Pulmonary Pathophysiology and Lung Mechanics in Anesthesiology: A Case-Based Overview

Marcos F. Vidal Melo, MD, PhD[a,b], Guido Musch, MD[a,b], David W. Kaczka, MD, PhD[a,c,*]

KEYWORDS

• Integrative physiology • Pulmonary mechanics • Ventilation • Pulmonary circulation • Gas exchange

KEY POINTS

- Alterations in patient condition and unpredictable requirements of surgery affect critical respiratory function and mechanics.
- Altered physiology of acute and chronic cardiopulmonary disease results in extreme changes in lung volumes, mechanics, and control of breathing.
- The anesthesiologist must integrate and apply a thorough understanding of basic respiratory physiology and mechanics under a variety of changing constraints to optimize anesthetic delivery to patients.

INTRODUCTION

In the operating room, with the induction and maintenance of anesthesia and the requirements of surgery, respiratory physiology and lung mechanics present a diverse and dynamic set of challenges for the anesthesiologist. For example, changing from spontaneous to controlled ventilation, reduced chest wall recoil with muscle relaxation, increased intra-abdominal pressure from laparoscopic insufflation or retractor placement, as well as the loss of airway tone and hypoxic pulmonary vasoconstriction from inhaled anesthetics, all contribute to changing ventilation distribution and poor ventilation-to-perfusion ($\dot{V}/\dot{Q}$) matching. Blood loss and fluid resuscitation, patient

Conflicts of interest: Nil.
This work was partially supported by NIH HL086827 (MFVM), HL094639 (GM), and HL089227 (DWK).
[a] Department of Anaesthesia, Harvard Medical School, Boston, MA, USA; [b] Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Gray-Bigelow 444, 55 Fruit Street, Boston, MA 02114, USA; [c] Department of Anesthesia, Critical Care, and Pain Medicine, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Dana 717A, Boston, MA 02215, USA
* Corresponding author. Department of Anesthesia, Critical Care, and Pain Medicine, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Dana 717A, Boston, MA 02215.
E-mail address: dkaczka@bidmc.harvard.edu

Anesthesiology Clin 30 (2012) 759–784
http://dx.doi.org/10.1016/j.anclin.2012.08.003 **anesthesiology.theclinics.com**
1932-2275/12/$ – see front matter

positioning requirements, surgical stress and inflammation, infections and sepsis, cardiopulmonary bypass (CPB), regional anesthesia, changing composition of inhaled gases, and many other issues arise during surgery that affect pulmonary function. Moreover, patients present with the full spectrum of cardiopulmonary disorders of varying causes and severities.

This article takes a case-based approach to discuss the complex interactions that affect respiratory physiology and mechanics. First it considers an elderly patient with advanced chronic obstructive pulmonary disease (COPD) requiring a lung resection for cancer. Preoperative risk stratification and prediction of postoperative pulmonary function, physiologic considerations of lung isolation and lateral positioning to facilitate surgery, and the impact of anesthetic technique on gas exchange, lung mechanics, $\dot{V}/\dot{Q}$ matching, and postoperative pain control are addressed. Next, the example of a patient undergoing coronary artery bypass grafting under CPB is used to discuss mechanical ventilation, as well as the complex impact of CPB on lung inflammation, gas exchange, and mechanics, and postoperative pulmonary dysfunction.

CASE I: LUNG RESECTION IN A PATIENT WITH COPD

A 67-year-old woman with a 50-pack-year smoking history is diagnosed with a recurrence of lung cancer. Two years ago, the patient presented with right lower lobe adenocarcinoma for which she underwent a segmentectomy, because results from pulmonary function testing were deemed too poor for a lobectomy. Because her cancer has recurred, the decision is now made to perform a completion right lower lobectomy. Her forced expiratory volume in 1 second (FEV_1) is 0.96 L (46% of predicted), and lung diffusion capacity for carbon monoxide (DLCO) is 28% of predicted. Her peripheral oxygen saturation on room air is 96% at rest, and 88% with mild exercise.

Risk Stratification and Prediction of Postoperative Pulmonary Function After Lung Resection

One goal of preoperative risk stratification is to identify patients at risk for perioperative pulmonary complications and long-term pulmonary disability. Smoking is a significant risk factor for both lung cancer and COPD, and patients who present for lung resection often have impaired pulmonary function and increased risk of intraoperative and postoperative respiratory complications. Spirometry in this patient revealed a pattern consistent with severe obstructive disease, because her FEV_1 was markedly reduced. This is mainly caused by loss of lung recoil and by the tethering forces that keep intrapulmonary airways open during expiration. This dynamic airway compression occurs during exhalation, resulting in a so-called equal-pressure point along the airway tree in which extramural pressure equals intraluminal pressure. These airways thus behave as Starling resistors.[1] In this situation, expiratory flow becomes independent of pleural pressure, and cannot be increased with greater expiratory muscle effort. This phenomenon is known as expiratory flow limitation. Reduced FEV_1 is thus a measure of decreased ventilatory function. Patients with FEV_1 less than 1 to 2 L are at increased risk for pulmonary morbidity and mortality following lung resection, with the lower limit applying to minor resections (such as segmentectomies) and the higher limit to pneumonectomies.[2–4] To account for patient age, stature, and gender, these limits are usually compared with predicted normal values. Perioperative risk increases substantially for FEV_1 of 40% to 70% of the predicted normal value.[5,6] DLCO less than 50% to 60% of predicted is similarly associated with increased perioperative morbidity and mortality.[7,8]

Patients with impaired pulmonary function tests may also undergo split lung function studies to better estimate postoperative pulmonary function. These studies may predict residual pulmonary function following resection according to the formula:

$$\text{Predicted postoperative (PPO) } FEV_1 = \text{Preoperative } FEV_1 \times (1 - \text{fraction of lung function lost after resection})$$

The functional portion of resected lung has been estimated using several methods. Bronchospirometry was used in early studies in which a double-lumen endobronchial tube was inserted in the awake subject to selectively measure right and left pulmonary function.[9,10] Less invasive methods are now available with radionuclide lung scanning. These techniques allow determination of the fraction of ventilation (as measured with inhaled ^{133}Xe[11–15]) or perfusion (as measured with ^{99m}Tc-macroaggregates[16–18]) of the lung portion to be resected. PPO FEV_1 has been shown to predict postoperative complications in one large study.[19] Perioperative morbidity and mortality may be substantial when PPO FEV_1 is less than 1 L or 40% of predicted.[15,20,21] Operability should be regarded with skepticism when PPO FEV_1 is less than 0.7 L or 30% of predicted.[5,20] Long-term disability, as shown by the need for home oxygen, is also increased when PPO FEV_1 is less than 40%.[22] In the same way as FEV_1, PPO DLCO can be calculated from whole lung measurement of DLCO and regional measurements of ventilation or perfusion. Markos and colleagues[20] found that PPO DLCO less than 40% of predicted is associated with increased postoperative complications. Lung volume reduction surgery, in which emphysematous lung tissue is resected to restore parenchymal recoil, improve chest wall mechanics, and increase expiratory flow, has shown that patients with preoperative FEV_1 of 25% to 30% of predicted can undergo successful resection under certain conditions.[23,24] In addition, preoperative hypercapnia with $Paco_2$ greater than 45 mm Hg has been associated with increased risk of postoperative pulmonary complications, thus it is not likely to be an independent risk factor,[19] but rather is a marker of impaired ventilatory function. Preoperative hypoxemia with arterial oxygen saturation lower than 90% has also been associated with increased risk of postoperative complications,[25] as has arterial desaturation greater than 4% during exercise testing.[20,25–28] Based on these criteria, this patient could be classified as being at extremely high risk for pulmonary resection because of her low FEV_1, DLCO lower than 30% of predicted, and arterial oxygen desaturation of 8% during mild exercise.

Before surgery, an epidural catheter is placed between the sixth and seventh thoracic vertebrae for intraoperative and postoperative analgesia. After induction of general anesthesia, the patient is intubated with a left-sided double-lumen endobronchial tube, which allows independent lung ventilation. After intubation, the ventilator circuit is connected and a continuously increasing exhaled CO_2 pattern is observed. Furthermore, an expiratory flow-volume pattern showing a marked upper concavity and significant end-expiratory flow despite a prolonged expiratory time is observed, similar to that reproduced in **Fig. 1**. The patient is ventilated with 100% oxygen, her arterial oxygen saturation is 100%, with plateau airway pressures of 25 cm H_2O. Anesthesia is maintained with isoflurane. The patient is turned into lateral decubitus position with her right side up for thoracotomy. Unilateral ventilation of the left lung is initiated by occluding the right arm of the double-lumen tube, with the operative lung emptied to atmosphere.

Five minutes after the start of unilateral ventilation and thoracotomy, oxygen saturation slowly decreases to 89%, and end-tidal CO_2 concentration increases. Increasing the plateau pressures and respiratory rate are not successful at relieving hypercapnia. During the operation, a branch of the right pulmonary artery is inadvertently severed,

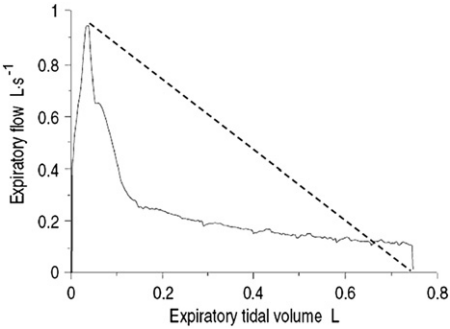

Fig. 1. Expiratory flow-volume curve of an anesthetized mechanically ventilated patient with severe COPD. Note the marked upper concavity and an end-expiratory flow of approximately 0.1 L/s. Both these features indicate heterogeneous emptying of alveolar units. Units with higher resistance and longer time constants are still emptying when the mechanical ventilator initiates the next inspiration. This flow-volume pattern is consistent with the steadily increasing exhaled CO_2 capnogram that was observed in the patient undergoing lung resection. The dashed line represents a hypothetical expiratory flow-volume pattern expected in a subject without pulmonary disease. (*Adapted from* Musch G, Foti G, Cereda M, et al. Lung and chest wall mechanics in normal anesthetized subjects and in patients with COPD at different PEEP levels. Eur Respir J 1997;10(11):2550; with permission.)

resulting in a brisk blood loss of approximately 3 L. Crystalloid is administered and a phenylephrine infusion is initiated to promote vasoconstriction and counteract the hypotension. Oxygen saturation initially increases to 96%, and then to 100% when the surgeon clamps the right pulmonary artery to control bleeding. To repair the vascular tear, the surgeon extends the resection to a bi-lobecotomy, removing both the lower and middle right lobes.

