Chapter

43

Pulmonary Hypertension and Moyamoya Disease

Timothy D. Switzer and Neil M. Goldenberg

Case Scenario

A 12-year-old boy with a history of moyamoya disease presents for surveillance brain magnetic resonance imaging. Transthoracic echocardiography at age 3 years revealed mild to moderate aortic coarctation for which he underwent balloon dilation with minimal improvement due to the stiffness of his aorta. At age 9 years he underwent cerebral revascularization surgery (temporal artery bypass) to address his moyamoya disease. Right and left heart catheterization at age 10 years demonstrated severe pulmonary hypertension with an initial pulmonary vascular resistance of 10.2 indexed Wood units; at that time, balloon dilation of his patent foramen ovale was performed. He is now taking tadalafil, ambrisentan, and treprostinil for his pulmonary hypertension. He also takes atenolol for systemic hypertension and uses nasal prong oxygen at 0.5–1 L/minute for hemoglobin–oxygen desaturations to the 80s noted during a 6-minute walk test.

Recent cardiac catheterization demonstrated the following:

- *Pulmonary vascular resistance of 6.1 indexed Wood units*
- *Right ventricular systolic pressure that is 60% systemic*

Key Objectives

- Describe the pathophysiology and treatment of moyamoya disease.
- Describe classification systems for pulmonary hypertension.
- Outline anesthetic management goals for patients with moyamoya disease.
- Describe medical therapy for pulmonary hypertension and potential anesthetic interactions.
- Outline anesthetic management options for patients with cerebrovascular disease and pulmonary hypertension.

Pathophysiology

What is moyamoya disease?

Moyamoya disease is a cerebrovasculopathy of unknown etiology characterized by chronic progressive stenosis of the arteries of the circle of Willis. An extensive collateralized circulation forms, giving rise to the smoky appearance seen on cerebral angiography (moyamoya is Japanese for "puff of smoke"). Primary clinical features of moyamoya disease, especially in children, are related to cerebral ischemia and include transient ischemic attacks and stroke. However, hemorrhagic strokes and seizures have also been described. Hyperventilation, crying, exercise, or fever can all trigger symptomatic ischemia in children.

Clinical Pearl

Hyperventilation, crying, exercise, or fever can all trigger symptomatic ischemia in children with moyamoya disease.

What other conditions are associated with moyamoya disease?

The characteristic angiographic appearance seen in moyamoya disease has also been described in other medical conditions, giving rise to the distinction between moyamoya disease and moyamoya syndrome, with the syndrome being associated with other medical conditions. These medical conditions may include chromosomal abnormalities (Down syndrome), neurocutaneous diseases (neurofibromatosis), connective tissue diseases (pseudoxanthoma elasticum), and extracranial vasculopathies.

How is moyamoya disease diagnosed?

Neuroradiology studies are the cornerstone of diagnosis for moyamoya disease. Commonly utilized imaging modalities include head computed tomography with angiography (CT, CTA), digital subtraction angiography, and

https://doi.org/10.1017/9781108657341.044 Published online by Cambridge University Press

magnetic resonance angiography (MRA). Although CT can show gross ischemic events, magnetic resonance imaging (MRI) is superior for the detection of smaller lesions. Noninvasive studies including magnetic resonance angiography and CTA can demonstrate the vascular abnormalities. Invasive cerebral angiography remains the gold standard in the diagnosis of the disease but is performed less frequently than either MRA or CTA.

The radiographic severity of moyamoya disease is graded on the Suzuki scale between 1 (least severe) and 6 (most severe), with grading based on the angiographic progression of the disease. Disease progression occurs in a proximal to distal manner with the internal carotid arteries affected first, leading to the eventual involvement of all cerebral arteries.

What is the effect of moyamoya disease on cerebral autoregulation?

The blood pressure limits of cerebral autoregulation in children are not known, but moyamoya has an impact on this autoregulation. A steal phenomenon may occur, leading to hypoperfusion of the areas most affected by moyamoya, as they are operating at full vasodilation and therefore dilation of other cerebral vessels will lead to decreased flow in these stenotic vessels.

What are the treatment options for moyamoya?

