, pressure-volume; RA, right atrium; RV, right ventricle. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

TABLE 36.5 Underestimation of Left Ventricular End-Diastolic Pressure

Condition	Site of Discrepancy	Cause of Discrepancy
Diastolic dysfunction	Mean LAP <LVEDP	Increased end-diastolic a wave
Aortic regurgitation	LAP a wave <LVEDP	Mitral valve closure before end-diastole
Pulmonic regurgitation	PADP <LVEDP	Bidirectional runoff for pulmonary artery flow
Right bundle branch block	PADP <LVEDP	Delayed pulmonic valve opening
Post-pneumonectomy	PAWP <LAP or LVEDP	Obstruction of pulmonary blood flow

LAP, Left atrial pressure; LVEDP, left ventricular end-diastolic pressure; PADP, pulmonary artery diastolic pressure; PAWP, pulmonary artery wedge pressure.

Modified from Mark JB. Predicting left ventricular end-diastolic pressure. In: Mark JB, ed. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998:59.

pressure, and resistance to flow related in a manner similar to Ohm's law:

$$PVR = \frac{MPAP - PAWP}{CO} \cdot (80) \quad (36.1)$$

$$SVR = \frac{MAP - CVP}{CO} \cdot (80)$$

Where,

SVR = systemic vascular resistance (dyne·s/cm⁵)

PVR = pulmonary vascular resistance (dyne·s/cm⁵)

MAP = mean arterial pressure (mm Hg)

CVP = central venous pressure (mm Hg)

MPAP = mean pulmonary artery pressure (mm Hg)

PAWP = pulmonary artery wedge pressure (mm Hg)

CO = cardiac output (L/min)

Normal values for SVR and PVR are given in Table 36.7. Note that these calculations of systemic and pulmonary vascular resistance are based on a hydraulic fluid model that

TABLE 36.6 Overestimation of Left Ventricular End-Diastolic Pressure

Condition	Site of Discrepancy	Cause of Discrepancy
Positive end-expiratory pressure	Mean PAWP > Mean LAP	Creation of lung zone 1 or 2, or pericardial pressure changes
Pulmonary arterial hypertension	PADP > Mean PAWP	Increased pulmonary vascular resistance
Pulmonary venoocclusive disease	Mean PAWP > Mean LAP	Obstruction to flow in large pulmonary veins
Mitral stenosis	Mean LAP > LVEDP	Obstruction to flow across mitral valve
Mitral regurgitation	Mean LAP > LVEDP	Retrograde systolic v wave raises mean atrial pressure
Ventricular septal defect	Mean LAP > LVEDP	Antegrade systolic v wave raises mean atrial pressure
Tachycardia	PADP > Mean LAP > LVEDP	Short diastole creates pulmonary vascular and mitral valve gradients

LAP, Left atrial pressure; LVEDP, left ventricular end-diastolic pressure; PADP, pulmonary artery diastolic pressure; PAWP, pulmonary artery wedge pressure.

Modified from Mark JB. Predicting left ventricular end-diastolic pressure. In: Mark JB, ed. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998:59.

assumes continuous, laminar flow through a series of rigid pipes.²⁹⁹ This is an oversimplification. A more physiologic model of the systemic circulation considers the vasculature to be a series of collapsible vessels with intrinsic tone. This model, also called the vascular waterfall, describes a critical closing pressure in the downstream end of the circuit that exceeds right atrial pressure and serves to limit flow—an effective downstream pressure that is higher than the right

Transduced PAWP	20	20	20
Transmural PAWP	25	10	25
LV compliance	Normal	Normal	Stiff
LV volume	Increased	Normal (or reduced)	Normal (or reduced)

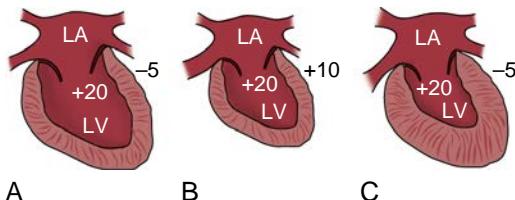


Fig. 36.50 Influence of juxtacardiac pressure and ventricular compliance on left ventricular (LV) preload. Three interpretations of an increased transduced pulmonary artery wedge pressure (PAWP, 20 mm Hg) are possible. (A) Juxtacardiac pressure (-5 mm Hg) and LV compliance are normal, transmural PAWP is increased (25 mm Hg), and LV volume is increased. (B) Juxtacardiac pressure is increased ($+10$ mm Hg), LV compliance is normal, transmural PAWP is decreased (10 mm Hg), and LV volume is normal or decreased. (C) Juxtacardiac pressure is normal, LV compliance is decreased, transmural PAWP is increased (25 mm Hg), and LV volume is normal or decreased. LA, Left atrial. (From Mark JB. *Atlas of Cardiovascular Monitoring*. New York: Churchill Livingstone; 1998.)

atrial pressure used in the SVR formula. A detailed consideration of these issues is beyond the scope of this discussion and is available in other sources.^{300,301} The important point for clinicians, though, is that therapy focused on the fine adjustment of SVR may be very misleading and should be avoided.

Additional problems arise in considering the pulmonary vasculature and using the above formulae as a measure of resistance to flow through the lung.³⁰² The pulmonary vasculature is more compliant than the systemic vasculature, and marked increases in pulmonary blood flow may not produce any significant increase in PAP. In addition, flow usually ceases at end-diastole in the low resistance pulmonary circuit. Thus, changes in pulmonary vascular resistance may result from intrinsic alterations in pulmonary vascular tone (constriction or dilation), vascular recruitment, or rheologic changes. For the pulmonary circuit, a better approach to evaluating the changes in pulmonary vascular resistance may be to examine the pressure gradient between the PAD and wedge pressures, or the gradient between the mean pulmonary artery and wedge pressures (also termed the trans-pulmonary gradient).

Another set of common calculations derived from standard hemodynamic variables adjusts these measurements for the patient's body surface area (BSA) in an attempt to normalize these measurements for patients of different sizes. The BSA is generally determined from a standard nomogram based on height and weight. The most commonly indexed variables are the cardiac index (cardiac index = cardiac output/body surface area) and stroke volume index (stroke volume index = stroke volume/body surface area). On occasion, the systemic and pulmonary vascular resistances are indexed as well by multiplying by BSA. In theory, normalizing hemodynamic values through "indexing" should help clinicians determine appropriate normal physiologic ranges

TABLE 36.7 Normal Hemodynamic Values

	Average	Range
Cardiac output (L/min)	5.0	4.0-6.5
Stroke volume (mL)	75	60-90
Systemic vascular resistance (Wood units) (Dynes-sec-cm ⁻⁵)	1200	800-1600
Pulmonary vascular resistance (Wood units) (Dynes-sec-cm ⁻⁵)	80	40-180
Arterial oxygen content (mL/dL)	18	16-20
Mixed venous oxygen content (mL/dL)	14	13-15
Mixed venous oxygen saturation (%)	75	70-80
Arteriovenous oxygen difference (mL/dL)	4	3-5
Oxygen consumption (mL/min)	225	200-250

to help guide therapy. Unfortunately, there is little evidence that these additional calculations provide valid normalizing adjustments. BSA is a biometric measurement with an obscure relationship to blood flow and cardiac output, and it does not adjust for variations between individuals based on age, sex, body habitus, or metabolic rate.³⁰³ Although it is important to be aware of a patient's size and medical history in interpreting and treating changes in any of the measured or calculated hemodynamic variables, it is not appropriate to target therapy solely at achieving normal indexed values.

PULMONARY ARTERY CATHETERIZATION: INDICATIONS AND OUTCOME CONTROVERSY

The PAC allows continuous tracking of hemodynamic variables, which seems particularly valuable in critically ill high-risk patients with circulatory dysfunction. Measurement of cardiac output (see below section on Thermodilution cardiac output) can separate shock states into hypovolemic etiology (low cardiac output with low filling pressures), cardiogenic etiology (low cardiac output and high filling pressures), and distributive etiology (high cardiac output and low SVR). Through measurement of cardiac output and left and right filling pressures (PAWP and CVP, respectively), it can separate out predominantly LV or RV dysfunction or global dysfunction. For RV dysfunction, the PAC allows distinction of RV dysfunction predominantly related to increased afterload (high PAP) versus dysfunction related mostly to pump failure (high CVP and low PAP).^{304,305}

Despite these advantages, the PAC has stimulated a great deal of vigorous controversy.^{306,307} It is an expensive, invasive technique that is widely used but still not proven to improve patient outcomes. This controversy was much fueled by a study published by Connors and associates in 1996, showing that PAC-monitored patients in the ICU had 20% increased mortality, increased length of hospital stay, and incurred increased costs.³⁰⁸ The publication of this study was accompanied by a strongly worded editorial calling for a moratorium on PAC use or a randomized controlled trial to define its efficacy.³⁰⁹

Surrounding that time and in subsequent years, several large, randomized, adequately powered studies have been published regarding the use of the PAC in various settings: general non-cardiac surgery,²⁴⁴ vascular surgery,³¹⁰ CABG surgery,^{311,312} non-surgical patients with congestive heart failure,³¹³ patients with acute lung injury,³¹⁴ and critically ill patients in the ICU.³¹⁵ Generally, these studies have shown no benefit to PAC use, but also no increase in mortality or in hospital or ICU length of stay.

One common drawback to most of these large randomized studies is that they have necessarily examined the routine use of PAC and enrolled a sequential cohort of patients, most of them with a relatively moderate risk of death or complications. Also, not all of them have employed a specific therapeutic intervention protocol.³¹⁶ Indeed, in especially high-risk patients, marked either by old age, severe comorbidity, or increased disease acuity, several recent nonrandomized studies were indeed able to demonstrate a clinical benefit from PAC use.³¹⁷⁻³²⁰

The most recent recommendations pertaining to the perioperative use of PACs are the ASA practice guidelines published in 2003.²⁵² The task force considered PAC monitoring to be appropriate in high-risk surgical patients undergoing high-risk procedures. Furthermore, the specific practice setting as well as the proficiency and experience of clinicians should be considered.

PAC use must be tailored to the degree of risk for the patient and the risk posed by the procedure itself. For example, a patient with advanced ischemic cardiomyopathy who needs lower extremity amputation under regional anesthesia would not warrant PAC monitoring while a patient with stable ischemic heart disease scheduled for extensive abdominal cancer resection may benefit from perioperative use. Furthermore, practice setting must be considered such as the operators' technical skill, knowledge, and experience in PAC use.²⁵²

A reasonable conclusion from the bulk of published research would be that PAC use should be limited, although a moratorium on use is ill-advised. Indeed, data demonstrate a significant and continuing decrease in PAC usage.³²¹ Use should be reserved to centers with significant experience and expertise. The PAC generally should be used to monitor and guide therapy in patients at high risk for hemodynamic instability, those who are judged more critically ill by a variety of clinical means, and those who are in shock, especially if elderly and suffering from other systemic diseases.