Lung Isolation: Methods, Physiology, and Mechanics

Methods of lung isolation

Lung isolation prevents ventilation to the operative lung to facilitate surgical exposure. Double-lumen endobronchial tubes have two channels: one extends into either the left or right bronchus, and the other terminates in the trachea. Separate inflatable cuffs seal each of these airflow pathways, and using clamps it is possible to ventilate either lung separately or both together. These tubes add substantial resistance in series to the lung's airway resistance, because of the small inner diameter and increased length of each channel, especially for the bronchial lumen. This resistance may enhance the effects of increased airway resistance in patients with COPD, further slowing expiration and leading to dynamic hyperinflation and air trapping. In this patient, the presence of dynamic hyperinflation can be inferred by the nonzero end-expiratory flow. Moreover, in the presence of expiratory flow limitation, dynamic hyperinflation can be present even when end-expiratory flow is negligible. In this case, the severity of hyperinflation is indicated by the persistence of end-expiratory flow despite prolonged expiratory time. The continuously increasing exhaled CO_2 capnograph reflects the sequential emptying of short to long time constant units. Because units with longer time constants have reduced alveolar ventilation and higher local alveolar CO_2 concentrations, phase III of the capnograph steadily increases, achieving a final value that reflects truncation of expiration by the subsequent inspiration.[29]

In the presence of expiratory flow limitation, dynamic hyperinflation occurs even when end-expiratory flow is low (typically less than 50 mL/s and therefore hard to

detect on clinical monitors). Thus, prolonging the expiratory time does not result in meaningful reductions in lung volume. Furthermore, because the flow-limited airway behaves as a Starling resistor, expiratory flow cannot be augmented by increased expiratory effort or decreased pressure at the airway opening. Therefore, dynamic hyperinflation resulting from expiratory flow limitation cannot be effectively controlled by changing the mechanical ventilator's settings. Although dynamic hyperinflation during anesthesia may lead to hypotension caused by increased intrathoracic pressure and decreased venous return, it may also have some favorable consequences. For example, increased end-expiratory lung volume allows higher oxygen reserve, which is advantageous during single-lung ventilation by decreasing the propensity to atelectasis.

Physiologic effects of unilateral ventilation and lateral decubitus position

Unilateral ventilation is accompanied by a reduction of the distribution volume for tidal volume. The left lung normally accounts for 45% of functional residual capacity (FRC) and the right lung for 55%. Previous recommendations were to maintain the same minute ventilation for unilateral ventilation as during bilateral ventilation. To minimize the risk of volutrauma, more recent studies recommend maintaining similar airway plateau pressures for unilateral and bilateral ventilation,[30] with modest increases in respiratory rate. In patients with expiratory flow limitation, higher rates may not be tolerated or may not improve effective alveolar ventilation.[31]

In the lateral decubitus position, the weight of the mediastinum and cephalad displacement of the lower diaphragm caused by increased intra-abdominal pressure reduce FRC and the compliance of the dependent ventilated lung. This reduction may be alleviated by judicious application of positive end-expiration pressure (PEEP) to the dependent lung, which returns it to a more compliant portion of its pressure-volume curve and minimizes atelectasis.[32,33] In COPD, higher expiratory flows are supported by the higher lung volumes resulting from PEEP, and alveolar ventilation improves. Once tidal volume and expiratory time are maximized, residual hypercarbia may be unavoidable. For short periods of time, respiratory acidosis under anesthesia and mechanical ventilation is well tolerated, so long as the hypercarbia is relieved when two-lung ventilation is resumed before spontaneous ventilation and emergence.

Unilateral ventilation is also accompanied by shunt in the nonventilated lung, leading to arterial hypoxemia.[34] Hypoxic pulmonary vasoconstriction (HPV) counteracts this hypoxemia by increasing pulmonary vascular resistance and diverting blood flow to the ventilated lung. Animal studies have shown that such flow diversion occurs within 30 seconds of unilateral bronchial occlusion, and blood flow to the occluded lung is approximately half that during double-lung ventilation by 2 minutes.[35] If HPV is intact, shunt fraction during single-lung ventilation may be only 20% to 30% of cardiac output, as opposed to the 50% that might be expected in its absence.

In lateral decubitus position with a nonventilated nondependent lung, gravity favors blood flow to the dependent lung, further adding to the favorable effects of HPV on perfusion redistribution. However, even the dependent lung may be regionally hypoxic because of compression or absorption atelectasis (the latter favored by the use of high forced inspiratory oxygen [Fio_2] during unilateral ventilation). If these hypoxic compartments are substantial (ie, greater than 70% of the lung), the effectiveness of HPV will be reduced because the normoxic portions of lung are not sufficient to receive diverted blood flow.[32]

The gradual decrease in peripheral arterial oxygen saturation for this patient during unilateral ventilation and thoracotomy can be explained by resorption of oxygen from the nonventilated lung, which becomes progressively atelectatic and shunting. This

patient's pulmonary disease was such that HPV and baseline lung function were not sufficient to maintain normal saturation during unilateral ventilation. Her arterial saturation improved after blood loss and vasoconstrictor therapy, most likely because of the reduced shunt fraction associated with decreased cardiac output and pulmonary arterial pressure, because pulmonary hypoperfusion functionally enhances the effects of HPV. The HPV may also have been further potentiated by the vasoconstrictor phenylephrine. The beneficial effect of a reduction in shunt fraction deriving from a reduction in pulmonary perfusion on arterial oxygenation can be offset by a concomitant reduction in mixed venous oxygen tension ($P_{\bar{v}}O_2$), which may accompany a decrease in cardiac output. For a given shunt fraction, lower $P_{\bar{v}}O_2$ results in lower arterial oxygen tension.[36] Augmenting cardiac output through fluid management or inotropic agents could potentially increase $P_{\bar{v}}O_2$ and improve arterial oxygenation in the presence of shunt. Surgical clamping of the right pulmonary artery virtually eliminates all shunt through the nonventilated lung, further improving arterial oxygen saturation.

To restore $\dot{V}/\dot{Q}$ matching and improve gas exchange during unilateral ventilation in the lateral decubitus position, selective application of PEEP to the dependent ventilated lung or continuous positive airway pressure (CPAP) to the nondependent lung have been investigated. The rationale for the use of PEEP is to optimize the function of the ventilated lung by bringing it to a more compliant portion of the pressure-volume curve and, mainly, reverse atelectasis.[33] This technique generally improves alveolar ventilation and reduces shunt flow in this lung. However, excessive PEEP can also increase the vascular resistance of the dependent lung, thus diverting blood flow back to the nonventilated lung and increasing shunt, especially if additional recruitment of atelectatic parenchyma does not occur.[37] The global effects of PEEP to the dependent lung thus represent the trade-off between these two opposing effects. Some studies have shown PEEP to improve oxygenation during unilateral ventilation,[34] whereas others have shown no improvement or even worsening of oxygenation.[38,39]

Another remedy for hypoxemia during unilateral ventilation is application of low levels of CPAP with 100% oxygen to the nondependent lung. By applying ~5 cm H_2O of CPAP to the nonventilated lung, it is possible to use this lung for apneic oxygenation and thus reduce hypoxemia. Although selective application of CPAP to the nondependent lung is generally more reliable than application of PEEP to the dependent lung for improving hypoxemia, to be maximally effective it must be applied before the nonventilated lung is allowed to deflate completely.[40] CPAP may also interfere with surgical exposure. Some investigators have combined the application of PEEP to the dependent lung and CPAP to the nondependent lung, although it is controversial whether this strategy offers any advantages compared with PEEP or CPAP alone.[34,39] As a mitigating maneuver, intermittent insufflation of oxygen at low pressure into the conducting airways of the operative lung may provide enough apneic oxygenation to allow surgery to continue without compromising surgical exposure. If these maneuvers fail to improve oxygenation and saturation decreases to a dangerous level, urgent reexpansion of the operative lung should be considered, depending on the stage of surgery. Clamping of the pulmonary artery to the operative lung should also be considered.

Modulation of HPV

Inhalational anesthetics inhibit HPV because of their vasodilatory effect. However, this effect seems to be more pronounced *in vitro* and *ex vivo* than in the intact respiratory system. Domino and colleagues[41] showed a dose-response relation between isoflurane concentration and inhibition of HPV in vivo during canine single-lung ventilation. This effect seems to be small, because one minimum alveolar concentration (MAC) of

isoflurane causes an increase in shunt fraction of only 4%, which rarely compromises clinical management. These values agree with clinical measurements performed by Spies and colleagues.[42] Intravenous anesthetics, in particular propofol, seem to have even less (if any) of an inhibitory effect on HPV during unilateral ventilation.[42–45] It is therefore possible that this patient's hypoxemia would have been less with intravenous rather than inhalational anesthesia, although the effect of isoflurane on arterial oxygenation in patients with emphysema undergoing unilateral ventilation in the lateral decubitus position seems to be minimal.[46]

Inflammation, as caused by systemic sepsis or localized pneumonia, is another potent inhibitor of HPV,[47–50] and it exacerbates the hypoxemia caused by shunt. Pharmacologic agents such as almitrine (which augments HPV) and inhaled nitric oxide (a selective pulmonary arterial vasodilator) have been shown both separately and in concert to improve oxygenation during single-lung ventilation,[51] although these are not typically used in clinical practice.