The goal of treatment is primarily to restore blood flow to the affected areas, either by direct or indirect bypass. There is no curative treatment for moyamoya disease. Direct bypass involves grafting of the superficial temporal artery to the middle cerebral or middle meningeal arteries (external carotid-to-internal carotid bypass). However, these procedures are technically difficult in children due to the small caliber of the vessels in this population. The indirect bypass method aims to promote the formation of a new vascular network over time by the placement of rich vascular tissue on the surface of the brain. Several procedures have been described, including encephaloduroarteriosynangiosis, encephalomyosynangiosis, and omental-cerebral transplantation. While outcomes are comparable with both direct and indirect revascularization techniques, it must be remembered that those who have had direct revascularization have an immediate postoperative improvement in cerebral blood flow (CBF), whereas those who have received indirect revascularization are dependent on angiogenesis and thus remain at risk for ischemia in the immediate postoperative period.

What is the underlying cardiac pathology in this patient?

The underlying cardiac pathology consists of a failed coarctation dilation with a residual aortic gradient. A patent foramen ovale (PFO) has also been ballooned and therefore in the setting of pulmonary hypertension (PH) the potential exists for bidirectional shunting across the PFO. Depending on the physiologic condition of the patient, flow across the PFO will be determined by the degree of PH, as the residual coarctation is a fixed afterload on the left ventricle (LV), unless acute LV failure occurs. The most recent investigations indicate that the right ventricular (RV) pressure is 60% that of the systemic arterial pressure. A right-to-left (R-to-L) shunt at the atrial level can result in a decrease in oxygen saturations, depending on the volume of blood being shunted. (See Figure 43.1.)

What are the implications of the failed coarctation repair in this patient?

The residual gradient after the unsuccessful balloon dilation of the aortic coarctation means that there is a hemodynamically significant persistence of fixed obstruction to flow in the

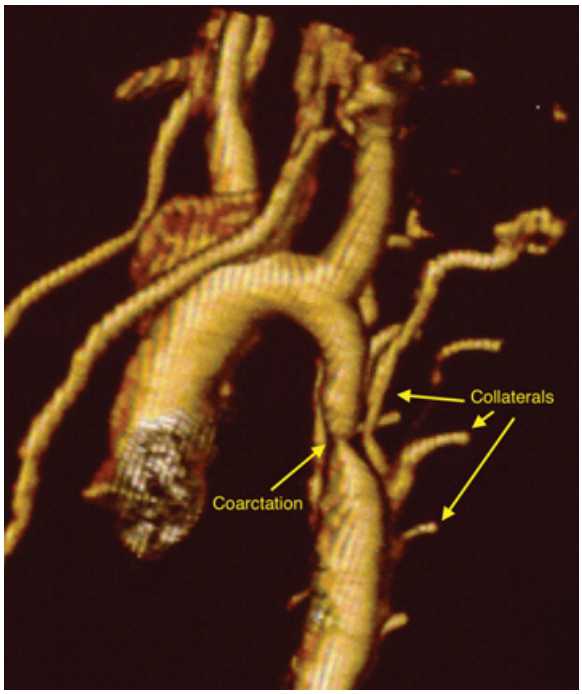

Figure 43.1 Coarctation of the aorta. 3D magnetic resonance imaging of juxtaductal coarctation of the aorta. There are multiple collaterals from the head and neck vessels that flow toward the descending aorta and effectively bypass the aortic narrowing. Courtesy of Michael Taylor, MD.

https://doi.org/10.1017/9781108657341.044 Published online by Cambridge University Press

proximal descending aorta. There are several implications to this obstruction. The fixed increase in afterload may lead to LV hypertrophy and a subsequent increase in LV pressures, which will lead to increased myocardial workload, thus increasing myocardial oxygen demand. It will also lead to eventual diastolic dysfunction and altered lusitropy.

The rise in LV pressure will also be transmitted to the left atrium (LA), leading to two potential issues given the patient's intracardiac anatomy. First, an increase in LA pressure can act as an impediment to pulmonary blood flow, thus increasing the pulmonary arterial pressure. The second potential issue relates to the presence of the previously ballooned PFO. A rise in LA pressure may lead to an increased left-to-right (L-to-R) shunt across the PFO, which can contribute to RV volume overload and increased RV pressure. These factors increase myocardial workload and place the patient at risk for inadequate coronary perfusion.

The position of the residual aortic coarctation implies that the patient's cerebral vasculature has been exposed to relatively high perfusion pressures for a prolonged period of time. A blood pressure surge due to sympathetic activity, as might occur during laryngoscopy, has the potential to precipitate an intracerebral hemorrhage. It also means that the cerebral autoregulation limits for this child are likely to be higher than those for a similarly aged child without a coarctation, and therefore any decrease in blood pressure has the potential to compromise cerebral perfusion.