Obviously, the PAC itself has no potential for benefit unless it guides therapies that improve patient outcomes. Future research should focus on defining subgroups of patients who might benefit from use of the PAC, as well as defining effective therapeutic interventions based on the hemodynamic information gained from the PAC.^{316,322,323} Heart failure patients in shock are one such population for which data from clinical registries suggest benefit despite lack of confirmatory evidence from randomized trials.^{323,324}

SPECIAL TYPES OF PULMONARY ARTERY CATHETERS

Specific PAC modifications were designed to allow for continuous cardiac output (CCO) measurement (described in the Cardiac Output section), mixed venous oxygen

saturation monitoring, or right heart function evaluation, vastly expanding the types of physiologic information available to those caring for critically ill patients.

Mixed Venous Oximetry Pulmonary Artery Catheter

Although the formal Fick cardiac output method is not widely applied in clinical practice outside the cardiac catheterization laboratory, the physiologic relations described by the Fick equation form the basis for another PAC-based monitoring technique termed continuous mixed venous oximetry.³²⁵ Rearrangement of the Fick equation reveals the four determinants of mixed venous hemoglobin saturation ($S_{\bar{V}}O_2$):

$$S_{\bar{V}}O_2 = S_aO_2 - \frac{\dot{V}O_2}{\dot{Q} \cdot 1.36 \cdot Hgb} \quad (36.2)$$

Where,

$S_{\bar{V}}O_2$ = mixed venous hemoglobin saturation (%)

S_aO_2 = arterial hemoglobin saturation (%)

$\dot{V}O_2$ = oxygen consumption (mL•O₂/min)

\dot{Q} = cardiac output (L/min)

Hgb = hemoglobin concentration (g/dL)

To the extent that arterial hemoglobin saturation, oxygen consumption, and hemoglobin concentration remain stable, mixed venous hemoglobin saturation may be used as an indirect indicator of cardiac output. Thus, when cardiac output falls, tissue oxygen extraction increases and the mixed venous blood will have a lower hemoglobin oxygen saturation. Monitoring this variable provides more comprehensive information about the balance of oxygen delivery and consumption by the body—not just the cardiac output value, but also the adequacy of that cardiac output compared to tissue oxygen requirements.³²⁵ It is important to remember that mixed venous hemoglobin saturation values reflect global, whole-body measurement. Therefore, regionally inadequate blood flow and tissue oxygen delivery (like limb or intestinal ischemia) can coexist with a normal or high mixed venous hemoglobin saturation.

Although mixed venous hemoglobin saturation may be determined by intermittent blood sampling from the distal port of the PAC, a specially designed PAC can provide this information reliably and continuously. Fiberoptic bundles incorporated into the PAC determine the hemoglobin oxygen saturation in pulmonary artery blood based on the principles of reflectance oximetry using either a two or three wavelength system. A special computer connected to this PAC displays the mixed venous hemoglobin saturation continuously. The technology is typically incorporated into the standard PAC or the CCO PAC (see later), in the latter case providing both CCO and venous oximetry data. These catheters are calibrated at the bedside prior to use but may also be calibrated *in vivo* from a pulmonary artery blood gas sample. Recalibration every 24 hours is usually recommended due to a drift artifact.

Recently, the technology to continuously measure oxygen saturation has been incorporated into central venous catheters as well. These catheters measure central venous saturation, measured in the superior vena cava. Normally, this saturation is around 70% versus 75% in the pulmonary artery.³²⁵ Low central venous

saturation has been associated with increased complications both in trauma patients and in major surgery patients.^{326,327}

The real value of measuring venous oxygen saturation lies in its ability to guide therapeutic interventions. Because one of the body's physiologic compensations for anemia is increased oxygen extraction, low venous hemoglobin saturation has been used to guide the need for blood transfusion.³²⁸ Several studies have used venous hemoglobin saturation to guide interventions aimed at increasing cardiac output—a goal-directed approach. A study in patients undergoing cardiac surgery has shown better outcomes in patients randomized to protocol-driven interventions aimed at achieving mixed venous hemoglobin saturation above 70% (and blood lactate <2mg/dL).³²⁹ Similarly, optimizing the central venous oxygen saturation has been shown to improve outcome in high-risk non-cardiac and off-pump cardiac surgical patients.^{330,331} Although an early study showed similar benefit in patients with early sepsis,³³² a more recent study could not confirm these results.³³³

It is important to note that these studies have employed strict protocol-driven therapeutic interventions. In contrast, a large Veterans Affairs observational trial of 3265 cardiac surgical patients noted that 49% of patients received continuous mixed venous oximetry PACs, and use of this catheter was associated with increased cost but no better outcome than the standard PAC group.³³⁴ In this study, however, no protocol was used to guide therapeutic interventions based on monitoring results.

Right Ventricular Ejection Fraction Pulmonary Artery Catheter

Although cardiovascular monitoring has focused predominantly on LV performance, in some instances RV dysfunction may be the more important factor limiting circulation. Patient populations at increased risk for RV dysfunction include those with chronic obstructive pulmonary disease, adult respiratory distress syndrome, pulmonary hypertension, and RV ischemia and infarction.³³⁵

Measurement of right ventricular ejection fraction (RVEF) with a specially designed PAC offers another method for evaluating RV function. This method uses a standard PAC equipped with a rapid response thermistor that detects and quantifies the small changes in pulmonary artery blood temperature that occur with each heartbeat, in a manner somewhat analogous to a standard CCO PAC. The cardiac output computer measures the residual fraction of thermal signal following each heart beat and derives the RVEF.³³⁶ RV end-diastolic volume can be calculated from RVEF and stroke volume, and can be used as an index of RV preload. Clearly, all factors that confound standard thermodilution cardiac output measurement (described later) will also interfere with accurate determination of RVEF. In addition, because the temperature changes measured by the RVEF PAC are small beat-to-beat changes, the method will not work if the ECG R waves cannot be detected accurately, the R-R interval is short owing to tachycardia, or the cardiac rhythm is irregular.³³⁷

Clinical use of the RVEF PAC has been described in critically ill patients, especially in those with respiratory failure,^{338,339} as well as intraoperatively during cardiac

surgery, where a reduced RVEF has been noted following cardiopulmonary bypass, particularly in patients with pre-existing right coronary artery obstruction.³⁴⁰ However, as in the case of standard PAC monitoring, the benefit of RVEF PAC monitoring in terms of patient outcomes remains unproven.²⁵²

Cardiac Output Monitoring

Cardiac output is the total blood flow generated by the heart, and in a normal adult at rest ranges from 4.0 to 6.5 L/min. Measurement of cardiac output provides a global assessment of the circulation, and in combination with other hemodynamic measurements (heart rate, arterial blood pressure, CVP, PAP, and wedge pressure), it allows calculation of additional important circulatory variables, such as systemic and pulmonary vascular resistance and ventricular stroke work (see Table 36.7).

Three factors have driven efforts to measure cardiac output in clinical practice. The first is the recognition that in many critically ill patients, low cardiac output leads to significant morbidity and mortality.³⁴¹ Secondly, clinical assessment of cardiac output is often inaccurate; for example, seriously ill patients with decreased cardiac output might have normal systemic arterial blood pressures.³⁴² Finally, newer techniques for cardiac output measurement are becoming less invasive and thus might provide benefit to many patients without the attendant risks of invasive monitoring.^{342,343} The advantages and disadvantages of each technique must be appreciated for proper clinical application.

THERMODILUTION CARDIAC OUTPUT MONITORING

The thermodilution technique is considered the gold standard for measuring cardiac output because of its ease of implementation and the long clinical experience with its use in various settings. It is a variant of the **indicator dilution** method, in which a known amount of a tracer substance is injected into the blood stream and its concentration change is measured over time at a downstream site.³⁴⁴ For thermodilution, a known volume of room temperature fluid is injected as a bolus into the proximal (right atrium) lumen of the PAC, and the resulting change in the pulmonary artery blood temperature is recorded by the thermistor at the catheter tip. In adults, an injectate volume of 10 mL should be used, while in children, an injectate volume of 0.15 mL/kg is recommended.³⁴⁵ As in all other forms of cardiovascular monitoring, it is important to have a real-time display of the thermodilution curve resulting from each cardiac output measurement.³⁴⁵ This allows the clinician to discern artifacts that would invalidate the cardiac output measurement, such as unstable blood temperature, recirculation, or incomplete indicator injection.

Usually three cardiac output measurements performed in rapid succession are averaged to provide a more reliable result. If only a single injection is used to determine cardiac output, a difference between sequential cardiac output measurements of 22% is required to suggest a clinically significant change. In contrast, when three injections are

BOX 36.8 Factors Influencing Accuracy of Thermodilution Cardiac Output Measurement

- Intracardiac shunts
- Tricuspid or pulmonic valve regurgitation
- Inadequate delivery of thermal indicator
 - Central venous injection site within catheter introducer sheath
 - Warming of iced injectate
- Thermistor malfunction from fibrin or clot
- Pulmonary artery blood temperature fluctuations
 - Following cardiopulmonary bypass
 - Rapid intravenous fluid administration
- Respiratory cycle influences

averaged to determine the thermodilution measurement, a change greater than 13% indicates a clinically significant change in cardiac output.³⁴⁶

Even when carefully performed, some studies have found that thermodilution cardiac output measurements may not agree with other reference methods.^{347,348} However, few complications are directly attributable to the technique itself, and following the trend in cardiac output is probably more clinically useful than emphasizing any absolute value.

Sources of Error in Thermodilution Cardiac Output Monitoring

Several important technical issues and potential sources of error must be considered to interpret thermodilution cardiac output measurements properly (Box 36.8).^{344,345} The thermodilution technique measures RV output. With **intracardiac shunt**, RV and LV outputs will not be equal.