At the end of the operation, the patient is transported to the intensive care unit intubated. Overnight, she is hemodynamically stabilized and an epidural infusion of bupivacaine 0.1% with hydromorphone 20 μg/mL is started for pain control. On the following day, she is successfully extubated and remains pain free with epidural analgesia.

Regional Thoracic Anesthesia and Lung Mechanics

Thoracic epidural analgesia (TEA) is an effective method to relieve pain after thoracotomy. Effective pain relief is critical in facilitating deep breathing and coughing to minimize atelectasis and clear secretions. However, two potential concerns arise in the application of TEA to patients with severe COPD. First, local anesthesia may cause partial respiratory motor blockade, thus further impairing ventilatory function. Second, it may also result in pulmonary sympathetic blockade, which could theoretically lead to increased bronchial tone and airway resistance, as well as decreased pulmonary vasoconstrictor response. Groeben and colleagues[52] showed that TEA leads to a ~11% decrease of FEV_1 and ~15% decrease of vital capacity (VC) in women with severe COPD or asthma. Because the ratio of FEV_1 to VC increased by 4%, they concluded that the decrease of FEV_1 and VC was caused by mild motor blockade of respiratory muscles rather than increased airway resistance resulting from increased bronchial tone caused by pulmonary sympathetic blockade. They hypothesized that systemic absorption of local anesthetic from the epidural space was responsible for a direct bronchodilatory effect of TEA that overrode the indirect bronchoconstrictor effect.

Garutti and colleagues[53] showed that, when TEA was added to general anesthesia during unilateral ventilation for thoracic surgery, Pa_{O_2} and shunt fraction were slightly worse (by ~60 mm Hg and 5%, respectively) compared with general anesthesia alone. They hypothesized that this was caused by the inhibition of HPV resulting from sympathetic blockade of the noradrenergic innervation to the pulmonary vasculature. Despite these possible limitations, the advantages of improved pulmonary function from effective pain control, without the sedation and respiratory depression that occurs with systemic opioids, has made the use of TEA a virtual standard of care in patients with severe emphysema undergoing lung volume reduction surgery.[54,55]

CASE II: CARDIAC SURGERY

A 69-year-old woman with history of severe three-vessel coronary artery disease and COPD is scheduled to undergo coronary artery bypass graft (CABG) surgery using 4 distal anastomosis, including a left internal mammary artery (LIMA) graft to the left

anterior descending coronary artery. The patient is preoxygenated by breathing 100% oxygen through a mask before induction of anesthesia.

Preoxygenation and Induction of Anesthesia

Preoxygenation at the beginning of general anesthesia is intended to avoid hypoxemia during the period of apnea required to obtain endotracheal intubation. The increased time constant inequalities present in COPD lungs[56] require longer preoxygenation times to achieve similar end-expiratory oxygen fractions in COPD than in normal lungs.[57] General anesthesia and muscle paralysis result in decreased FRC, cross-sectional chest area, and thoracic volume, with a concomitant cranial shift of the diaphragm.[58,59] These changes are associated with atelectasis and airway closure[60] in dependent lung regions caused by tissue compression,[61] as well as loss of respiratory muscle tone and gas resorption[62,63] resulting in increased intrapulmonary shunt and regions of low $\dot{V}/\dot{Q}$.[64,65]

The risk of hypoxemia in a patient with critical coronary artery stenosis takes precedence over the minor risks from breathing 100% oxygen, such as the increased likelihood of absorption atelectasis[66] or short-term risks of oxygen toxicity.[62] Use of moderate PEEP (ie, 6–10 cm H_2O) during induction of anesthesia prevents atelectasis and improves oxygenation.[67,68] A diagnosis of COPD in this patient suggests increased $\dot{V}/\dot{Q}$ heterogeneity with anesthesia and positive pressure ventilation. However, she will be less prone than a healthy patient to develop atelectasis and shunt because of the reduced elastic recoil and air trapping in COPD.[69]

A direct laryngoscopy is performed, the patient is endotracheally intubated, and mechanical ventilation is initiated.

Mechanical Ventilation During Cardiac Surgery

Mechanical ventilation during cardiac surgery requires considerations of factors promoting ventilator-induced lung injury, similar to patients at risk for acute lung injury. Respiratory complications are frequent after cardiac surgery,[70–72] and mechanical ventilation for more than 48 hours is one of the most frequent complications,[73,74] although development of acute respiratory distress is rare.[75]

Mechanical ventilation can produce lung injury,[76] and ventilator settings can influence patient morbidity and mortality in intensive care units (ICUs).[77,78] Furthermore a two-hit condition, in which the mechanical ventilation insult is accompanied by an inflammatory or other cellular-level injurious stimulus, can significantly aggravate the lung injury.[79,80] Surgical trauma, exposure to CPB,[81,82] endotoxemia,[83,84] ischemia-reperfusion of the lung[85] (including reduction of bronchial perfusion),[86–88] and frequent blood transfusion[89] are some of the mechanisms associated with the inflammatory response in cardiac surgery that may amplify lung injury during mechanical ventilation.[90] These processes are particularly important because the physiologic mechanisms that produce ventilator-associated lung injury (ie, tidal recruitment and overinflation) are frequently present in patients with and without previous lung disease undergoing cardiac surgery.[91]

Previous studies suggest that intraoperative use of protective modes of ventilation, with higher PEEP values (10 cm H_2O) and lower tidal volumes (6–8 mL/kg of predicted body weight), reduce the inflammatory response and improve pulmonary mechanics in patients after cardiac surgery (**Fig. 2**).[92,93] In one of these studies, the protective mode explicitly included a recruitment maneuver by increasing peak inspiratory pressure to 40 cm H_2O for 15 seconds. The inflammatory response for the cases of protective ventilation was characterized by lower levels of interleukin IL-6 and IL-8 in plasma and bronchoalveolar lavage (BAL) fluid. Protective ventilation did not prevent adverse

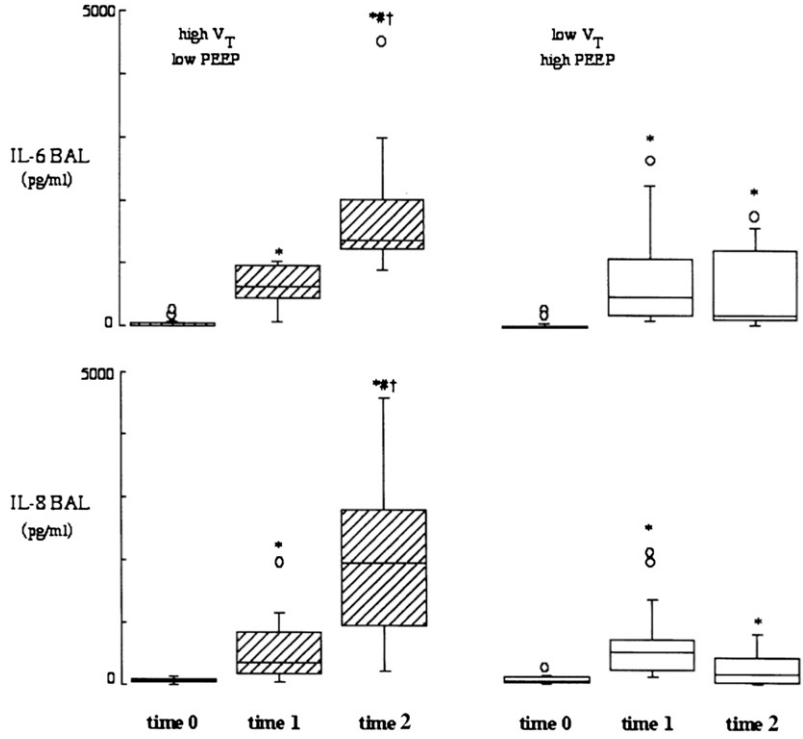

Fig. 2. The effect of high tidal volume (V_T)/low PEEP versus low V_T/high PEEP ventilation strategies on lung inflammation as indicated by bronchioalveolar lavage (BAL) fluid interleukin IL-6 and IL-8 concentrations at 3 time points during cardiac surgery. Time 0, before sternotomy; time 1, during CPB; and time 2, 6 hours after resuming mechanical ventilation. (*Reprinted from* Zupancich E, Paparella D, Turani F, et al. Mechanical ventilation affects inflammatory mediators in patients undergoing cardiopulmonary bypass for cardiac surgery: a randomized clinical trial. J Thorac Cardiovasc Surg 2005;130(2):380; with permission.)

effects of CPB in the lungs in one study,[94] but these investigators used a PEEP of 5 cm H_2O in their protective mode in contrast with 10 cm H_2O used in other studies. This finding suggests that low lung volumes may be an important component of ventilator-induced lung injury during cardiac surgery.

The fraction of inspired oxygen (Fio_2) during cardiac surgery involves a balance between maximizing oxygenation and minimizing oxidative stress, absorption atelectasis, and ventilator-induced lung injury. The use of $Fio_2 = 1.0$ compared with $Fio_2 = 0.5$ throughout surgery is associated with delayed recovery of oxygenation and increased levels of tumor necrosis factor-α in BAL.[95] Despite these considerations, outcome data for specific ventilator settings during cardiac surgery are still lacking.

After intubation, placement of central venous access, and positioning, the patient is prepped, draped, the skin incision is made, and sternotomy is performed.

Opening of the chest results in partial reduction of the contribution of the chest wall to the impedance of the respiratory system.[96] This reduction is partial because the chest wall is not completely separated from the lungs but instead is usually spread at the sternum, with remaining contact of lung and chest wall in dorsal and lateral areas. This technique may result in increased inflation of the lung FRC,[97] with

decreased elastance and resistance of the respiratory system and an inadvertently increased delivered tidal volume if pressure-controlled ventilation is used.