What are possible explanations for his intermittent desaturations?

Potential causes for this patient's desaturations during the 6-minute walk test include one or a combination of the following:

- Decreased diffusion capacity
- Ventilation-perfusion mismatch
- Decreased cardiac output (CO)
- The presence of intrapulmonary shunts

This patient has a known intracardiac shunt with the potential for R-to-L shunting.

How is pulmonary hypertension classified in children?

Pulmonary hypertension was first classified by the World Health Organization (WHO) in 1973 and this system has evolved over the years; it currently includes five groups. The aim of this classification system is to better understand the differing etiologies of each group and the natural history of the disease. However, it was recognized that the WHO classification system had some deficits when applied to the pediatric population given the significant developmental contribution to the disease. A consensus conference held in Panama in 2011 developed a new classification system for pediatric PH. (See Table 43.1.)

In this case the etiology of the PH is unclear but is most likely multifactorial.

Clinical Pearl

Understanding the etiology of PH is a critical step toward both risk stratification and appropriate acute and long-term management. Such understanding necessitates a multidisciplinary team, and investigations including imaging, invasive hemodynamic testing, and functional testing.

How is pulmonary hypertension graded?

There are several scales by which PH can be graded. The WHO uses a functional scale based on the level of physical activity that the patient can tolerate and is analogous to the New York Heart Association scale for heart failure. The consensus meeting in Panama also produced a functional classification of pediatric PH based on five different age groups: 0–0.5 years, 0.5–1 years, 1–2 years, 2–5 years, and 5–16 years. These provide child-specific measures of function such as play and school attendance. There is also a scale based on echocardiography and catheterization data that determines a patient's risk status depending on cardiac chamber size, ventricular function, measurement of pulmonary artery, and RA pressures and systemic venous saturations.

Table 43.1 Pulmonary Hypertension Classifications

WHO classification	Panama classification
1. Pulmonary arterial hypertension	1. Prenatal or developmental pulmonary hypertension
2. Pulmonary hypertension due to left heart disease	2. Perinatal vascular maladaptation (persistent pulmonary hypertension of the newborn)
3. Pulmonary hypertension due to lung disease	3. Pulmonary hypertension associated with congenital heart disease
4. Pulmonary hypertension due to thromboembolic disease	4. Bronchopulmonary dysplasia
5. Pulmonary hypertension associated with systemic disease/unclear etiology	5. Isolated pediatric pulmonary arterial hypertension
	6. Multifactorial in congenital malformation syndromes
	7. Pediatric lung disease
	8. Pediatric thromboembolic disease
	9. Hypobaric hypoxic exposure
	10. Pulmonary vascular disease associated with other disorders

https://doi.org/10.1017/9781108657341.044 Published online by Cambridge University Press

What is the purpose of a right heart catheterization and what information should be sought?

The American Heart Association and American Thoracic Society have guidelines regarding the management of pediatric PH, including the performance and timing of cardiac catheterization. Right heart catheterization should include acute vasoreactivity testing (AVT), with a positive response defined as a 20% or greater decrease in pulmonary vascular resistance (PVR) without a decrease in CO. It is also recommended that patients undergo serial catheterizations to assess progress of the disease. After a change in therapy catheterization should occur within 3 to 12 months. Timing after this should be based on clinical judgment.

This patient's recent catheterization gives us the following important information:

- Pulmonary vascular resistance has decreased from 10.2 indexed Wood units (iWu) to 6.1 iWu, indicating significant responsiveness to the triple therapy of tadalafil, ambrisentan, and treprostinil that was initiated.
- The patient continues to have significant PH, as RV systolic pressure is 60% of systemic systolic pressure.
- The patient is not on a long-term calcium channel blocker, indicating that he most likely does not have AVT-positive PH.

A right heart catheterization also usually includes a pulmonary capillary wedge pressure (PCWP) measurement. This is helpful in determining whether there is increased LA pressure (PCWP >15 mm Hg), indicative of LV failure. This is important in the setting of an uncorrected coarctation of the aorta. Lastly, catheterization provides information regarding the size and morphology of the patient's pulmonary arteries and veins. If pulmonary artery or pulmonary vein stenosis is identified, he may be a candidate for surgical correction of any hypoplastic or stenotic portions of these vessels.

What are mechanisms of action and potential side effects of pulmonary hypertension medications?

The mechanisms of action and potential side effects of pulmonary hypertension medications are given in Table 43.2.