Patients with **tricuspid or pulmonic valve regurgitation** pose additional problems for thermodilution cardiac output measurement owing to recirculation of the indicator across the incompetent valve. Although minor degrees of valvular regurgitation have little effect on thermodilution cardiac output monitoring, these values are unreliable with more severe valvular regurgitation, either underestimated or overestimated, depending on the severity of valvular regurgitation and the magnitude of the cardiac output.^{345,349}

Unrecognized **fluctuation in blood temperature** may also influence cardiac output measurement. In most patients, pulmonary artery blood temperature falls somewhat in the initial minutes **following cardiopulmonary bypass**, when the rewarmed vascular and vessel rich tissues redistribute the heat gained to the less well perfused body core. Therefore, the thermal baseline is unstable and measurements made in the minutes following bypass are notoriously unreliable, most often leading to marked underestimation of the true cardiac output.³⁵⁰ Pulmonary artery blood temperature can also change due to **rapid fluid infusion**.³⁵¹

One controversy surrounding bolus thermodilution cardiac output monitoring is the proper timing of measurement in relation to the **respiratory cycle**, particularly in patients receiving positive pressure mechanical ventilation, because RV stroke output varies as much as 50% during the respiratory cycle. Although reproducibility of consecutive measurements improves markedly

when the bolus injections are synchronized to the same phase of the respiratory cycle, an accurate measurement of average cardiac output is achieved more reliably by making multiple injections during the different phases of the respiratory cycle and then averaging the results.^{345,352}

Last, the measured thermodilution cardiac output can overestimate true cardiac output during low flow states because of significant heat loss from slow injectate transit.³⁵³

Continuous Thermodilution Cardiac Output Monitoring

Newer technologies applied to PAC monitoring allow nearly continuous cardiac output monitoring using warm thermal indicator.^{344,354} In brief, small quantities of heat are released from a 10-cm thermal filament incorporated into the RV portion of a PAC, approximately 15 to 25 cm from the catheter tip, and the resulting thermal signal is measured by the thermistor at the tip of the catheter in the pulmonary artery. The heating filament is cycled on and off in a pseudorandom binary sequence, and the cardiac output is derived from cross correlation of the measured pulmonary artery temperature with the known sequence of heating filament activation.³⁵⁴ Typically, the displayed value for cardiac output is updated every 30 to 60 seconds and represents the average value for the cardiac output measured over the previous 3 to 6 minutes. On the one hand, this will lead to a delayed response during unstable hemodynamic conditions.³⁵⁵ On the other hand, reproducibility and precision appear to be better compared with the single instantaneous bolus thermodilution technique, especially during positive pressure ventilation.^{356,357}

The CCO PAC has been widely accepted into clinical use for a number of practical reasons. Although these catheters are more expensive than standard PACs, obviating the need for bolus injections reduces nursing workload and the potential risk of fluid overload or infection. However, like cold bolus thermodilution techniques, warm thermal CCO has certain methodological pitfalls that must be recognized and avoided. The CCO computer and catheter require a significant amount of time to warm up and may work poorly in an environment where there is a great deal of thermal noise, such as the cardiac operating room. Recent observations also suggest that the use of pneumatic compression devices may introduce artifacts that appear as large variations (oscillations) in CCO values in otherwise stable patients.³⁵⁸ As already emphasized, CCO monitors have an inherent 5- to 15-minute delay in responding to abrupt changes in cardiac output, and the magnitude of this delay depends on the type of physiologic perturbation, as well as the CCO computer monitor algorithm.³⁵⁵ Although modifications of CCO algorithms provide a "STAT Mode" rapid response time, acute changes in cardiac output are still detected more slowly by CCO monitoring than by other methods, such as direct arterial pressure or mixed venous oximetry. In effect, the CCO technique involves a fundamental tradeoff between rapid response time and overall accuracy and stability of the displayed value.³⁵⁶ While it might be useful for clinical decision making, no studies exist that demonstrate improved patient outcomes from use of the CCO PAC.

Transpulmonary Thermodilution Cardiac Output

For transpulmonary thermodilution measurement, ice-cold saline is injected into a central venous line while the change in temperature is measured in a large peripheral artery (femoral, axillary, or brachial artery) via a special arterial catheter equipped with a thermistor.³⁵⁹ Several studies have shown adequate agreement with standard thermodilution cardiac output.^{360,361} In contrast to the standard thermodilution method, the transpulmonary thermodilution measurement lasts over several respiratory cycles and thereby obviates the respiratory effects on stroke volume and measured cardiac output.³⁶²

Mathematical derivation from the transpulmonary thermodilution curve can produce several additional useful indices. Extravascular lung water is a measure of pulmonary edema and can be used to guide fluid therapy in patients with acute lung injury or sepsis.³⁶³⁻³⁶⁵ Other derived indices are the global end-diastolic volume and intrathoracic blood volume. Several studies have found these indices to be a better measure of cardiac preload than traditional measurements such as CVP or PAWP.^{366,367} However, it appears that these indices still cannot predict cardiac output response to fluid loading.³⁶⁸ Another parameter derived from the transpulmonary thermodilution curve is the cardiac function index, calculated using cardiac output and the intrathoracic blood volume. In patients without RV failure, it has been shown to correlate with LV ejection fraction and its response to inotropic therapy.³⁶⁹

LITHIUM DILUTION CARDIAC OUTPUT MONITORING

The lithium dilution technique is another cardiac output monitoring method that derives its fundamental basis from indicator dilution principles.³⁷⁰ In brief, following an intravenous bolus injection of a small dose of lithium chloride, an ion-selective electrode attached to a peripheral arterial catheter measures the lithium dilution curve, from which the cardiac output is derived. Several studies have shown that this is an accurate technique compared with standard thermodilution or electromagnetic flowmetry.^{371,372} The lithium indicator can be injected through a peripheral intravenous catheter with similar measurement accuracy, thus eliminating the need for a central venous line.³⁷³ This technique can also be used in children.³⁷⁴ Lithium dilution cannot be used in patients who are taking lithium or those who have just received nondepolarizing neuromuscular blockers, since the latter also alter the lithium sensor electrode measurement.

OTHER METHODS FOR MONITORING CARDIAC OUTPUT AND PERfusion

In recent years, much work has been dedicated to developing minimal or non-invasive methods to measure cardiac output. While it seems that these methods' overall agreement with the traditional thermodilution method is not very high,³⁷⁵ they do offer other advantages. Some of these newer methods are discussed herein.

Esophageal Doppler Cardiac Output Monitoring

All of the ultrasound-based methods for cardiac output monitoring employ the Doppler principle as described in

detail in [Chapter 37](#). While cardiac output can be intermittently measured by the Doppler technique during transthoracic or transesophageal echocardiography examinations, for monitoring purposes, a special esophageal Doppler probe has been developed that allows continuous monitoring of cardiac output by measuring the Doppler shift of the interrogated blood flow in the descending thoracic aorta. The Doppler probe is inserted into the esophagus to a depth of approximately 35 cm from the incisor teeth and is adjusted to optimize the audible Doppler flow sound from the descending aorta, which lies in close proximity and runs essentially parallel to the esophagus at this location.³⁷⁶

Several limitations of the esophageal Doppler technique must be appreciated by the physician to avoid pitfalls in data interpretation. This monitoring method interrogates blood flow in the descending thoracic aorta and therefore only measures a fraction of total cardiac output. To report total cardiac output, either the esophageal Doppler measurement must be "calibrated" by some alternative method, or an empirically determined correction constant of 1.4 is used.³⁷⁶ This constant is accurate for most patients but does not apply universally, especially in the presence of conditions that redistribute blood flow, such as pregnancy, aortic cross-clamping, and following cardiopulmonary bypass.^{377,378} In addition, the descending thoracic aorta diameter is either measured using A-mode ultrasound or calculated from a nomogram based on the patient's age, sex, height, and weight.³⁷⁶ When calculated, it is assumed that the aortic diameter does not change throughout the cardiac cycle. In addition to these considerations, the technique is likely to be inaccurate in the presence of aortic valve stenosis or regurgitation, or in patients with thoracic aortic disease. It is not easily applied in nontracheally intubated non-sedated patients, and it cannot be used in individuals with esophageal pathology. Finally, like all ultrasound techniques, the acoustic window needed to acquire the Doppler signal may not be adequate in some individuals, thereby precluding use of this method.

Advantages of the esophageal Doppler monitoring technique include its ease of use, minimal invasiveness, and inherent safety. It appears that limited experience is needed for clinical success—as few as 10 to 12 cases for accurate application of the technique.³⁷⁷ A review of 25 clinical trials comparing esophageal Doppler cardiac output measurement with PAC thermodilution measurements noted that the Doppler cardiac output values correlated well with thermodilution measurements and showed minimal overall bias and good tracking of directional changes in thermodilution cardiac output with low intra- and inter-observer measurement variability.³⁷⁷

Recently, the esophageal Doppler method has seen renewed popularity.^{379,380} Current devices provide a clear visual display of the spectral Doppler waveform and also calculate and display additional hemodynamic variables including the peak blood flow velocity, flow acceleration, and heart rate-corrected flow time ([Fig. 36.51](#)). Some studies have shown that these additional measures provide useful information about LV preload, fluid responsiveness, contractility, and systemic vascular resistance.³⁸¹⁻³⁸³ Additionally, respiratory variability of the aortic blood flow velocity can be used to predict cardiac output response to a fluid bolus.³⁸⁴ One of the more important benefits of this monitor may be focusing clinical attention on optimizing

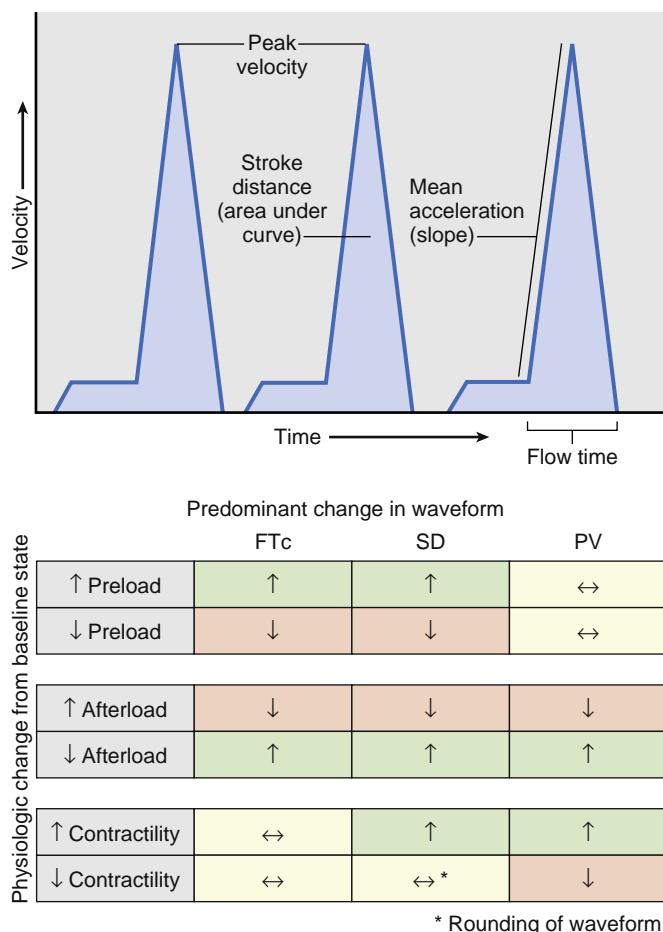


Fig. 36.51 The velocity-time waveform displayed by esophageal Doppler cardiac output monitoring devices reflects alterations in contractility, preload, and afterload. Stroke distance (SD) is directly related to calculated stroke volume and provides a useful surrogate measure of cardiac output. FTc, Systolic flow time corrected for heart rate; PV, peak velocity.