The LIMA is dissected in order to be used as a graft to the left anterior descending coronary artery.

The LIMA (also called internal thoracic artery) branches from the subclavian artery near its origin, and travels downward on the inside of the chest wall, approximately a centimeter from the sides of the sternum, and medial to the nipple. Because of its anatomic position, dissection of the LIMA usually involves the opening of the left pleura and packing of the left lung to facilitate exposure. Temporary reduction of tidal volume for better visualization and surgical manipulation may be required. Such interventions can cause significant left lung atelectasis and respiratory dysfunction that persist into the postoperative period.[98–100] Worsening of lung mechanics after CABG surgery is more marked when pleurotomy is performed.[100–102] Imaging studies using computed tomography showed significantly more densities after surgery in the left lung of patients having CABG than patients undergoing mitral valve repair,[103] potentially a result of left internal mammary harvesting.

The aorta and right atrium are cannulated and the patient is placed on extracorporeal circulation with CPB for the performance of the bypass grafting.

For many decades, pulmonary complications were a major cause of death following CPB.[104] Acute respiratory distress following CPB is now unusual, but milder forms of acute lung injury are more frequently observed after cardiac surgery[75,105] and can be critical in the patient at risk.[106,107]

Lung Histology After CPB

Lung parenchyma following CPB usually reveals mild changes. Although data on histopathologic changes after CPB are limited because of the difficulty in obtaining samples, microbiopsies performed 20 minutes following CPB show poorly aerated alveoli, different degrees of alveolar edema, thickening of alveolar septa, alveolar capillaries with perivascular halo, and alveolar flooding.[108] Neutrophils are found in the interstitium and alveolar space, with large alveolar macrophages containing numerous vacuoles indicating activation. Electron microscopy may show additional details on injury to the alveolar-capillary barrier. In some cases, only edema of the endothelial cells is found, whereas both endothelial and type I epithelial cells may be swollen in other cases. In severe cases, there may be necrosis of epithelial cells with denuded basement membranes. Alveolar capillaries are often congested with signs of leakage (ie, airspaces filled with edema fluid). Many polymorphonuclear neutrophils are found in blood vessels. Pulmonary surfactant seems to be normal in well-aerated alveoli, although not in fluid-filled alveoli.[108]

Lung Management During CPB

During CPB, the lungs are either opened to atmosphere, kept at a constant positive airway pressure, or ventilated at a slow rate. That management of the lungs during CPB could have an effect on post-CPB pulmonary function was recognized decades ago with the finding of improved compliance and shunt in calves when lungs were not ventilated during CPB.[109] Using inert gases, Loeckinger and colleagues[110] showed that 10 cm H_2O of CPAP during CPB resulted in more perfusion to areas with normal $\dot{V}/\dot{Q}$, with significantly less shunt and low $\dot{V}/\dot{Q}$ perfusion 4 hours following CPB. This result was accompanied by improved postoperative oxygenation. In contrast, CPAP of 5 cm H_2O during CPB did not improve lung function when used in patients[111] or pigs.[112] More recently, experiments in pigs suggested that a slow ventilatory rate

(5 per min) may lead to even better postoperative outcome because of a reduction in ischemic injury (**Fig. 3**).[113]

Bypass of the pulmonary artery flow produces lung ischemia and respiratory dysfunction.[86] This mechanism has recently been explored with use of pulsatile pulmonary perfusion during experimental CPB, which further reduced the inflammatory response in pigs.[114] Also potentially contributing to this effect is a reduction of bronchial artery blood flow during CPB, which increases the risk of lung ischemia, and a tissue-level constriction in response to hypocapnia that develops when there is ventilation in the absence of pulmonary blood flow.[115]

Inflammatory Response to CPB

Exposure of blood to foreign surfaces, ischemia-reperfusion, and endotoxemia during CPB trigger a strong inflammatory response and the complement system, the cytokine cascade, the coagulation-fibrinolytic system, the cellular-immune system, and the endothelium are all activated.[90] Gene array and multiplex protein analysis suggest that circulating leukocytes overexpress adhesion and signaling factors after CPB, which could facilitate their trapping in the lungs and promote a subsequent tissue-associated inflammatory response.[116] There is evidence of lung-specific inflammatory responses after CPB,[82,117] underscoring the relevance of addressing compromised pulmonary function in patients at risk.

Off-pump CABG Surgery

Because of the marked inflammatory response to CPB, cardiac surgery without CPB ("off-pump" surgery) has been theorized to reduce respiratory impairment after surgery.[118–120] Off-pump CPB yields lower levels of several inflammatory markers, such as cytokines, polymorphonuclear elastase, thrombin-antithrombin III complex, and complement factor (C3a), oxidative stress, and blood endotoxin than on-pump CPB.[121–124]

Although some studies report improvement in shunting and hypoxemia,[125] other studies partitioning lung and chest wall mechanics do not support a significant effect of off-pump CABG on respiratory dysfunction.[126] Studies using the forced oscillation technique (FOT) found that off-pump CABG does not affect airway mechanics, but still

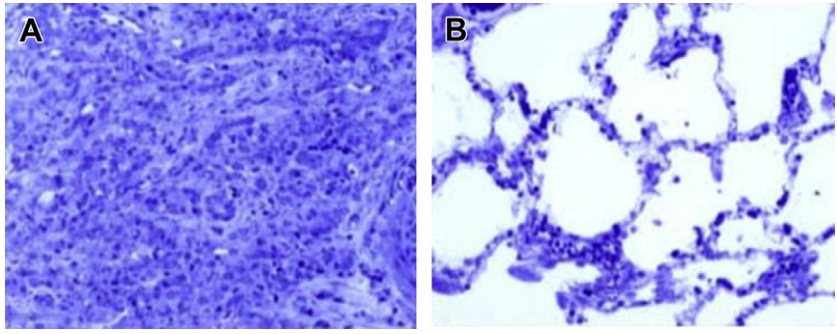

Fig. 3. Lung tissue light micrographs depicting alveolar regions 90 minutes after CPB. (*A*) When the lung was either open to the atmosphere or received 5 cm H_2O CPAP there was significant atelectasis and pulmonary edema. (*B*) Low-frequency ventilation (5 breaths per minute) led to normal-appearing lung tissue. (*Modified from* Imura H, Caputo M, Lim K, et al. Pulmonary injury after cardiopulmonary bypass: beneficial effects of low-frequency mechanical ventilation. J Thorac Cardiovasc Surg 2009;137(6):1535; with permission.)

impairs the parenchymal tissues to degrees similar to those occurring with CPB.[127] Although it is hypothesized that off-pump CABG improves outcomes in patients at risk for respiratory dysfunction, such as patients with COPD,[128] it is questionable whether off-pump CABG results in better outcomes overall.[107,120,129]

Once the grafts are finished, the lungs are reexpanded and mechanical ventilation resumed as part of the sequence of procedures preceding the discontinuation of extracorporeal circulation.

Optimal ways to reexpand the lungs have been studied. Based on animal data for CPB[130] and human data under anesthesia and mechanical ventilation,[131] some investigators suggest recruiting the lungs using Fio_2 less than 1.0. For instance, Fio_2 of 0.4 has been used to prevent alveolar derecruitment through reabsorption atelectasis following experimental CPB.[130] Expansion to pressures of 35 cm H_2O for 15 seconds with Fio_2 = 0.4 before separation from CPB, combined with a second VC maneuver within 20 to 30 minutes after arrival in the ICU (Fio_2 = 0.4, inflation pressure = 30 cm H_2O for 5 seconds) reduces hypoxemia in the first 24 hours after surgery,[132] and a single VC maneuver after CPB may lead to improved intraoperative oxygenation and shorter times to extubation.[133]

Following discontinuation of CPB, mechanical ventilation is resumed with settings of Fio_2 = 1.0, PEEP = 5 cm H_2O, tidal volume = 8 mL/kg predicted body weight, and a respiratory rate of 12 per minute. After a few minutes of mechanical ventilation, peak inspiratory pressure increases to 35 cm H_2O, plateau pressure to 28 cm H_2O, and the expiratory flow curves show nonzero flow at the end of exhalation. Direct inspection of the lungs shows slow deflation.

Effects of Cardiac Surgery and CPB on Respiratory Mechanics

Deterioration of lung mechanics is frequently encountered following cardiac surgery[134] and can exacerbate the already compromised respiratory function commonly found in patients undergoing cardiac surgery caused by preexisting cardiac disease, smoking habits, and other comorbidities.[135] Lung resistance and elastance are usually increased after cardiac surgery.[101,136–140] Immediately after anesthesia induction and endotracheal intubation for CABG surgery, frequency and tidal volume dependence of elastance and resistance are similar to those observed in seated healthy subjects.[141] After CABG surgery, lung elastance and resistance markedly decrease with increasing tidal volume, whereas resistance shows a greater dependence on frequency compared with presurgical conditions.[137] Reductions in FRC,[142] as well as increases in airway and tissue heterogeneity,[143,144] may contribute to such enhanced frequency and tidal volume dependencies. Changes in chest wall mechanics caused by cardiac surgery with CPB are inconsistent in other studies.[126,135,137,145,146] Pleurotomy and positive fluid balance accentuate the deterioration of lung mechanics.[101,138]

Changes in respiratory mechanics following heart surgery seem to depend on the specific cardiac disease. Comparison of mechanically ventilated patients with ischemic versus valvular disease indicated that valvular patients had significantly higher lung elastance (but not chest wall elastance), as well as higher lung resistance that was associated with uneven time constants (stress relaxation and pendelluft).[135,146] After surgery, both groups had significant increases in lung elastance, whereas chest wall elastance was not modified.[135] These changes may represent increases in extravascular lung water, capillary volume, and/or alveolar collapse. Both groups also showed postoperative decrease in lung resistance and increase in chest wall resistance.[135] Decreases in lung resistance are postulated to be related to release of smooth muscle active substances such as prostaglandin E2, pulmonary hypoxia, and lung interdependence with collapse leading to remote bronchial distension. Presence of preoperative

pulmonary hypertension in valvular patients, a factor relieved at least partially after surgery, may also contribute to alterations in lung mechanics.[135,147,148]