Clinical Pearl

Intraoperative administration of PH medications requires planning regarding intravenous access, special delivery equipment, and interactions with anesthesia, particularly the risks of systemic hypotension and acute discontinuation syndromes.

Anesthetic Implications

What other investigations should be considered prior to proceeding?

Investigations can be broadly divided into imaging, blood/serum tests and functional tests. A review of previous cerebral MRI exams may provide information regarding the patient's cerebral reactivity, along with any evidence of ischemic or hemorrhagic lesions. An electrocardiogram (ECG) should be performed to ensure that no arrhythmias are present. In this patient, LV remodeling may have led to muscular hypertrophy and decreased cavity size. This, in turn, will reduce the passive filling of the ventricle during diastole, increasing dependence on the atrial kick. Pulmonary hypertension may have led to RA dilation, thus increasing the risk of

Table 43.2 Pulmonary Hypertension Medications

Medication	Mechanism	Side Effects
Conventional Oxygen Diuretics Anticoagulation	Prevent hypoxemia/hypoxic pulmonary vasoconstriction Optimize preload for right heart failure Prevent thrombosis in low flow states and hypercoagulable patients	Nasal prongs can dry out the nasal mucosa Intravascular depletion Bleeding potential
PDE_5 inhibitors Sildenafil, tadalafil	Reduce breakdown of cGMP to potentiate nitric oxide signaling, causing pulmonary vasodilation and decreasing vascular remodeling	Flushing, nausea, headaches Systemic hypotension in combination with other vasodilators
Endothelin receptor antagonists Bosentan, ambrisentan	Block actions of ET-1, a potent endogenous pulmonary vasoconstrictor	Hepatotoxicity, fluid retention
Prostacyclin analogues Iloprost (inhaled) Treprostinil (oral/inhaled)	Pulmonary and systemic vasodilators	Inhibit platelet aggregation, hypotension, flushing, rebound syndrome if discontinued

https://doi.org/10.1017/9781108657341.044 Published online by Cambridge University Press

atrial fibrillation. Atrial fibrillation may make the patient unstable from a cardiovascular perspective, but this may only become evident when increased CO is required. Brain natriuretic peptide (BNP) or N-terminal proBNP can be useful serologic markers for tracking progressive heart failure, but it is necessary to have baseline values for the results to truly be meaningful.

If the patient has not been investigated for obstructive sleep apnea, it is advisable to do so, as this is a potentially reversible contributor to PH. Pulmonary function tests can also help to rule out a pulmonary disorder as a contributor to PH.

Functional tests include a 6-minute walk test, which was performed in this patient. Other examples include cardiopulmonary exercise testing, which has been correlated with PH prognosis in adults, and a dobutamine stress echo.

Clinical Pearl

This child must be completely optimized from a cardiorespiratory standpoint before undergoing his surveillance MRI. Involvement of his entire care team in the timing of this procedure is critical.

What unique issues does MRI present for the anesthesiologist?

Caring for patients undergoing MRI provides a number of challenges for the anesthesiologist. Many children find it a loud and claustrophobic environment, often resulting in movement during the procedure, interfering with image quality. The presence of the magnetic fields also disallows the use of any equipment that contains >2% ferromagnetic components. This impacts both anesthesia delivery systems and the monitoring used to ensure patient safety during the case. Anesthesia machines must be MRI safe, syringe pumps must be placed in a Faraday shield, and any emergencies require the prompt removal of the patient from the MRI scanning room given that the majority of resuscitation equipment is ferromagnetic. Monitoring can also prove challenging as the magnetic fields can induce artifacts on the ECG. There have also been reports of the pulse oximetry probe causing burns. Specialized pulse oximeters, blood pressure cuffs, and ECG electrodes must be used, and all suffer from artifacts during periods of scanning. High-fidelity monitoring of ST segments on ECG can be near impossible at times.

Magnetic resonance suites are often remote from operating room suites, limiting the availability of help should an emergency occur. This may also limit availability of certain pieces of equipment should a patient become unstable – in this case the availability of inhaled nitric oxide should the patient develop a pulmonary hypertensive crisis.

Clinical Pearl

High-risk anesthesia in a remote location necessitates careful planning to ensure adequate support and equipment are available for crisis management.

What anesthetic techniques may be utilized for MRI?