stroke volume rather than total cardiac output. Indeed, in critically ill patients, complications may be better predicted by low stroke volume than by low cardiac output.³⁸⁵ Several studies have shown that hemodynamic optimization, guided by maximizing esophageal Doppler-measured stroke volume in moderate-risk surgical patients, reduces perioperative morbidity and shortens hospital stay.^{379,380,386}

Bioimpedance and Bioreactance Cardiac Output Monitoring

The technique of bioimpedance cardiac output monitoring was first described by Kubicek and associates and is based on changes in electrical impedance of the thoracic cavity or the whole body occurring with ejection of blood during cardiac systole.³⁸⁷ As blood has a significantly lower electrical resistance compared with tissues, changes in impedance to electrical flow reflect a change in blood volume, and this can be used to calculate stroke volume.³⁸⁸

For bioimpedance measurement, disposable electrodes are applied to the skin surface along the sides of the neck and lateral aspect of the costal margin (thoracic bioimpedance) or to the four limbs (whole body bioimpedance); a high-frequency, low-amplitude electrical current is applied;

and the voltage change is measured. Patient height, weight, and gender are used to calculate the volume of the thoracic cavity. Bioimpedance cardiac output is computed for each cardiac cycle and continuously displayed as an average value over several heart beats.

Although many studies suggest that the bioimpedance method is accurate in healthy volunteers, its reliability deteriorates in surgical and critically ill patients.³⁸⁹ This led to attempts at improving the technology used. A newer technique, termed bioreactance cardiac output monitoring, measures not only the amplitude change of the received signal, but also its phase shift compared to the applied electrical signal. It utilizes four dual-electrode patches, placed two on each side of the body.³⁸⁸ Compared to the standard bioimpedance method, the bioreactance method shows somewhat better agreement with traditional cardiac output calculations. Several clinical scenarios where this new method has been validated include the prediction of fluid responsiveness when using the passive leg raising test in patients after cardiac surgery and evaluating cardiac output change during exercise stress testing.³⁸⁸

Partial CO₂ Rebreathing Cardiac Output Monitoring

Another method for cardiac output monitoring that does not require a PAC is the partial CO₂ rebreathing technique.^{390,391} Owing to the difficulty encountered in the standard Fick method involving measuring oxygen consumption and mixed venous hemoglobin saturation, this alternative technique is based upon a restatement of the Fick Equation for carbon dioxide elimination rather than oxygen uptake.

$$\dot{Q} = \frac{\dot{V}CO_2}{(C_vCO_2 - C_aCO_2)} \quad (36.3)$$

Where,

\dot{Q} = cardiac output

$\dot{V}CO_2$ = rate of carbon dioxide elimination

C_vCO_2 = carbon dioxide content of mixed venous blood

C_aCO_2 = carbon dioxide content of arterial blood

This method uses the change in CO₂ production and end-tidal CO₂ concentration in response to a brief, sudden change in minute ventilation. With a specifically designed breathing system and monitoring computer, this measurement is easily performed in any tracheally intubated patient. Changes in end-tidal CO₂ in response to the rebreathing maneuver are used to calculate cardiac output by a differential version of the Fick equation for carbon dioxide. The attractive features of this method are that it is entirely non-invasive, it can be performed every few minutes, and the brief episodes of rebreathing pose no substantial risk to most patients, with end-tidal CO₂ measurements increasing by less than 3 mm Hg. However, as currently designed, accurate measurements with this technique require tracheal intubation for precise measurement of exhaled gasses. Furthermore, changing patterns of ventilation may have an unpredictable influence on the measurement. As with all Fick-based techniques, the partial CO₂ rebreathing method measures pulmonary capillary blood flow as an indicator of total cardiac output and thus requires correction for pulmonary shunt.

Initial clinical trials suggested reasonably good agreement between the partial rebreathing CO_2 cardiac output method and other techniques, such as thermodilution. However, as with most of these alternative monitoring methods, the clinical trials are small and mainly focused on specific patient groups, particularly coronary artery bypass surgery patients.³⁹² At present, the clinical role for this technique is mainly focused on short-term intraoperative applications or mechanically ventilated postoperative patients. Due to the mandatory increase in arterial pCO_2 , the technique is relatively contraindicated in patients with increased intracranial pressure.

Pulse Contour Cardiac Output Monitoring

Much of recent development in the area of cardiac output monitoring has been focused on continuous measurement of cardiac output derived from the analysis of the arterial pulse pressure waveform. These methods, generally termed pulse contour cardiac output, determine stroke volume from computerized analysis of the area under the arterial pressure waveform recorded from an arterial catheter or even a noninvasive finger blood pressure waveform.³⁹³⁻³⁹⁶ Pulse contour methods offer the potential for non-invasive, continuous, beat-to-beat cardiac output monitoring. Also, the change in stroke volume from beat to beat (termed SVV) in response to tidal ventilation can be used to evaluate volume status in ventilated patients.^{147,397}

However, several shortcomings need to be considered.^{398,399} First, a baseline calibration with a known cardiac output is required to account for individual differences in vascular resistance, impedance, and wave reflectance. Additionally, recalibration is required every 8 to 12 hours to account for changes in vascular characteristics over time. Also, the use of vasopressors might affect the accuracy of pulse contour methods.⁴⁰⁰ This need for external calibration might require the use of a more invasive technique, negating the non-invasiveness advantage of pulse contour methods. Recently, several systems were developed with the capability for an auto-calibration based on a patient's demographic variables. However, the accuracy of this auto-calibration in various clinical situations is questionable.⁴⁰¹

A reasonably well-defined arterial pressure waveform with a discernible dicrotic notch is required for accurate identification of systole and diastole, a condition that might not exist under severe tachycardia or dysrhythmia, or other very low-output states. Last, for a meaningful use of beat-to-beat variation in stroke volume (as well as systolic pressure or PPV), the patient needs to be on controlled mechanical ventilation with a tidal volume of at least 8 mL/kg body weight and to be in a regular cardiac rhythm.⁴⁰²

Notwithstanding these shortcomings, clinical trials in surgical patients have shown that the pulse contour cardiac output methods provide an acceptable level of accuracy with a bias of less than 0.5 L/min compared to thermodilution cardiac output.^{395,403,404} SVV above 10% has been shown to be a useful predictor of fluid responsiveness.¹³⁸ Last, several recent studies have shown that goal-directed therapy based on either maximizing pulse contour derived cardiac output or minimizing SVV results in improved perioperative outcomes.⁴⁰⁵⁻⁴⁰⁷

Acknowledgment

This chapter is a consolidation of two chapters in the eighth edition, **Chapter 45** Cardiovascular Monitoring and **Chapter 47** Electrocardiography, Perioperative Ischemia, and Myocardial Infarction. The editors and publisher would like to thank the following authors: Shahar Bar-Yosef, Giora Landesberg, and Zak Hillel for their contributions to the prior edition of this work. Their contributions have served as the foundation for the current chapter.

Complete references available online at expertconsult.com.

References

1. Gravenstein JS. *J Clin Monit Comput.* 1998;14:451.
2. Block FE. *J Clin Monit.* 1994;10:366.
3. Zong W, et al. *Med Biol Eng Comput.* 2004;42(5):698.
4. American Society of Anesthesiologists. *Standards for basic anesthetic monitoring. ASA standards, guidelines and statements.* Park Ridge, Illinois: American Society of Anesthesiologists; 1993:5.
5. Sandau KE, et al. *Circ.* 2017;136:e273-e344.
6. Kligfield P, et al. *Journal of the American College of Cardiology.* 2007;49:1109-1127.
7. Ortega R, et al. *N Engl J Med.* 2015;372:e11.
8. Mason RE, Likar I. *Am Heart Jnl.* 1966;71:196-205.
9. Krucoff MW, et al. *Am J Card.* 1994;74:997-1001.
10. Drew BJ. *Cardiol Clin.* 2006;24:309-315. vii.
11. Chaitman BR, Hanson JS. *Am J Card.* 1981;47:1335-1349.
12. Blackburn H, Katigbak R. *Am Heart Jnl.* 1964;67:184-185.
13. Kubota I, et al. *Am Heart Jnl.* 1985;110:949-955.
14. Kaplan JA, et al. *Anesth Analg.* 1978;57:364-367.
15. London MJ, et al. *Anesthesiology.* 1988;69:232-241.
16. Landesberg G, et al. *Anesthesiology.* 2002;96:264-270.
17. Klein HO, et al. *Circ.* 1983;67:558-565.
18. Griffin RM, Kaplan JA. *Anaesthesia.* 1987;42:155-159.
19. Slogoff S, et al. *Anesthesiology.* 1990;73:1074-1081.
20. Takla G, et al. *Anesth Analg.* 2006;103:1196-1204.
21. Weinfurt PT. *J Clin Monitor.* 1990;6:132-138.
22. Khambatta HJ, et al. *Anesth Analg.* 1990;71:88-91.
23. Patel SI, Souter MJ. *Anesthesiology.* 2008;108:138-148.
24. Patton JA, et al. *Am J Crit Care: an official publication, American Association of Critical-Care Nurses.* 2001;10:23-32. quiz 3-4.
25. Mark JB, et al. *Anesth Analg.* 1992;74:26-31.
26. Stern S. *Card Electro Rev.* 2002;6:204-208.
27. Helwani MA, et al. *Anesthesiology.* 2018;128:1084-1091.
28. Miller TD, et al. *J Electrocard.* 1987;20:131-137.
29. ASA. Standards for Basic Anesthetic Monitoring. 2005. (Accessed May 5, 2008, 2008, at <http://www.asahq.org/publicationsAndServices/standards/02.pdf>.)
30. Bruner JMR, et al. *Med Instrum.* 1981;15:11.
31. Riva-Rocci S. *Gaz Med Torino.* 1896;47:981.
32. Korotkoff NS. *Bull Imp Med Acad St Petersburg.* 1905;11:365.
33. Kuck K, Baker PD. *Anesth Analg.* 2018 Aug;127(2):408-411.
34. Alpert BS, et al. *J Am Soc Hyper: JASH.* 2014;8:930-938.
35. Lakhral K, et al. *Chest.* 2017.
36. Pickering TG, et al. *Hypertension.* 2005;45(1):142.
37. Cohn JN. *JAMA.* 1967;199:972.
38. Lakhral K, et al. *Crit Care Med.* 2012;40(4):1207.
39. Ribezzo S, et al. *Sci World Jnl.* 2014;2014:353628.
40. Wan Y, et al. *J Hum Hypertens.* 2010;24(7):431.
41. AAMI. American national standard for non-invasive sphygmomanometers—part 2: clinical validation of automated measurement type. *AAMI.* 2009;25.
42. Lakhral K, et al. *Anesth Analg.* 2009;109(2):494.
43. Liu B, et al. *Blood pressure.* 2016;25:155-161.
44. Riley LE, et al. *Blood pressure monitoring.* 2017;22:202-207.
45. Wax DB, et al. *Anesthesiology.* 2011;115(5):973.
46. Jankowski P, et al. *Hypertension.* 2008;51:848-855.
47. Min JY, et al. *BMC anesthesiology.* 2017;17:110.
48. Leblanc ME, et al. *Obesity (Silver Spring, Md).* 2013;21:E533-E541.
49. Celler BG, et al. *Annual Conference.* 2015;2015:5964-5967.
50. Lakhral K, et al. *J Clin Monit Comput.* 2017.