Human studies addressed the discrimination between airway and parenchymal tissue contributions to the deterioration of perioperative lung mechanics. The forced oscillation method[140] was used to measure lung and respiratory system impedance (Z_{rs}), based on the observation that frequency dependency at low oscillation frequencies is different for the airways and the parenchyma, allowing the separation of their contributions to total lung impedance.[149–152] Babik and colleagues[140] found that cardiac surgery with extracorporeal circulation increased tissue elastance, tissue damping, and airway resistance, and significantly reduced airway inertance (**Fig. 4**). Inhomogeneous narrowing of peripheral airways from mucosal thickening or release of inflammatory mediators seems to be the main mechanism producing CPB-induced increase in airways resistance. Restrictive processes caused by lung derecruitment also contribute to alterations in elastance and tissue damping. Dopamine, an adrenergic inotrope frequently administered during cardiac surgery, counteracted the bronchoconstriction seen in patients who undergo CPB (see **Fig. 4**). These observations seem to be independent from increases in extravascular lung water and in the pulmonary circulation.[140]

Measurements of Z_{rs} and its components after extubation and the first postoperative week showed that airway resistance increased immediately after extubation and gradually decreased to baseline values at postoperative day 5.[127] Worsening of elastance peaked at postoperative day 2 and persisted at higher than baseline levels for the whole first postoperative week. Peak increase in elastance was higher and its increase lasted longer in patients undergoing CPB than those undergoing off-pump CABG.[127] The total volume of fluids administered to patients seems to also play a role in the respiratory mechanics. Positive fluid balance was associated with worsening in respiratory mechanics and indices of oxygenation.[101]

Together with the changes in respiratory mechanics, the patient develops hypoxemia with arterial oxygen saturation (Sa_{O_2}) = 90% to 92%.

During the critical period immediately following discontinuation of CPB, even mild hypoxemia is undesirable because it reduces oxygen transport to the newly revascularized heart, as well as to other tissues. To manage this issue, it is important to realize that there are multiple causes for lung dysfunction during and after cardiac surgery including accumulation of extravascular fluid in the alveolar-capillary membrane,[153] alveolar collapse,[154,155] a decrease in FRC,[97] retention of airway secretion, or insufficient cough as a consequence of pain (after surgery).

Effects of Cardiac Surgery and CPB on Gas Exchange

Increases in venous admixture and physiologic dead space, worsening of blood gas tensions, and reduction in FRC after CPB persisting for days after surgery have been reported for decades.[156–158] These changes are usually short lived, with modest effect on the postoperative clinical course.[159] They gain relevance in the management of patients with additional respiratory disease or risk factors.[106,160]

Despite complex and rapid changes in cardiopulmonary function on separation from bypass, atelectasis is still the main mechanism producing gas exchange impairment in the perioperative period of cardiac surgery.[155,161] An estimated average of 24% of lung tissue is collapsed 2.5 hours after the end of uncomplicated cardiac surgery.[162] Atelectasis following cardiac surgery is significantly greater than that observed after abdominal and lower extremity surgery on the first postoperative day.[163,164] This difference is attributed to the aforementioned effects of inflammation, internal mammary harvest, opening of the pleural space, ventilatory management, surfactant dysfunction, and

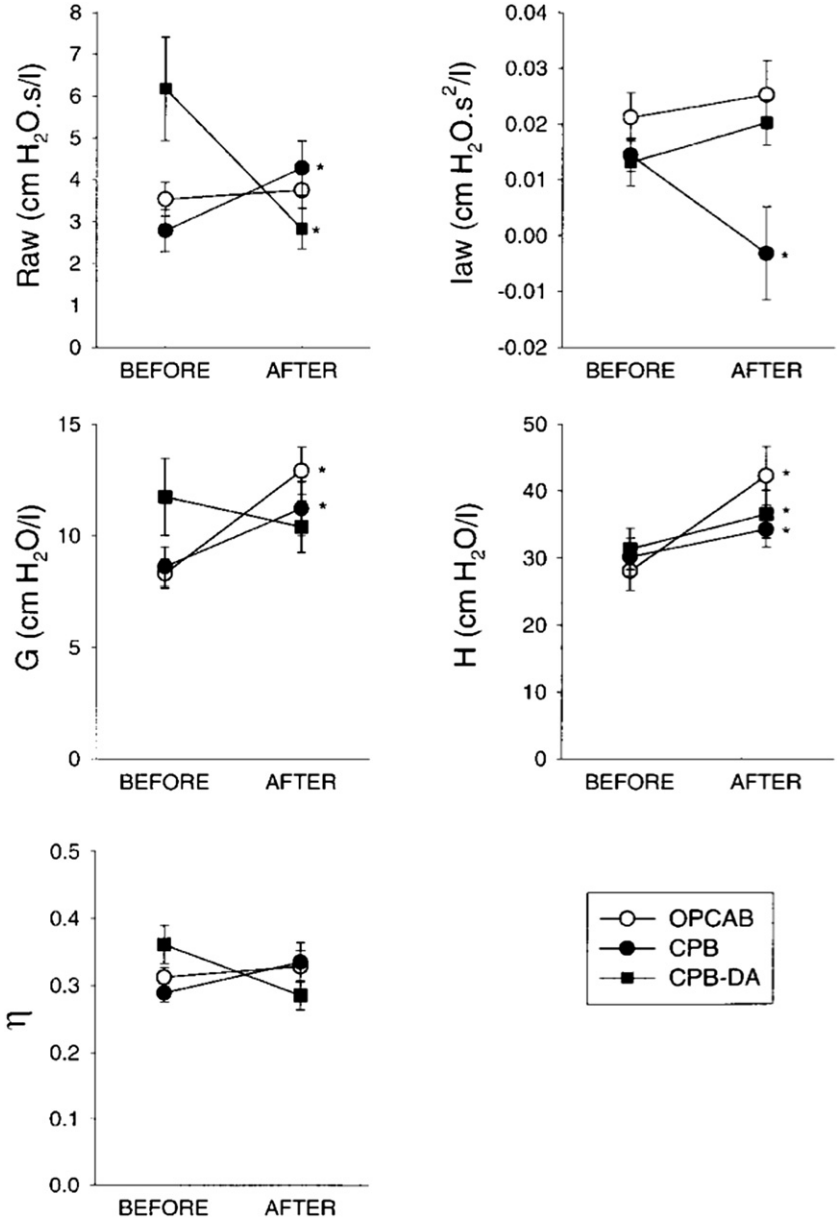

Fig. 4. Changes in airway and lung tissue mechanical properties in patients undergoing off-pump CABG (OPCAB) surgery, or with CPB. Group CPB-DA also had intravenous dopamine administered. G, tissue damping coefficient; H, tissue elastance coefficient; I_{aw}, airways inertance; R_{aw}, airways resistance; η, tissue hysteresivity. (*Reprinted from* Babik B, Asztalos T, Petak F, et al. Changes in respiratory mechanics during cardiac surgery. Anesth Analg 2003;96(5):1284; with permission.)

changes in lung recoil from pulmonary edema. The lungs after CPB exhibit poor $\dot{V}/\dot{Q}$ matching, in addition to the true shunt caused by atelectasis. Increases in $\dot{V}/\dot{Q}$ heterogeneity are associated with the inflammatory response to CPB, likely because of both the local redistribution of perfusion and of ventilation (although little is known about the regional characteristics of this $\dot{V}/\dot{Q}$ distribution following CPB). Gas exchange impairment improves along the first 24 hours after surgery, with low $\dot{V}/\dot{Q}$ regions comprising 11% and shunt 7.5% of total gas exchange regions, as measured with inert gases reported at 21 hours after cardiac surgery.[165–167]

Sequential intraoperative measurements showed that airway dead space increases with sternotomy by 32%.[168] Airway dead space is reduced following extracorporeal circulation and sternal closure. However, by the end of surgery, alveolar dead space increases significantly. Airway dead space at this stage can be smaller compared with the preoperative state, and so there is no net change in the physiologic dead space fraction at the end of surgery.[168] Despite such findings, some groups failed to find an increase in the arterial end-tidal gradient of P_{CO_2} after CPB.[169,170]

Although the magnitude of atelectasis has not been found to be different between CABG and mitral valve surgery, it seems that control of regional blood flow may differ in those conditions.[103,171] Atelectasis measured with computed tomography was better correlated with global shunt measured with oxygen in the first postoperative day after mitral valve replacement or repair than after CABG surgery. Effective HPV would be expected to reduce blood flow in regions of alveolar collapse, resulting in a limited relationship between lung collapse and shunt. These results suggest reduction in the effect of HPV to optimize gas exchange in mitral cases, perhaps related to the associated increased pulmonary vascular pressures.

A recruitment maneuver is performed by inflating the lungs to 30 cm H_2O for 30 seconds. During this procedure, systemic blood pressure is carefully monitored, because such increased intrathoracic pressure reduces venous return and cardiac output. Endotracheal suctioning is performed. The inspiratory/expiratory ratio in the mechanical ventilator is increased to 1:3.5 and PEEP of 5 cm H_2O is added. Incomplete deflation persists, and a β-agonist (albuterol) is delivered through inhalation. Following these interventions, the Sa_{O_2} increases to 100%.