A range of possibilities exist for providing patient comfort and ensuring lack of movement to facilitate MRI. The first involves physical therapies such as parental presence and distraction devices such as audiovisual equipment. At the other end of the spectrum is a full general anesthetic. The advantages of a general anesthetic include complete immobility, guaranteeing image quality, but this approach suffers from the disadvantages of administering anesthetic agents, the majority of which have effects on systemic, pulmonary, and CBF. (See Table 43.3.) Between these two options is sedation, which allows delivery of lower doses of anesthetic agents, but also has a reported failure rate of up to 20%.

Ventilation during the procedure is also of critical importance. The presence of PH favors the patient spontaneously breathing, as this will decrease RV afterload. However, the administration of anesthetic agents may lead to hypoventilation in these circumstances, leading to potential hypoxemia and hypercapnia, which may in turn impact both pulmonary and CBF. It may be advisable to insert an airway, either a laryngeal mask airway (LMA) or an endotracheal tube (ETT), in order to ensure appropriate respiratory support.

What are the anesthetic management goals for patients with moyamoya disease?

The primary anesthetic management goal in patients with moyamoya disease is to match oxygen delivery with oxygen consumption. This involves maintaining the cerebral blood flow/cerebral metabolic rate ($CBF/CMRO_2$) relationship. A two-pronged approach can be taken toward this goal.

- ***Minimize the cerebral oxygen requirement/$CMRO_2$.*** This requires achieving an adequate depth of anesthesia for any procedure the patient is undergoing, avoiding hyperthermia, maintaining euglycemia and treating any seizures.

https://doi.org/10.1017/9781108657341.044 Published online by Cambridge University Press

Table 43.3 Effects of Anesthetic Agents on Pulmonary Vascular Resistance and Cerebral Perfusion

Agent	Pulmonary Vascular Resistance	Cerebral Perfusion
Propofol	Decreased inotropy, no effect on pulmonary vascular tone	Decreases CBF due to decreased inotropy and vasodilation, decreased $CMRO_2$, preserves matching
Opiates	No direct effect on pulmonary vascular tone	No effect on CBF or $CMRO_2$
Volatile anesthetic agents	Inhibit HPV, decreasing V/Q matching	Increase CBF due to vasodilation, decrease $CMRO_2$
Dexmedetomidine	Mixed data regarding effect on PVR	Decreased HR but in low doses rarely clinically significant
Ketamine	Little change in PVR	Increases CBF and $CMRO_2$
Benzodiazepines	No change but potential for hypoventilation	No change CBF, decrease $CMRO_2$

CBF, cerebral blood flow; $CMRO_2$, cerebral metabolic rate of oxygen; HPV, hypoxic pulmonary vasoconstriction; HR, heart rate; PVR, pulmonary vascular resistance; V/Q, ventilation/perfusion.

- ***Optimize cerebral blood flow and oxygen delivery.*** This involves the avoidance of hypoxemia and maintenance of the patient's normal awake blood pressure while anesthetized. Maintenance of normocarbia is also vital. There are multiple case reports of pediatric patients with moyamoya who developed neurologic symptoms secondary to crying and subsequent hypocarbia, leading to cerebral vasoconstriction. Conversely, an increase in carbon dioxide (CO_2) may lead to a steal phenomenon with vasodilation of vessels in unaffected areas leading to ischemia in areas primarily affected by moyamoya, as these are operating at full vasodilation.

Patients who have undergone an indirect bypass procedure remain at risk for ischemia in the immediate postoperative period, as improved blood flow is dependent upon angiogenesis. This may take weeks to months to occur and these patients must be treated as high-risk during this time period. As this child has had a direct anastomosis involving the temporal artery, he should have had an immediate improvement in CBF postoperatively.

Clinical Pearl

The primary anesthetic management goal in patients with moyamoya disease is to match oxygen delivery with oxygen consumption. Blood pressure should be maintained at the patient's baseline awake level and normocarbia should be maintained.

What considerations exist in a patient with comorbid PH and moyamoya disease?

The dynamic phases of general anesthesia are the highest risk periods for patients with PH due to the sympathetic surge, which can precipitate a PH crisis, and they are also critical times for patients with moyamoya disease. If the child is upset and crying, this may lead to hypocapnia and subsequent hypoperfusion of the cerebral areas affected by the disease. While premedication may mitigate this risk, care must also be taken to avoid either hypoventilation or subsequent hypoxemia and hypercapnia, as these in turn may precipitate a PH crisis or neurologic deficits. Preoxygenation and the use of short-acting opiates prior to laryngoscopy can also aid in the prevention of sympathetic surge.