51. Anast N, et al. *Can J Anesth*. 2016;63:298–306.
52. Benmira A, et al. *Expert review of medical devices*. 2016;13:179–189.
53. Alford JW, et al. *J Clin Monit Comput*. 2002;17:163.
54. Kuck K, et al. *J Clin Monit*. 1997;13:424.
55. Tobias JD, et al. *Anesthesia*. 2014;28:861–865.
56. Kim SH, et al. *Anesthesiology*. 2014;120:1080–1097.
57. Balzer F, et al. *J Int Med Res*. 2016;44:832–843.
58. Benes J, et al. *J Clin Monit Comput*. 2015;29:11–17.
59. Bilo G, et al. *Blood Pressure Monitoring*. 2015;20:291–294.
60. Dueck R, et al. *J Clin Monit Comput*. 2012;26:75–83.
61. Belani K, et al. *Anesthesiology*. 1999;91(3):686.
62. Weiss BM, Pasch T. *Curr Opin Anaesthesiol*. 1997;10:459.
63. Cockings JGL, et al. *Anaesth Intensive Care*. 1993;21:565.
64. Eather KF, et al. *Anesthesiology*. 1949;10:125.
65. Mark JB. *Atlas of cardiovascular monitoring*. New York: Churchill Livingstone; 1998.
66. Perel A. *Anesthesiology*. 1998;89:1309–1310.
67. Rooke GA. *Curr Opin Anesth*. 1995;8:511–515.
68. Thiele RH, et al. *Can J Anesth*. 2015;62:169–181.
69. Gabriel RA, et al. *J Clin Monit Comput*. 2017;31:877–884.
70. Mandel MA, Dauchot PJ. *J Hand Surg*. 1977;2(6):482.
71. Scheer B, et al. *Crit Care*. 2002;6(3):199.
72. Slogoff S, et al. *Anesthesiology*. 1983;59:42.
73. Brezinski M, et al. *Anesth Analg*. 2009;109(6):1763.
74. Knoblock K, et al. *Ann Thorac Surg*. 2005;80(3):918.
75. Knoblock K, et al. *Ann Thorac Surg*. 2005;79(3):1026, discussion 30.
76. Ciria-Llorens G, et al. *Surg Radiol Anat*. 1998;20(5):377.
77. Ciria-Llorens G, et al. *Br J Plast Surg*. 1999;52(6):440.
78. Richardson D, et al. *Plast Reconstr Surg*. 1997;99(1):109.
79. Allen EV. *Am J Med Sci*. 1929;178:237.
80. Wilkins RG. *Anaesthesia*. 1985;40(9):896.
81. Abu-Omar Y, et al. *Ann Thorac Surg*. 2004;77(1):116.
82. Barbeau GR, et al. *Am Heart J*. 2004;147(3):489.
83. Jarvis MA, et al. *Ann Thorac Surg*. 2000;70(4):1362.
84. Rosenberg B, et al. *Anaesthesia*. 1988;43(6):515.
85. Williams JS, et al. *N Engl J Med*. 2009;360(5):e6.
86. Levin PD, et al. *Crit Care Med*. 2003;31(2):481.
87. Ganesh A, et al. *Pediatr Crit Care Med*. 2009;10(1):45.
88. Shiver S, et al. *Acad Emerg Med*. 2006;13(12):1275.
89. Ueda K, et al. *Anaesthesia*. 2015;70:1039–1044.
90. Gu WJ, et al. *Chest*. 2016;149:166–179.
91. Htet N, et al. *J Crit Care*. 2017;41:194–197.
92. Karacalar S, et al. *J Clin Anesth*. 2007;19(3):209.
93. Bazaral MG, et al. *Anesthesiology*. 1990;73:38.
94. Singh A, et al. *Anesthesiology*. 2017;126:1065–1076.
95. Muralidhar K. *J Cardiothorac Vasc Anesth*. 1998;12(1):128.
96. Chen Y, et al. *Blood pressure monitoring*. 2016;21:27–32.
97. Rehfeldt KH, Sanders MS. *Anesth Analg*. 2000;90:45.
98. Rose SH. *Anesthesiology*. 1993;78:587.
99. Singleton RJ, et al. *Anaesth Intensive Care*. 1993;21:664.
100. Bhananker SM, et al. *Anesth Analg*. 2009;109(1):124.
101. Gardner RM. *Anesthesiology*. 1981;54:227.
102. Kleinman B. *J Clin Monit*. 1989;5:137.
103. Kleinman B, et al. *Anesthesiology*. 1992;77:1215.
104. O’Quin R, Marini JJ. *Am Rev Respir Dis*. 1983;128:319.
105. Mark JB. Technical requirements for direct blood pressure measurement. In: Mark JB, ed. *Atlas of cardiovascular monitoring*. New York: Churchill Livingstone; 1998:99.
106. Geddes LA. *Handbook of blood pressure measurement*. Clifton, NJ: Humana Press; 1991.
107. Romagnoli S, et al. *Crit Care (London, England)*. 2014;18:644.
108. Schwid HA. *J Clin Monit*. 1988;4:181.
109. Sinha S, et al. *Anesthesia*. 2007;62(6):615.
110. Promont C, et al. *Anesthesiology*. 2000;92(1):208.
111. Gardner RM. *Crit Care Med*. 1996;24(5):879.
112. Skidmore K, et al. *Anesth Analg*. 2002;95:1192.
113. Courtois M, et al. *Circulation*. 1995;92:1994.
114. Seo JH, et al. *Anesthesiology*. 2007;107(2):260.
115. Ortega R, et al. *N Engl J Med*. 2017;376:e26.
116. Kovacs G, et al. *Euro Resp J*. 2013;42:1586–1594.
117. Braunwald E, et al. *Circ Res*. 1956;4:100.
118. Stouffer G. Arterial Pressure. In: Stouffer G, ed. *Cardiovascular hemodynamics for the clinician*. Malden, Mass: Blackwell Futura; 2008:57.
119. O’Rourke MF, Gallagher DE. *J Hyper*. 1996;14:S147–S157.
120. Franklin SS, Weber MA. *Am Heart J*. 1994;128:793.
121. Frank SM, et al. *Anesthesiology*. 1991;75:457.
122. Kinzer JB, et al. *Anesth Analg*. 1985;64:1134.
123. Mark JB. Arterial blood pressure. Direct vs. indirect measurement. In: Mark JB, ed. *Atlas of cardiovascular monitoring*. New York: Churchill Livingstone; 1998:81.
124. Dorman T, et al. *Crit Care Med*. 1998;26:1646.
125. Urzua J, et al. *J Clin Monit*. 1994;10:229.
126. Chauhan S, et al. *J Cardiothorac Vasc Anesth*. 2000;14(3):274.
127. Hynson JM, et al. *Crit Care Med*. 1998;26:1623.
128. McGregor M. *N Engl J Med*. 1979;301(480).
129. Shabetai R, et al. *Am J Cardiol*. 1970;26:480.
130. Mark JB. Pericardial constriction and cardiac tamponade. In: Mark JB, ed. *Atlas of cardiovascular monitoring*. New York: Churchill Livingstone; 1998:313.
131. Gelman S. *Anesthesiology*. 2008;108(4):735.
132. Marik PE. *Anaesth Intensive Care*. 1993;21:405.
133. Gunn SR, Pinsky MR. *Curr Opin Crit Care*. 2001;7:212.
134. Preisman S, et al. *Br J Anaesth*. 2005;95(6):746.
135. Perel A. *Anesth Analg*. 2008;106(4):1031.
136. Hofer CK, Cannesson M. *Acta Anaesthesiol Taiwan*. 2011;49(2):59.
137. Thiele RH, et al. *Anesth Analg*. 2012;115(1):176.
138. Berkenstadt H, et al. *Anesth Analg*. 2001;92(4):984.
139. Phillips R, Brierley J. *J Clin Monit Comput*. 2015;29:197–200.
140. Kong R, et al. *J Clin Monit Comput*. 2016;30:81–86.
141. Cannesson M, et al. *Anesth Analg*. 2008;106(4):1189.
142. Antonson LP, Kirkeboen KA. *Anesthesiol Res Pract*. 2012;617380:2012.
143. Cannesson M, et al. *J Clin Monit Comput*. 2011;25(1):45.
144. Michard F, et al. *Am J Respir Crit Care Med*. 2000;162(1):134.
145. Biais M, et al. *Br J Anaesth*. 2010;104(4):407.
146. Mahjoub Y, et al. *Intensive Care Med*. 2011;37(2):360.
147. Marik PE, et al. *Crit Care Med*. 2009;37:2642–2647.
148. De Hert SG. *Anesthesiology*. 2011;115:229–230.
149. Cannesson M. *J Card Vasc Anesth*. 2010;24:487–497.
150. Cannesson M, et al. *Anesth Analg*. 2008;106(4):1195.
151. Auler Jr JO, et al. *Anesth Analg*. 2008;106(4):1201.
152. Min JJ, et al. *J Clin Monit Comput*. 2017;31:397–405.
153. Audimoolam VK, et al. *Anesth Analg*. 2017;124:480–486.
154. Royer P, et al. *J Trauma Acute Care Surg*. 2015;78:994–999.
155. Wyffels PA, et al. *Am J Phys Hrt Circ Phys*. 2016;310:H1194–H1200.
156. Ho KM. *Anesth Int Care*. 2016;44:14–19.
157. Wyler von Ballmoos M, et al. *Crit Care*. 2010;14(3):R111.
158. Yi L, et al. *PLoS One*. 2017;12:e0177590.
159. Jeong DM, et al. *Anesthesia and analgesia*. 2017;125:1158–1165.
160. Hennings LI, et al. *Danish medical journal*. 2015;62.
161. Ikeda K, et al. *Sem Card Vasc Anesth*. 2016;20:188–196.
162. Myatra SN, et al. *Crit Care Med*. 2017;45:415–421.
163. Biais M, et al. *Anesthesiology*. 2017;126:260–267.
164. De Broca B, et al. *Medicine*. 2016;95:e4259.
165. Augusto JF, et al. *Intensive Care Med*. 2011;37(3):411.
166. Barodka VM, et al. *Anesth Analg*. 2011;112(5):1048.
167. Gravenstein N, Blackshear RH. *J Clin Monit*. 1991;7(1).
168. Fisher KL, Leung AN. *AJR Am J Roentgenol*. 1996;166(2):329.
169. Graham AS, et al. *N Engl J Med*. 2007;356(21):e21.
170. Peres PW. *Anaesth Intensive Care*. 1990;18(4):536.
171. Rupp SM, et al. *Anesthesiology*. 2012;116(3):539.
172. Troianos CA, et al. *Anesth Analg*. 2012;114(1):46.
173. Rothschild JM. *Ultrasound guidance of central vein catheterization. Evidence report/technology assessment, No. 43. Making health care safer. A critical analysis of patient safety practices*. Rockville, MD: Agency for Healthcare Research and Quality; 2001:245.
174. Schulman PM, et al. *N Engl J Med*. 2018;379:e1.
175. Tsui JY, et al. *N Engl J Med*. 2008;358:e30.
176. Ortega R, et al. *N Engl J Med*. 2010;362:e57.
177. Taylor RW, Palagiri AV. *Crit Care Med*. 2007;35:1390–1396.
178. McGee DC, Gould MK. *N Engl J Med*. 2003;348:1123–1133.
179. Imai M, et al. *Anesth Analg*. 1994;78:1041.
180. Wetzel LR, et al. *A & A case reports*. 2017;9:16–19.
181. Kainuma A, et al. *A & A case reports*. 2017;9:258–261.
182. Beilin Y, et al. *Anesthesiology*. 1998;88(5):1399.
183. Bernard RW, Stahl WM. *NY State J Med*. 1974;74:83–86.
184. Khalil KG, et al. *JAMA*. 1972;221:908–909.
185. Naguib M, et al. *Can Anaesth Soc J*. 1985;32(4):412.
186. Rudge CJ, et al. *Br Med J*. 1973;3:23.