Perioperative Respiratory Dysfunction and Mechanical Ventilation in Patients with COPD

Patients with COPD have early changes in the topographic distribution of regional perfusion that contribute to increased $\dot{V}/\dot{Q}$ mismatch.[172–174] This perfusion redistribution can compound the aforementioned perioperative factors to accentuate gas exchange dysfunction. Such patients present with loss of elastic recoil and longer regional time constants. They also have lower vertical gradients in aeration and ventilation during spontaneous breathing compared with normal subjects.[174] Such characteristics seem to make them less prone to the development of reabsorption atelectasis during spontaneous breathing and mechanical ventilation,[69,174,175] and worsening of lung mechanics and gas exchange during cardiac surgery.[176]

Although use of PEEP during mechanical ventilation of patients with COPD is not standard, in selected cases it can help with reduction of airway closure and work of breathing, relief of lung overinflation, and improving respiratory system time constants.[177] The presence of sticky airway closure, alterations in intraparenchymal tethering forces, and increases in airway wall rigidity caused by PEEP are possible mechanisms. *A priori* information regarding disease, respiratory mechanics, or ventilatory settings does not predict the response. As a consequence, an empirical PEEP trial

investigating plateau pressure response was suggested as a strategy to guide use of PEEP in patients with COPD during mechanical ventilation.[178]

Significant bronchoconstriction is sometimes observed at the end of the CPB period.[179,180] Because patients with COPD have a chronic lung inflammation and higher airway resistances, bronchoconstriction in these patients can be particularly critical. Bronchodilators, such as β-agonists, are administered either by inhalation or intravenously in these cases. In some cases of bronchospasm, inhaled nitric oxide may be considered with the aim of reducing pulmonary artery pressures, unloading the right ventricle, and relieving bronchospasm while improving $\dot{V}/\dot{Q}$ matching.[181–183] However, use of inhaled nitric oxide in patients with COPD can lead to deterioration of gas exchange. This deterioration is caused by $\dot{V}/\dot{Q}$ imbalances rather than by shunt, likely because of impaired hypoxic regulation of the matching between ventilation and perfusion.[184]

In addition, it has been recognized that patients with COPD have distinct elements of the inflammatory response in the perioperative period of cardiac surgery. For example, release of cysteinyl leukotrienes increases during cardiac surgery with CPB and is larger in patients with than without COPD.[185] This may be related to higher lung and airway production of cysteinyl leukotrienes and neutrophil activation, which could contribute to the postoperative deterioration in lung function.

The sternotomy is closed with stainless-steel wires, and the remaining tissue planes and skin are also closed. The peak inspiratory pressure is noticed to increase from 24 to 37 cm H_2O. Arterial blood gas at the end of the case shows that Pa_{O_2}/Fi_{O_2} = 287 mm Hg. The patient is transferred to the ICU while still intubated. Respiratory mechanics and gas exchange are still marginal at ICU arrival but improved 16 hours after surgery, allowing patient extubation.

Closure of the chest results in the restoration of the contribution of the chest wall to the impedance of the respiratory system. As a consequence, increases in the inspiratory pressures are expected. Deleterious effects to gas exchange and respiratory mechanics can occur because of increased derecruitment of dependent and subdiaphragmatic lung regions. Resistance is increased because of the chest wall contribution and likely, at least partially, because of interdependence, in which the collapse of alveolar units reduces traction on the small airways allowing a reduction in their diameter. FRC after chest closure can be lower than that at the beginning of surgery.[97] The observed Pa_{O_2}/Fi_{O_2} ratio, within the range defined for mild acute lung injury, is frequently found and tends to improve in the hours and days following admission to the ICU.[106,145]

SUMMARY

Nowhere more than in the operating room or delivery suite do rapid changes in a patient's condition and the dynamic and unpredictable requirements of surgery affect critical respiratory function and mechanics. Instrumentation of the airway, inhalation of halogenated hydrocarbon anesthetics, motor block resulting from neuraxial anesthesia, CPB, and single-lung ventilation have significant effects on respiratory function. The altered physiology of acute and chronic cardiopulmonary disease may result in extreme changes in lung volumes, mechanics, and control of breathing. Anesthetic challenges range from common problems of reducing atelectasis and maintaining ventilated lung volume, to mitigating changes in ventilation-to-perfusion matching, to reducing the risk of ventilator-associated lung injury in response to inflammation and iatrogenic ischemia-reperfusion injury. The anesthesiologist must integrate and apply a sound understanding of basic physiologic principles under a wide variety of changing constraints to balance life support and optimize the delivery of safe and effective anesthesia with minimal risk to each patient.

ACKNOWLEDGMENTS

The authors thank Dr Brett Simon for his helpful criticism during the preparation of this article.

REFERENCES

1. Bates JH. Physics of expiratory flow limitation. Physiologic basis of respiratory disease. Hamilton (Ontario): BC Decker; 2005. p. 55–60.
2. Bolliger CT, Perruchoud AP. Functional evaluation of the lung resection candidate. Eur Respir J 1998;11(1):198–212.
3. Gilbreth EM, Weisman IM. Role of exercise stress testing in preoperative evaluation of patients for lung resection. Clin Chest Med 1994;15(2):389–403.
4. Beckles MA, Spiro SG, Colice GL, et al. The physiologic evaluation of patients with lung cancer being considered for resectional surgery. Chest 2003; 123(Suppl 1):105S–14S.
5. Pate P, Tenholder MF, Griffin JP, et al. Preoperative assessment of the high-risk patient for lung resection. Ann Thorac Surg 1996;61(5):1494–500.
6. Mittman C. Assessment of operative risk in thoracic surgery. Am Rev Respir Dis 1961;84:197–207.
7. Ferguson MK, Little L, Rizzo L, et al. Diffusing capacity predicts morbidity and mortality after pulmonary resection. J Thorac Cardiovasc Surg 1988;96(6): 894–900.
8. Nagasaki F, Flehinger BJ, Martini N. Complications of surgery in the treatment of carcinoma of the lung. Chest 1982;82(1):25–9.
9. Carlens E. A new flexible double-lumen catheter for bronchospirometry. J Thorac Surg 1949;18(5):742–6.
10. Jacobaeus HC, Frenckner P, Björkman S. Some attempts at determining the volume and function of each lung separately. Acta Med Scand 1932;79: 174–215.
11. Neuhaus H, Cherniack NS. A bronchospirometric method of estimating the effect of pneumonectomy on the maximum breathing capacity. J Thorac Cardiovasc Surg 1968;55:144–8.
12. Ali MK, Mountain CF, Ewer MS, et al. Predicting loss of pulmonary function after pulmonary resection for bronchogenic carcinoma. Chest 1980;77(3):337–42.
13. Tonnesen KH, Dige-Petersen H, Lund JO, et al. Lung split function test and pneumonectomy. A lower limit for operability. Scand J Thorac Cardiovasc Surg 1978;12(2):133–6.
14. Kristersson S, Arborelius M Jr, Jungquist G, et al. Prediction of ventilatory capacity after lobectomy. Scand J Respir Dis 1973;54(6):315–25.
15. Kristersson S, Lindell SE, Svanberg L. Prediction of pulmonary function loss due to pneumonectomy using 133 Xe-radiospirometry. Chest 1972;62(6):694–8.
16. Ellis DA, Hawkins T, Gibson GJ, et al. Role of lung scanning in assessing the resectability of bronchial carcinoma. Thorax 1983;38(4):261–6.
17. Boysen PG, Harris JO, Block AJ, et al. Prospective evaluation for pneumonectomy using perfusion scanning: follow-up beyond one year. Chest 1981;80(2):163–6.
18. Olsen GN, Block AJ, Tobias JA. Prediction of postpneumonectomy pulmonary function using quantitative macroaggregate lung scanning. Chest 1974;66(1): 13–6.
19. Kearney DJ, Lee TH, Reilly JJ, et al. Assessment of operative risk in patients undergoing lung resection. Importance of predicted pulmonary function. Chest 1994;105(3):753–9.

20. Markos J, Mullan BP, Hillman DR, et al. Preoperative assessment as a predictor of mortality and morbidity after lung resection. Am Rev Respir Dis 1989;139(4): 902–10.
21. Olsen GN, Block AJ, Swenson EW, et al. Pulmonary function evaluation of the lung resection candidate: a prospective study. Am Rev Respir Dis 1975; 111(4):379–87.
22. Cerfolio RJ, Allen MS, Trastek VF, et al. Lung resection in patients with compromised pulmonary function. Ann Thorac Surg 1996;62(2):348–51.
23. Edwards MA, Hazelrigg S, Naunheim KS. The national emphysema treatment trial: summary and update. Thorac Surg Clin 2009;19(2):169–85.
24. Ingenito EP, Evans RB, Loring SH, et al. Relation between preoperative inspiratory lung resistance and the outcome of lung-volume-reduction surgery for emphysema. N Engl J Med 1998;338(17):1181–5.
25. Ninan M, Sommers KE, Landreneau RJ, et al. Standardized exercise oximetry predicts postpneumonectomy outcome. Ann Thorac Surg 1997;64(2):328–33.
26. Ribas J, Diaz O, Barbera JA, et al. Invasive exercise testing in the evaluation of patients at high-risk for lung resection. Eur Respir J 1998;12(6):1429–35.
27. Pierce RJ, Copland JM, Sharpe K, et al. Preoperative risk evaluation for lung cancer resection: predicted postoperative product as a predictor of surgical mortality. Am J Respir Crit Care Med 1994;150(4):947–55.
28. BTS guidelines: guidelines on the selection of patients with lung cancer for surgery. Thorax 2001;56(2):89–108.
29. Gravenstein JS, Paulus DA, Hayes TJ. Capnography in clinical practice. Boston: Butterworth Publishers; 1989.
30. Fernandez-Perez ER, Keegan MT, Brown DR, et al. Intraoperative tidal volume as a risk factor for respiratory failure after pneumonectomy. Anesthesiology 2006;105(1):14–8.
31. Musch G, Foti G, Cereda M, et al. Lung and chest wall mechanics in normal anaesthetized subjects and in patients with COPD at different PEEP levels. Eur Respir J 1997;10(11):2545–52.
32. Benumof JL. One-lung ventilation and hypoxic pulmonary vasoconstriction: implications for anesthetic management. Anesth Analg 1985;64(8):821–33.
33. Valenza F, Ronzoni G, Perrone L, et al. Positive end-expiratory pressure applied to the dependent lung during one-lung ventilation improves oxygenation and respiratory mechanics in patients with high FEV1. Eur J Anaesthesiol 2004; 21(12):938–43.
34. Fujiwara M, Abe K, Mashimo T. The effect of positive end-expiratory pressure and continuous positive airway pressure on the oxygenation and shunt fraction during one-lung ventilation with propofol anesthesia. J Clin Anesth 2001;13(7): 473–7.
35. Johansen B, Melsom MN, Flatebo T, et al. Time course and pattern of pulmonary flow distribution following unilateral airway occlusion in sheep. Clin Sci (Lond) 1998;94(4):453–60.
36. Vidal Melo MF. Effect of cardiac output on pulmonary gas exchange: role of diffusion limitation with VA/Q mismatch. Respir Physiol 1998;113(1):23–32.
37. Musch G, Harris RS, Vidal Melo MF, et al. Mechanism by which a sustained inflation can worsen oxygenation in acute lung injury. Anesthesiology 2004;100(2): 323–30.
38. Katz JA, Laverne RG, Fairley HB, et al. Pulmonary oxygen exchange during endobronchial anesthesia: effect of tidal volume and PEEP. Anesthesiology 1982; 56(3):164–71.