A balanced anesthetic will also aid in maintaining the PVR to systemic vascular resistance (PVR/SVR) ratio, along with the $CBF/CMRO_2$ relationship. This balanced anesthetic can involve the use of either a total intravenous anesthetic technique or the use of volatile anesthetic agents. However, if volatile anesthetic agents are used, the minimum alveolar concentration should be kept at ≤1% in order to maintain flow-metabolic coupling. This should be augmented with multimodal analgesia, the constituents of which should be determined by the nature of the procedure.

It may be necessary to control ventilation, necessitating the insertion of an LMA or ETT, should hypoventilation occur or seem likely, in order to maintain normoxemia and normocapnia. Blood pressure may also require augmentation via the use of vasopressors, positive inotropes, or both, in order to maintain preanesthetic induction levels. This is important to ensure maintenance of CBF, as cerebral autoregulation is impaired.

If general anesthesia is utilized for a procedure, consideration should be given to neuromonitoring, which could be used to guide positioning, as well as respiratory and hemodynamic management. Decisions surrounding

https://doi.org/10.1017/9781108657341.044 Published online by Cambridge University Press

neuromonitoring should involve (1) institutional availability and (2) the patient's baseline neurologic status, considering the possible presence of transient neurologic symptoms when awake. Should neuromonitoring be considered for this procedure, ***MRI compatibility of all equipment must be assured.***

What monitoring is required to ensure safe anesthesia?

Standard recommended American Society of Anesthesiologists monitoring should be utilized, as for any procedure involving sedation or anesthesia. These include ECG monitoring for rate, rhythm, and signs of ischemia. This can be complicated by the effect of the MRI on the ECG waveforms. Hemoglobin–oxygen saturation monitoring is required to ensure that the patient does not become hypoxemic during the procedure. End-tidal CO_2 monitoring is also necessary to ensure that either hypoventilation or apneic episodes are not occurring, as the anesthesiologist is often remote from the patient. Blood pressure monitoring is also necessary given the cardiovascular effects of the sedative and/or anesthetic agents that are commonly employed. This generally takes the form of noninvasive blood pressure cuff measurements. While an arterial line may be employed if circumstances require it, standard arterial monitoring equipment must be modified to ensure that the transducer remains outside the magnetic field.

What is the optimal postprocedural disposition for this patient?

Decisions regarding postprocedural disposition of the patient are dependent upon the patient, the anesthetic technique used, and the center or location in which the procedure is being performed. From a patient perspective, the procedure itself is nonstimulating and there should be no postprocedural pain. The type of anesthetic technique utilized will inform postprocedural decision-making. Only patients who received no sedative or anesthetic drugs (physical therapies only) can be discharged immediately after the procedure, whereas patients who received sedation and general anesthesia may require a prolonged stay in the post-anesthetic care unit before eventual discharge to the ward or home. Once the patient has fully recovered from the anesthetic, they may be suitable for same-day discharge if the facility's protocols regarding same-day discharge support this course of action. There should be a mechanism by which patients with these comorbidities can be assessed and, if necessary, admitted should they become unstable in the postprocedural phase. The post-discharge destination of the patient is of importance also, as the patient should be within 1 to2 hours of the hospital should he/she require readmission.

Suggested Reading

Abman S. H., Hansmann G., Archer S. L., et al. Pediatric pulmonary hypertension. *Circulation* 2015; **132**: 2037–99.

Appireddy R., Ranjan M., Durafourt B. A., et al. Surgery for moyamoya disease in children. *J Child Neurol* 2019; 088307381984485.

Arlachov Y. and Ganatra R. H. Sedation/anaesthesia in paediatric radiology. *Br J Radiol* 2012; **85**: e1018–31.

Del Cerro M. J., Abman S., Diaz G., et al. A consensus approach to the classification of pediatric pulmonary hypertensive vascular disease: Report from the PVRI Pediatric Taskforce, Panama 2011. *Pulm Circ* 2011; **1**: 286–98.

Lammers A. E., Adatia I., Del Cerro M. J., et al. Functional classification of pulmonary hypertension in children: Report from the PVRI Pediatric Taskforce, Panama 2011. *Pulm Circ* 2011; **1**: 280–5.

Pritts C. D. and Pearl R. G. Anesthesia for patients with pulmonary hypertension. *Curr Opin Anaesthesiol* 2010; **23**: 411–16.

https://doi.org/10.1017/9781108657341.044 Published online by Cambridge University Press