187. Shah KB, et al. *Anesthesiology*. 1984;61(3):271.
188. Heath KJ, et al. *Anesthesiology*. 1998;89(5):1273.
189. Ezri T, et al. *J Cardiothorac Vasc Anesth*. 2001;15(2):231.
190. Brennan MF, et al. *Arch Surg*. 1973;106:871.
191. Caron NR, et al. *Chest*. 1994;106:1917.
192. Danenberg HD, et al. *Euro Heart J*. 1995;16(2):279.
193. Collier PE, et al. *Angiology*. 1984;35:595.
194. Tocino IM, Watanabe A. *AJR Am J Roentgenol*. 1986;146(3):487.
195. Mansfield PF, et al. *N Engl J Med*. 1994;331(26):1735.
196. Gozubuyuk E, et al. *A & A case reports*. 2017;9:207–211.
197. Butsch JL, et al. *Arch Surg*. 1976;111:828.
198. Drachler DH, et al. *JAMA*. 1976;236(25):2880.
199. Burton AW, et al. *Anesthesiology*. 1998;89(3):804.
200. Merrer J, et al. *JAMA*. 2001;286:700–707.
201. Gilon D, et al. *Am Heart J*. 1998;135(3):457.
202. Ghani MK, et al. *Intensive Care Med*. 2003;29(10):1829.
203. Roguin A, Reisner SA. *Eur J Echocardiogr*. 2000;1:222.
204. Barbeito A, et al. *Can J Anaesth*. 2008;55(11):774.
205. Horner SM, et al. *Eur Heart J*. 1993;14(1):138.
206. Reynen K. *New Engl J Med*. 1993;329(13):970.
207. Grace DM. *Can J Surg*. 1977;20:51.
208. Miller SE, Maragakis LL. *Curr Opin Inf Dis*. 2012;25:412–422.
209. Healthcare-associated infections in the United States, 2006–2016: a story of progress. In: *Promotion DoHQa*. Atlanta, GA: National Center for Emerging and Zoonotic Infectious Diseases (NCEZID); 2018.
210. Marschall J. *Am J Infect Control*. 2008;36(10):S172 e5.
211. Zingg W, Pittet D. *Int J Antimicrob Agents*. 2009;34(suppl 4):S38.
212. Corona ML, et al. *Mayo Clin Proc*. 1990;65(July):979.
213. O’Grady NP, et al. *MMWR*. 2002;51:1–29.
214. Tebbs SE, et al. *Br J Anaesth*. 1994;72(5):587.
215. Long DA, Coulthard MG. *Anaesth Intensive Care*. 2006;34(4):481.
216. Gilbert RE, Harden M. *Curr Opin Infect Dis*. 2008;21(3):235.
217. Darouiche RO, et al. *N Engl J Med*. 1999;340(1):1.
218. Maki DG, et al. *Ann Intern Med*. 1997;127(4):257.
219. Veenstra DL, et al. *JAMA*. 1999;282(6):554.
220. Levy I, et al. *Pediatr Infect Dis J*. 2005;24(8):676.
221. Garland JS, et al. *Pediatrics*. 2001;107(6):1431.
222. O’Grady NP, et al. *Am J Infect Cont*. 2011;39:S1–34.
223. Parietti JJ, et al. *N Engl J Med*. 2015;373:1220–1229.
224. Magder S. *Crit Care Med*. 2006;34(8):2224.
225. Magder S, et al. *Crit Care Med*. 1998;26:1061–1064.
226. Mark JB. Pressure-volume relations, transmural pressure, and preload. In: Mark JB, ed. *Atlas of cardiovascular monitoring*. New York: Churchill Livingstone; 1998:247–259.
227. Dwyer EM. *Circ*. 1970;42:1111–1122.
228. Mark JB. Respiratory-circulatory interactions. In: Mark JB, ed. *Atlas of cardiovascular monitoring*. New York: Churchill Livingstone; 1998:261–285.
229. Magder S. *Curr Opin Crit Care*. 2006;12(3):219.
230. Kovacs G, et al. *Am J Resp Crit Care Med*. 2014;190:252–257.
231. Mark JB. Getting the most from your central venous pressure catheter. In: Barash PG, ed. *ASA refresher courses in anesthesiology*. Philadelphia: Lippincott-Raven; 1995:157–175.
232. Mark JB. *J Cardiothorac Vasc Anesth*. 1991;5:163.
233. O’Rourke RA, et al. General examination of the patient. In: Schlant RC, Alexander RW, eds. *The heart, arteries, and veins*. New York: McGraw-Hill; 1994:238.
234. Mackay IFS, Walker RL. *Am Heart J*. 1966;71(2):228.
235. Shinozaki T, et al. *Anesthesiology*. 1980;53:498.
236. Mark JB. Arrhythmias, An integrated ECG and hemodynamic approach. In: Mark JB, ed. *Atlas of cardiovascular monitoring*. New York: Churchill Livingstone; 1998:219.
237. Mark JB. Patterns of valvular heart disease. In: Mark JB, ed. *Atlas of cardiovascular monitoring*. New York: Churchill Livingstone; 1998:287.
238. Marik PE, et al. *Chest*. 2008;134(1):172.
239. Kuntscher MV, et al. *Resuscitation*. 2006;70:37–43.
240. Wiesenack C, et al. *Eur J Anaesthesiol*. 2005;22(9):658.
241. Coudray A, et al. *Crit Care Med*. 2005;33:2757–2762.
242. Swan HJC, et al. *N Engl J Med*. 1970;283(9):447.
243. Connors AF, et al. *N Engl J Med*. 1983;308(5):263.
244. Sandham JD, et al. *N Engl J Med*. 2003;348(1):5.
245. Kelly CR, Rabbani LE. *N Engl J Med*. 2013;369:e35.
246. Bennett D, et al. *Intensive Care Med*. 1991;17(1):I.
247. Szabo Z. *Br J Anaesth*. 2003;90(6):794.
248. Pipanmekaporn T. *J Cardiothorac Vasc Anesth*. 2012;26(3):391.
249. Tan CO. *World Anesthesiology*. 2015;4:30.
250. Cronin B, et al. *J Card Vasc Anesth*. 2017;31:178–183.
251. Evans DC, et al. *Scand J Surg*. 2009;98(4):199.
252. Roizen MF, et al. *Anesthesiology*. 2003;99(4):988.
253. Damen J, Bolton D. *Acta Anaesthesiol Scand*. 1986;30:386.
254. Procaccini B, et al. *Br J Anaesth*. 1998;80(suppl 2):A26.
255. Jain M, et al. *Intensive Care Med*. 2003;29:2059.
256. Squara P, et al. *Chest*. 2002;121(6):2009.
257. Iberti TJ, et al. *JAMA*. 1990;264(22):2928.
258. Gnaegi A, et al. *Crit Care Med*. 1997;25(2):213.
259. Jacka MJ, et al. *Crit Care Med*. 2002;30(6):1197.
260. Zarich S, et al. *Intensive Care Med*. 2000;26:698.
261. Marik P, et al. *Crit Care Med*. 1998;26(10):1761.
262. Mark JB. Pulmonary artery pressure. In: Mark JB, ed. *Atlas of cardiovascular Monitoring*. New York: Churchill Livingstone; 1998:27–37.
263. Mark JB. Pulmonary artery wedge pressure. In: Mark JB, ed. *Atlas of cardiovascular monitoring*. New York: Churchill Livingstone; 1998:39.
264. Levy MM. *Crit Care Clin*. 1996;12(4):819.
265. Mark JB, Chetham PM. *Anesthesiology*. 1991;74:375.
266. Zahorec R, Holoman M. *Eur J Cardiothorac Surg*. 1997;11(2):379.
267. Shin B, et al. *Crit Care Med*. 1977;5(3):125.
268. Mark JB. Pulmonary artery and wedge pressure artifacts. In: Mark JB, ed. *Atlas of cardiovascular monitoring*. New York: Churchill Livingstone; 1998:49.
269. Morris AH, et al. *Crit Care Med*. 1984;12:164.
270. Bashein G. *Anesthesiology*. 1988;68:310.
271. Fuchs RM, et al. *Am J Cardiol*. 1982;49:849.
272. Braunwald E, Awe WC. *Circ*. 1963;27:29.
273. Grossman W. *N Engl J Med*. 1991;325:1557.
274. Stott DK, et al. *Circ*. 1970;41:1031.
275. Wohlgelernter D, et al. *J Am Coll Cardiol*. 1978;10:491.
276. Leung JM, et al. *Anesthesiology*. 1990;73:802.
277. Sabbah HN, et al. *Am J Cardiol*. 1993;72:1074.
278. van Daele MERM, et al. *Circ*. 1990;81:865.
279. Goldstein JA, et al. *Circ*. 1990;82:359.
280. Trager MA, et al. *J Cardiothorac Anesth*. 1987;1:123.
281. Kushwaha SS, et al. *N Engl J Med*. 1997;336:267.
282. Kern MJ, Aguirre F. *Cathet Cardiovasc Diagn*. 1992;25:336.
283. Kern MJ, Aguirre F. *Cathet Cardiovasc Diagn*. 1992;26:34.
284. Kern MJ, Aguirre F. *Cathet Cardiovasc Diagn*. 1992;26:152.
285. Hirschmann JV. *Am Heart J*. 1978;96:110.
286. Beloucif S, et al. *Am J Physiol*. 1992;263:H125.
287. Lorell BH, Braunwald E. Pericardial disease. In: Braunwald E, ed. *Heart disease. A textbook of cardiovascular medicine*. Philadelphia: Saunders; 1992:1465.
288. Fowler NO. *Circ*. 1993;87:1738.
289. Mitchell MM, et al. *Anesthesiology*. 1987;67:294.
290. Teplick RS. *Anesthesiology*. 1987;67:289.
291. Cengiz M, et al. *Crit Care Med*. 1983;11:502.
292. Pinsky MR. *Intensive Care Med*. 2003;29(1):19.
293. Gidwani UK, et al. *Card Clin*. 2013;31:545–565.
294. Falicov RE, Resnekov L. *Circ*. 1970;42:65.
295. Scheinman M, et al. *Circ*. 1973;47:317.
296. Mark JB. Predicting left ventricular end-diastolic pressure. In: Mark JB, ed. *Atlas of cardiovascular monitoring*. New York: Churchill Livingstone; 1998:59.
297. Osman D, et al. *Crit Care Med*. 2007;35(1):64.
298. Tro RJ, et al. *Crit Care*. 2011;15:R73-R.
299. McGregor M, Sniderman A. *Am J Cardiol*. 1985;55:217.
300. Permutt S, Riley RL. *J Appl Physiol*. 1963;34:924.
301. Brengelmann GL. *J Appl Physiol*. 2006;101(5):1525. discussion 1526.
302. Naeije R. *Intensive Care Med*. 2003;29(4):526.
303. Reeves JT, et al. *J Appl Physiol*. 1961;16:276.
304. De Backer D, et al. *Int Care Med*. 2018;44:960–962.
305. De Backer D, Vincent JL. *Curr Opin Crit Care*. 2018;24:204–208.
306. Youssef N, Whitlock RP. *Can J Card*. 2017;33:135–141.
307. Lee M, et al. *Can J Card*. 2017;33:142–147.
308. Connors AF, et al. *JAMA*. 1996;276:889–897.
309. Dalen JE, Bone RC. *JAMA*. 1996;276:916.
310. Valentine RJ, et al. *J Vasc Surg*. 1998;27(2):203. discussion 211.
311. Tuman KJ, et al. *J Cardiothorac Anesth*. 1989;3:625–641.
312. Connors AF, et al. *JAMA*. 1997;277:113–114.