39. Cohen E, Eisenkraft JB, Thys DM, et al. Oxygenation and hemodynamic changes during one-lung ventilation: effects of CPAP10, PEEP10, and CPAP10/PEEP10. J Cardiothorac Anesth 1988;2(1):34–40.
40. Slinger P, Triolet W, Wilson J. Improving arterial oxygenation during one-lung ventilation. Anesthesiology 1988;68(2):291–5.
41. Domino KB, Borowec L, Alexander CM, et al. Influence of isoflurane on hypoxic pulmonary vasoconstriction in dogs. Anesthesiology 1986;64(4):423–9.
42. Spies C, Zaune U, Pauli MH, et al. [A comparison of enflurane and propofol in thoracic surgery]. Anaesthesist 1991;40(1):14–8.
43. Benumof JL, Wahrenbrock EA. Local effects of anesthetics on regional hypoxic pulmonary vasoconstriction. Anesthesiology 1975;43(5):525–32.
44. Kellow NH, Scott AD, White SA, et al. Comparison of the effects of propofol and isoflurane anaesthesia on right ventricular function and shunt fraction during thoracic surgery. Br J Anaesth 1995;75(5):578–82.
45. Abe K, Shimizu T, Takashina M, et al. The effects of propofol, isoflurane, and sevoflurane on oxygenation and shunt fraction during one-lung ventilation. Anesth Analg 1998;87(5):1164–9.
46. Satoh D, Sato M, Kaise A, et al. Effects of isoflurane on oxygenation during one-lung ventilation in pulmonary emphysema patients. Acta Anaesthesiol Scand 1998;42(10):1145–8.
47. Easley R, Mulreany D, Lancaster C, et al. Redistribution of pulmonary blood flow impacts thermodilution-based extravascular lung water measurements in a model of acute lung injury. Anesthesiology 2009;111(5):1065–74.
48. Easley RB, Fuld MK, Fernandez-Bustamante A, et al. Mechanism of hypoxemia in acute lung injury evaluated by multidetector-row CT. Acad Radiol 2006;13(7): 916–21.
49. Gust R, Kozlowski J, Stephenson AH, et al. Synergistic hemodynamic effects of low-dose endotoxin and acute lung injury. Am J Respir Crit Care Med 1998; 157(6 Pt 1):1919–26.
50. Ichinose F, Zapol W, Sapirstein A, et al. Attenuation of hypoxic pulmonary vasoconstriction by endotoxemia requires 5-lipoxygenase in mice. Circ Res 2001; 88(8):832–8.
51. Silva-Costa-Gomes T, Gallart L, Vallès J, et al. Low- vs high-dose almitrine combined with nitric oxide to prevent hypoxia during open-chest one-lung ventilation. Br J Anaesth 2005;95(3):410–6.
52. Groeben H, Schafer B, Pavlakovic G, et al. Lung function under high thoracic segmental epidural anesthesia with ropivacaine or bupivacaine in patients with severe obstructive pulmonary disease undergoing breast surgery. Anesthesiology 2002;96(3):536–41.
53. Garutti I, Quintana B, Olmedilla L, et al. Arterial oxygenation during one-lung ventilation: combined versus general anesthesia. Anesth Analg 1999;88(3): 494–9.
54. Brister N, Barnette R, Kim V, et al. Anesthetic considerations in candidates for lung volume reduction surgery. Proc Am Thorac Soc 2008;5(4):432–7.
55. Hillier J, Gillbe C. Anaesthesia for lung volume reduction surgery. Anaesthesia 2003;58(12):1210–9.
56. Guerin C, Coussa ML, Eissa NT, et al. Lung and chest wall mechanics in mechanically ventilated COPD patients. J Appl Physiol 1993;74(4):1570–80.
57. Samain E, Biard M, Farah E, et al. Monitoring expired oxygen fraction in preoxygenation of patients with chronic obstructive pulmonary disease. Ann Fr Anesth Reanim 2002;21(1):14–9.

58. Hedenstierna G, Strandberg A, Brismar B, et al. Functional residual capacity, thoracoabdominal dimensions, and central blood volume during general anesthesia with muscle paralysis and mechanical ventilation. Anesthesiology 1985; 62(3):247–54.
59. Hedenstierna G, Strandberg A, Brismar B, et al. What causes the lowered FRC during anaesthesia? Clin Physiol 1985;5(Suppl 3):133–41.
60. Rothen HU, Sporre B, Engberg G, et al. Airway closure, atelectasis and gas exchange during general anaesthesia. Br J Anaesth 1998;81(5):681–6.
61. Brismar B, Hedenstierna G, Lundquist H, et al. Pulmonary densities during anesthesia with muscular relaxation–a proposal of atelectasis. Anesthesiology 1985;62(4):422–8.
62. Davis WB, Rennard SI, Bitterman PB, et al. Pulmonary oxygen toxicity. Early reversible changes in human alveolar structures induced by hyperoxia. N Engl J Med 1983;309(15):878–83.
63. Edmark L, Kostova-Aherdan K, Enlund M, et al. Optimal oxygen concentration during induction of general anesthesia. Anesthesiology 2003;98(1):28–33.
64. Tokics L, Hedenstierna G, Strandberg A, et al. Lung collapse and gas exchange during general anesthesia: effects of spontaneous breathing, muscle paralysis, and positive end-expiratory pressure. Anesthesiology 1987;66(2):157–67.
65. Tokics L, Hedenstierna G, Svensson L, et al. V/Q distribution and correlation to atelectasis in anesthetized paralyzed humans. J Appl Physiol 1996;81(4): 1822–33.
66. Dantzker DR, Wagner PD, West JB. Proceedings: instability of poorly ventilated lung units during oxygen breathing. J Physiol (Lond) 1974;242(2):72P.
67. Coussa M, Proietti S, Schnyder P, et al. Prevention of atelectasis formation during the induction of general anesthesia in morbidly obese patients. Anesth Analg 2004;98(5):1491–5.
68. Rusca M, Proietti S, Schnyder P, et al. Prevention of atelectasis formation during induction of general anesthesia. Anesth Analg 2003;97(6):1835–9.
69. Gunnarsson L, Tokics L, Lundquist H, et al. Chronic obstructive pulmonary disease and anaesthesia: formation of atelectasis and gas exchange impairment. Eur Respir J 1991;4(9):1106–16.
70. Athanasiou T, Al-Ruzzeh S, Del Stanbridge R, et al. Is the female gender an independent predictor of adverse outcome after off-pump coronary artery bypass grafting? Ann Thorac Surg 2003;75(4):1153–60.
71. Daganou M, Dimopoulou I, Michalopoulos N, et al. Respiratory complications after coronary artery bypass surgery with unilateral or bilateral internal mammary artery grafting. Chest 1998;113(5):1285–9.
72. Taggart DP, el-Fiky M, Carter R, et al. Respiratory dysfunction after uncomplicated cardiopulmonary bypass. Ann Thorac Surg 1993;56(5):1123–8.
73. Hammermeister KE, Burchfiel C, Johnson R, et al. Identification of patients at greatest risk for developing major complications at cardiac surgery. Circulation 1990;82(Suppl 5):IV380–9.
74. Sundar S, Novack V, Jervis K, et al. Influence of low tidal volume ventilation on time to extubation in cardiac surgical patients. Anesthesiology 2011;114(5): 1102–10.
75. Milot J, Perron J, Lacasse Y, et al. Incidence and predictors of ARDS after cardiac surgery. Chest 2001;119(3):884–8.
76. Webb HH, Tierney DF. Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure. Am Rev Respir Dis 1974;110(5):556–65.