313. Binanay C, et al. *JAMA*. 2005;294(13):1625.
314. Wheeler AP, et al. *N Engl J Med*. 2006;354(21):2213.
315. Harvey S, et al. *Lancet*. 2005;366(9484):472.
316. De Backer D. *Intensive Care Med*. 2003;29(11):1865.
317. Friese RS, et al. *Crit Care Med*. 2006;34(6):1597.
318. Chittock DR, et al. *Crit Care Med*. 2004;32(4):911.
319. Kavarana MN, et al. *Am Surg*. 2003;69(5):411.
320. Sotomi Y, et al. *Int J Card*. 2014;172:165–172.
321. Ikuta K, et al. *JAMA Cardiology*. 2017;2.
322. Pinsky MR, Vincent JL. *Crit Care Med*. 2005;33(5):1119.
323. Sotomi Y, et al. *Int J Card*. 2014;172:165–172.
324. Allen LA, et al. *J Card Fail*. 2008;14:661–669.
325. Hartog C, Bloos F. *Anesthesiology*. 2014;28:419–428.
326. Scalea TM, et al. *J Trauma*. 1990;30(12):1539.
327. Pearse R, et al. *Crit Care*. 2005;9(6):R694.
328. Vallet B, et al. *Crit Care*. 2010;14(2):213.
329. Pöllönen P, et al. *Anesth Analg*. 2000;90:1052.
330. Donati A, et al. *Chest*. 2007;132(6):1817.
331. Smetkin AA, et al. *Acta Anaesthesiol Scand*. 2009;53(4):505.
332. Rivers E, et al. *N Engl J Med*. 2001;345(19):1368.
333. Pro CI, et al. *N Engl J Med*. 2014;370:1683–1693.
334. London MJ, et al. *Anesthesiology*. 2002;96(4):860.
335. Haddad F, et al. *Circ*. 2008;117(13):1717.
336. Dhainaut J-F, et al. *Crit Care Med*. 1987;15(2):148.
337. Nelson LD. *New Horizons*. 1997;5:251–258.
338. Chang MC, et al. *Arch Surg*. 1996;131(7):728.
339. Her C, Lees DE. *Crit Care Med*. 1993;21(11):1665.
340. Boldt J, et al. *Crit Care Med*. 1989;17:518–522.
341. Dupont H, Squara P. *Curr Opin Anaesthesiol*. 1996;9:490.
342. Linton RAF, et al. *J Cardiothorac Vasc Anesth*. 2002;16(1):4.
343. Funk DJ, et al. *Anesth Analg*. 2009;108(3):887.
344. Reuter DA, et al. *Anesth Analg*. 2010;110(3):799.
345. Nishikawa T, Dohi S. *Can J Anaesth*. 1993;40(2):142.
346. Stetz CW, et al. *Am Rev Respir Dis*. 1982;126(6):1001.
347. Dhingra VK, et al. *Chest*. 2002;122(3):990.
348. Ganz W, et al. *Am J Cardiol*. 1971;27:392.
349. Heerd PM, et al. *J Cardiothorac Vasc Anesth*. 2001;15(2):183.
350. Bazzaral MG, et al. *Anesthesiology*. 1992;77(1):31.
351. Wetzel RC, Latson TW. *Anesthesiology*. 1985;62(5):684.
352. Groeneveld ABJ, et al. *J Appl Physiol*. 2000;89:89.
353. van Grondelle A, et al. *Am J Physiol*. 1983;245(4):H690.
354. Yelderman M. *J Clin Monit*. 1990;6(4):322.
355. Siegel LC, et al. *Anesth Analg*. 1996;83:1173.
356. Gardner RM. *Crit Care Med*. 1998;26(8):1302.
357. Le Tulzo Y, et al. *J Clin Monit*. 1996;12(5):379.
358. Hatton KW, et al. *J Cardiothorac Vasc Anesth*. 2017;31:e61–e62.
359. Monnet X, Teboul J-L. *Crit Care*. 2017;21.
360. Mielck F, et al. *J Cardiothorac Vasc Anesth*. 2003;17(2):211.
361. Segal E, et al. *J Clin Anesth*. 2002;14(3):210.
362. von Spiegel T, et al. *Anaesthetist*. 1996;45(11):1045.
363. Michard F. *Crit Care Med*. 2007;35(4):1186.
354. Matejovic M, et al. *Acta Anaesthesiol Scand*. 2004;48(1):69.
365. Mitchell JP, et al. *Am Rev Respir Dis*. 1992;145(5):990.
366. Hoeft A, et al. *Anesthesiology*. 1994;81(1):76.
367. Wiesenack C, et al. *J Cardiothorac Vasc Anesth*. 2001;15(5):584.
368. Briegel J, et al. *Anaesthetist*. 2009;58(2):122.
369. Perny J, et al. *BioMed Res Int*. 2014;2014:1–7.
370. Linton RAF, et al. *Br J Anaesth*. 1993;71:262.
371. Kurita T, et al. *Br J Anaesth*. 1997;79:770.
372. Linton R, et al. *Crit Care Med*. 1997;25(11):1796.
373. Garcia-Rodriguez C, et al. *Crit Care Med*. 2002;30(10):2199.
374. Linton RA, et al. *Intensive Care Med*. 2000;26(10):1507.
375. Joosten A, et al. *Br J Anaesth*. 2017;118:298–310.
376. Colquhoun DA, Roche AM. *Anesthesiology*. 2014;28:353–362.
377. Laupland KB, Bands CJ. *Can J Anaesth*. 2002;49(4):393.
378. Mark JB, et al. *Anesth Analg*. 1986;65:1013.
379. Roche AM, et al. *Best Pract Res Clin Anaesthesiol*. 2009;23(3):327.
380. Abbas SM, Hill AG. *Anaesthesia*. 2008;63(1):44.
381. Singer M. *Int Anesthesiol Clin*. 1993;31:99–125.
382. Thys DM, Hillel Z. *Anesthesiology*. 1988;69:728.
383. Lee JH, et al. *Br J Anaesth*. 2007;99(3):343.
384. Guinot P-G, et al. *Br J Anaesth*. 2013;110:28–33.
385. Poeze M, et al. *Crit Care Med*. 1999;27(7):1288.
386. Calvo-Vecino JM, et al. *Br J Anaesth*. 2018;120:734–744.
387. Kubicek WG, et al. *Aviat Space Environ Med*. 1966;37(12):1208.
388. Jakovljevic DG, et al. *Anesthesiology*. 2014;28:381–394.
389. Peyton PJ, Chong SW. *Anesthesiology*. 2010;113:1220–1235.
390. Jaffe MB. *J Clin Monit*. 1999;15:387.
391. Orr J, et al. *J Clin Monit*. 1996;12:464.
392. Osterlund B, et al. *Acta Anaesthesiol Scand*. 1995;39(6):727.
393. Thiele RH, Durieux ME. *Anesth Analg*. 2011;113(4):766.
394. Wesseling KH, et al. *J Appl Physiol*. 1993;74(5):2566.
395. Linton NWF, Linton RAF. *Br J Anaesth*. 2001;86(4):486.
396. Bogert LW, et al. *Anaesthesia*. 2010;65(11):1119.
397. Michard F. *Anesthesiology*. 2005;103(2):419, quiz 449.
398. Lieshout JJ, Wesseling KH. *Br J Anaesth*. 2001;86(4):467.
399. Cecconi M, et al. *Int Care Med*. 2013;39:787–789.
400. Monnet X, et al. *Br J Anaesth*. 2012;108:615–622.
401. Camporota L, Beale R. *Crit Care*. 2010;14(2):124.
402. De Backer D, et al. *Intensive Care Med*. 2005;31(4):517.
403. Goedje O, et al. *Crit Care Med*. 1999;27(11):2407.
404. Pittman J, et al. *Crit Care Med*. 2005;33(9):2015.
405. Benes J, et al. *Crit Care*. 2010;14(3):R118.
406. Mayer J, et al. *Crit Care*. 2010;14(1):R18.
407. Salzwedel C, et al. *Crit Care*. 2013;17:1.

References

1. Gravenstein JS. Monitoring with our good senses. *J Clin Monit Comput.* 1998;14:451–453.
2. Block FE. What is heart rate, anyway? *J Clin Monit.* 1994;10:366–370.
3. Zong W, Moody GB, Mark RG. Reduction of false arterial blood pressure alarms using signal quality assessment and relationships between the electrocardiogram and arterial blood pressure. *Med Biol Eng Comput.* 2004;42:698–706.
4. American Society of Anesthesiologists. *Standards for basic anesthetic monitoring. ASA standards, guidelines and statements.* Park Ridge, Illinois: American Society of Anesthesiologists; 1993:5.
5. Sandau KE, Funk M, Auerbach A, et al. Update to practice standards for electrocardiographic monitoring in hospital settings: a scientific statement from the American Heart Association. *Circulation.* 2017;136:e273–e344.
6. Kligfield P, Gettes LS, Bailey JJ, et al. Recommendations for the standardization and interpretation of the electrocardiogram: part I: the electrocardiogram and its technology a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society Endorsed By the International Society for Computerized Electrocardiology. *Journal of the American College of Cardiology.* 2007;49:1109–1127.
7. Ortega R, Mazzini M, Xue K, Espaillat D. Videos in clinical medicine. Electrocardiographic monitoring in adults. *New England Journal of Medicine.* 2015;372:e11.
8. Mason RE, Likar I. A new system of multiple-lead exercise electrocardiography. *American Heart Journal.* 1966;71:196–205.
9. Krucoff MW, Loeffler KA, Haisty Jr WK, et al. Simultaneous ST-segment measurements using standard and monitoring-compatible torso limb lead placements at rest and during coronary occlusion. *The American Journal of Cardiology.* 1994;74:997–1001.
10. Drew BJ. Pitfalls and artifacts in electrocardiography. *Cardiol Clin.* 2006;24:309–315. vii.
11. Chaitman BR, Hanson JS. Comparative sensitivity and specificity of exercise electrocardiographic lead systems. *The American Journal of Cardiology.* 1981;47:1335–1349.
12. Blackburn H, Katigbak R. WHAT electrocardiographic leads to take after exercise? *American Heart Journal.* 1964;67:184–185.
13. Kubota I, Ikeda K, Ohyama T, et al. Body surface distributions of ST segment changes after exercise in effort angina pectoris without myocardial infarction. *American Heart Journal.* 1985;110:949–955.
14. Kaplan JA, Dunbar RW, Hatcher CR. Diagnostic value of the V5 precordial electrocardiographic lead: a case report. *Anesthesia and Analgesia.* 1978;57:364–367.
15. London MJ, Hollenberg M, Wong MG, et al. Intraoperative myocardial ischemia: localization by continuous 12-lead electrocardiography. *Anesthesiology.* 1988;69:232–241.
16. Landesberg G, Mosseri M, Wolf Y, Vesselov Y, Weissman C. Perioperative myocardial ischemia and infarction: identification by continuous 12-lead electrocardiogram with online ST-segment monitoring. *Anesthesiology.* 2002;96:264–270.
17. Klein HO, Tordjman T, Ninio R, et al. The early recognition of right ventricular infarction: diagnostic accuracy of the electrocardiographic V4R lead. *Circ.* 1983;67:558–565.
18. Griffin RM, Kaplan JA. Myocardial ischaemia during non-cardiac surgery. A comparison of different lead systems using computerised ST segment analysis. *Anaesthesia.* 1987;42:155–159.
19. Slogoff S, Keats AS, David Y, Igo SR. Incidence of perioperative myocardial ischemia detected by different electrocardiographic systems. *Anesthesiology.* 1990;73:1074–1081.
20. Takla G, Petre JH, Doyle DJ, Horibe M, Gopakumaran B. The problem of artifacts in patient monitor data during surgery: a clinical and methodological review. *Anesthesia and Analgesia.* 2006;103:1196–1204.
21. Weinfurt PT. Electrocardiographic monitoring: an overview. *Journal of Clinical Monitoring.* 1990;6:132–138.
22. Khambatta HJ, Stone JG, Wald A, Mongero LB. Electrocardiographic artifacts during cardiopulmonary bypass. *Anesthesia and Analgesia.* 1990;71:88–91.
23. Patel SI, Souter MJ. Equipment-related electrocardiographic artifacts: causes, characteristics, consequences, and correction. *Anesthesiology.* 2008;108:138–148.
24. Patton JA, Funk M. Survey of use of ST-segment monitoring in patients with acute coronary syndromes. *American Journal of Critical Care : an Official Publication, American Association of Critical-Care Nurses.* 2001;10:23–32, quiz 3-4.
25. Mark JB, Chien GL, Steinbrook RA, Fenton T. Electrocardiographic R-wave changes during cardiac surgery. *Anesthesia and Analgesia.* 1992;74:26–31.
26. Stern S. State of the art in stress testing and ischaemia monitoring. *Cardiac Electrophysiology Review.* 2002;6:204–208.
27. Helwani MA, Amin A, Lavigne P, et al. Etiology of acute coronary syndrome after noncardiac surgery. *Anesthesiology.* 2018;128:1084–1091.
28. Miller TD, Desser KB, Lawson M. How many electrocardiographic leads are required for exercise treadmill tests? *Journal of Electrocardiology.* 1987;20:131–137.
29. ASA. *Standards for Basic Anesthetic Monitoring;* 2005:2008. <http://www.asahq.org/publicationsAndServices/standards/02.pdf>
30. Bruner JMR, Krenis LJ, Kunsman JM, Sherman AP. Comparison of direct and indirect methods of measuring arterial blood pressure. *Medical Instrumentation.* 1981;15:11–21, 97–101, 82–88.
31. Riva-Rocci S. Un nuovo sfigmomanometro. *Gaz Med Torino.* 1896;47:981.
32. Korotkoff NS. On the subject of methods of determining blood pressure. *Bull Imp Med Acad St Petersburg.* 1905;11:365.
33. Kuck K, Baker PD. Perioperative Noninvasive Blood Pressure Monitoring. *Anesthesia and Analgesia.* 2017.
34. Alpert BS, Quinn D, Gallick D. Oscillometric blood pressure: a review for clinicians. *Journal of the American Society of Hypertension : JASH.* 2014;8:930–938.
35. Lakhal K, Ehrmann S, Boulain T. Noninvasive BP monitoring in the critically ill: time to abandon the arterial catheter? *Chest.* 2017.
36. Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: blood pressure measurement in humans: a statement for professionals from the subcommittee of professional and public education of the American Heart Association council on high blood pressure research. *Hypertension.* 2005;45:142–161.
37. Cohn JN. Blood pressure measurement in shock. Mechanism of inaccuracy in auscultatory and palpitory methods. *JAMA.* 1967;199:972–976.
38. Lakhal K, Macq C, Ehrmann S, Boulain T, Capdevila X. Noninvasive monitoring of blood pressure in the critically ill: reliability according to the cuff site (arm, thigh, or ankle). *Critical Care Medicine.* 2012;40:1207–1213.
39. Ribezzo S, Spina E, Di Bartolomeo S, Sanson G. Noninvasive techniques for blood pressure measurement are not a reliable alternative to direct measurement: a randomized crossover trial in ICU. *Scientificworldjournal.* 2014;2014:353628.
40. Wan Y, Heneghan C, Stevens R, et al. Determining which automatic digital blood pressure device performs adequately: a systematic review. *Journal of Human Hypertension.* 2010;24:431–438.
41. AAMI. American national standard for non-invasive sphygmomanometers-part 2. Clinical validation of automated measurement type. *AAMI.* 2009;25–26.
42. Lakhal K, Ehrmann S, Runge I, et al. Tracking hypotension and dynamic changes in arterial blood pressure with brachial cuff measurements. *Anesthesia and Analgesia.* 2009;109:494–501.
43. Liu B, Li Q, Qiu P. Comparison between invasive and non-invasive blood pressure in young, middle and old age. *Blood Pressure.* 2016;25:155–161.
44. Riley LE, Chen GJ, Latham HE. Comparison of noninvasive blood pressure monitoring with invasive arterial pressure monitoring in medical ICU patients with septic shock. *Blood Pressure Monitoring.* 2017;22:202–207.
45. Wax DB, Lin HM, Leibowitz AB. Invasive and concomitant noninvasive intraoperative blood pressure monitoring: observed differences in measurements and associated therapeutic interventions. *Anesthesiology.* 2011;115:973–978.
46. Jankowski P, Kawecka-Jaszczyk K, Czarnecka D, et al. Pulsatile but not steady component of blood pressure predicts cardiovascular events in coronary patients. *Hypertension.* 2008;51:848–855.
47. Min JY, Kim HI, Park SJ, Lim H, Song JH, Byon HJ. Adequate interval for the monitoring of vital signs during endotracheal intubation. *BMC anesthesiology.* 2017;17:110.