77. Amato MB, Barbas CS, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998;338(6):347–54.
78. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342(18):1301–8.
79. Altemeier WA, Matute-Bello G, Frevert CW, et al. Mechanical ventilation with moderate tidal volumes synergistically increases lung cytokine response to systemic endotoxin. Am J Physiol Lung Cell Mol Physiol 2004;287(3):L533–42.
80. Costa EL, Musch G, Winkler T, et al. Mild endotoxemia during mechanical ventilation produces spatially heterogeneous pulmonary neutrophilic inflammation in sheep. Anesthesiology 2010;112(3):658–69.
81. Bruins P, te Velthuis H, Yazdanbakhsh AP, et al. Activation of the complement system during and after cardiopulmonary bypass surgery: postsurgery activation involves C-reactive protein and is associated with postoperative arrhythmia. Circulation 1997;96(10):3542–8.
82. Massoudy P, Zahler S, Becker BF, et al. Evidence for inflammatory responses of the lungs during coronary artery bypass grafting with cardiopulmonary bypass. Chest 2001;119(1):31–6.
83. Andersen LW, Baek L, Degn H, et al. Presence of circulating endotoxins during cardiac operations. J Thorac Cardiovasc Surg 1987;93(1):115–9.
84. Riddington DW, Venkatesh B, Boivin CM, et al. Intestinal permeability, gastric intramucosal pH, and systemic endotoxemia in patients undergoing cardiopulmonary bypass. JAMA 1996;275(13):1007–12.
85. Kuratani T, Matsuda H, Sawa Y, et al. Experimental study in a rabbit model of ischemia-reperfusion lung injury during cardiopulmonary bypass. J Thorac Cardiovasc Surg 1992;103(3):564–8.
86. Chai PJ, Williamson JA, Lodge AJ, et al. Effects of ischemia on pulmonary dysfunction after cardiopulmonary bypass. Ann Thorac Surg 1999;67(3):731–5.
87. Dodd-O JM, Welsh LE, Salazar JD, et al. Effect of bronchial artery blood flow on cardiopulmonary bypass-induced lung injury. Am J Physiol Heart Circ Physiol 2004;286(2):H693–700.
88. Schlensak C, Doenst T, Preusser S, et al. Cardiopulmonary bypass reduction of bronchial blood flow: a potential mechanism for lung injury in a neonatal pig model. J Thorac Cardiovasc Surg 2002;123(6):1199–205.
89. Koch CG, Li L, Sessler DI, et al. Duration of red-cell storage and complications after cardiac surgery. N Engl J Med 2008;358(12):1229–39.
90. Laffey JG, Boylan JF, Cheng DC. The systemic inflammatory response to cardiac surgery: implications for the anesthesiologist. Anesthesiology 2002; 97(1):215–52.
91. Carvalho AR, Ichinose F, Schettino IA, et al. Tidal lung recruitment and exhaled nitric oxide during coronary artery bypass grafting in patients with and without chronic obstructive pulmonary disease. Lung 2011;189(6):499–509.
92. Chaney MA, Nikolov MP, Blakeman BP, et al. Protective ventilation attenuates postoperative pulmonary dysfunction in patients undergoing cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2000;14(5):514–8.
93. Zupancich E, Paparella D, Turani F, et al. Mechanical ventilation affects inflammatory mediators in patients undergoing cardiopulmonary bypass for cardiac surgery: a randomized clinical trial. J Thorac Cardiovasc Surg 2005;130(2): 378–83.

94. Koner O, Celebi S, Balci H, et al. Effects of protective and conventional mechanical ventilation on pulmonary function and systemic cytokine release after cardiopulmonary bypass. Intensive Care Med 2004;30(4):620–6.
95. Pizov R, Weiss YG, Oppenheim-Eden A, et al. High oxygen concentration exacerbates cardiopulmonary bypass-induced lung injury. J Cardiothorac Vasc Anesth 2000;14(5):519–23.
96. Barnas GM, Gilbert TB, Watson RJ, et al. Respiratory mechanics in the open chest: effects of parietal pleurae. Respir Physiol 1996;104(1):63–70.
97. Jonmarker C, Nordstrom L, Werner O. Changes in functional residual capacity during cardiac surgery. Br J Anaesth 1986;58(4):428–32.
98. Guizilini S, Gomes WJ, Faresin SM, et al. Influence of pleurotomy on pulmonary function after off-pump coronary artery bypass grafting. Ann Thorac Surg 2007; 84(3):817–22.
99. Peng MJ, Vargas FS, Cukier A, et al. Postoperative pleural changes after coronary revascularization. Comparison between saphenous vein and internal mammary artery grafting. Chest 1992;101(2):327–30.
100. Singh NP, Vargas FS, Cukier A, et al. Arterial blood gases after coronary artery bypass surgery. Chest 1992;102(5):1337–41.
101. Gilbert TB, Barnas GM, Sequeira AJ. Impact of pleurotomy, continuous positive airway pressure, and fluid balance during cardiopulmonary bypass on lung mechanics and oxygenation. J Cardiothorac Vasc Anesth 1996;10(7): 844–9.
102. Gullu AU, Ekinci A, Sensoz Y, et al. Preserved pleural integrity provides better respiratory function and pain score after coronary surgery. J Cardiovasc Surg 2009;24(4):374–8.
103. Hachenberg T, Tenling A, Hansson HE, et al. The ventilation-perfusion relation and gas exchange in mitral valve disease and coronary artery disease. Implications for anesthesia, extracorporeal circulation, and cardiac surgery. Anesthesiology 1997;86(4):809–17.
104. Pennock JL, Pierce WS, Waldhausen JA. The management of the lungs during cardiopulmonary bypass. Surg Gynecol Obstet 1977;145(6):917–27.
105. Messent M, Sullivan K, Keogh BF, et al. Adult respiratory distress syndrome following cardiopulmonary bypass: incidence and prediction. Anaesthesia 1992;47(3):267–8.
106. Apostolakis E, Filos KS, Koletsis E, et al. Lung dysfunction following cardiopulmonary bypass. J Cardiovasc Surg 2010;25(1):47–55.
107. Ng CS, Wan S, Yim AP, et al. Pulmonary dysfunction after cardiac surgery. Chest 2002;121(4):1269–77.
108. Wasowicz M, Sobczynski P, Drwila R, et al. Air-blood barrier injury during cardiac operations with the use of cardiopulmonary bypass (CPB). An old story? A morphological study. Scand Cardiovasc J 2003;37(4):216–21.
109. Stanley TH, Liu WS, Gentry S. Effects of ventilatory techniques during cardiopulmonary bypass on post-bypass and postoperative pulmonary compliance and shunt. Anesthesiology 1977;46(6):391–5.
110. Loeckinger A, Kleinsasser A, Lindner KH, et al. Continuous positive airway pressure at 10 cm H_2O during cardiopulmonary bypass improves postoperative gas exchange. Anesth Analg 2000;91(3):522–7.
111. Berry CB, Butler PJ, Myles PS. Lung management during cardiopulmonary bypass: is continuous positive airways pressure beneficial? Br J Anaesth 1993; 71(6):864–8.

112. Magnusson L, Zemgulis V, Wicky S, et al. Effect of CPAP during cardiopulmonary bypass on postoperative lung function. An experimental study. Acta Anaesthesiol Scand 1998;42(10):1133–8.
113. Imura H, Caputo M, Lim K, et al. Pulmonary injury after cardiopulmonary bypass: beneficial effects of low-frequency mechanical ventilation. J Thorac Cardiovasc Surg 2009;137(6):1530–7.
114. Siepe M, Goebel U, Mecklenburg A, et al. Pulsatile pulmonary perfusion during cardiopulmonary bypass reduces the pulmonary inflammatory response. Ann Thorac Surg 2008;86(1):115–22.
115. Simon BA, Tsuzaki K, Venegas JG. Changes in regional lung mechanics and ventilation distribution after unilateral pulmonary artery occlusion. J Appl Physiol 1997;82(3):882–91.
116. Tomic V, Russwurm S, Moller E, et al. Transcriptomic and proteomic patterns of systemic inflammation in on-pump and off-pump coronary artery bypass grafting. Circulation 2005;112(19):2912–20.
117. Friedman M, Sellke FW, Wang SY, et al. Parameters of pulmonary injury after total or partial cardiopulmonary bypass. Circulation 1994;90(5 Pt 2):II262–8.
118. Al-Ruzzeh S, Hoare G, Marczin N, et al. Off-pump coronary artery bypass surgery is associated with reduced neutrophil activation as measured by the expression of CD11b: a prospective randomized study. Heart Surg Forum 2003;6(2):89–93.
119. Al-Ruzzeh S, Nakamura K, Athanasiou T, et al. Does off-pump coronary artery bypass (OPCAB) surgery improve the outcome in high-risk patients?: a comparative study of 1398 high-risk patients. Eur J Cardiothorac Surg 2003;23(1): 50–5.
120. Staton GW, Williams WH, Mahoney EM, et al. Pulmonary outcomes of off-pump vs on-pump coronary artery bypass surgery in a randomized trial. Chest 2005; 127(3):892–901.
121. Aydin NB, Gercekoglu H, Aksu B, et al. Endotoxemia in coronary artery bypass surgery: a comparison of the off-pump technique and conventional cardiopulmonary bypass. J Thorac Cardiovasc Surg 2003;125(4):843–8.
122. Cavalca V, Sisillo E, Veglia F, et al. Isoprostanes and oxidative stress in off-pump and on-pump coronary bypass surgery. Ann Thorac Surg 2006;81(2):562–7.
123. Hazama S, Eishi K, Yamachika S, et al. Inflammatory response after coronary revascularization: off-pump versus on-pump (heparin-coated circuits and poly2methoxyethylacrylate-coated circuits). Ann Thorac Cardiovasc Surg 2004; 10(2):90–6.
124. Wan S, Izzat MB, Lee TW, et al. Avoiding cardiopulmonary bypass in multivessel CABG reduces cytokine response and myocardial injury. Ann Thorac Surg 1999;68(1):52–6 [discussion: 56–7].
125. Tschernko EM, Bambazek A, Wisser W, et al. Intrapulmonary shunt after cardiopulmonary bypass: the use of vital capacity maneuvers versus off-pump coronary artery bypass grafting. J Thorac Cardiovasc Surg 2002;124(4):732–8.
126. Roosens C, Heerman J, De Somer F, et al. Effects of off-pump coronary surgery on the mechanics of the respiratory system, lung, and chest wall: comparison with extracorporeal circulation. Crit Care Med 2002;30(11):2430–7.
127. Albu G, Babik B, Kesmarky K, et al. Changes in airway and respiratory tissue mechanics after cardiac surgery. Ann Thorac Surg 2010;89(4):1218–26.
128. Guler M, Kirali K, Toker ME, et al. Different CABG methods in patients with chronic obstructive pulmonary disease. Ann Thorac Surg 2001;71(1):152–7.

129. Moller CH, Perko MJ, Lund JT, et al. No major differences in 30-day outcomes in high-risk patients randomized to off-pump versus on-pump coronary bypass surgery: the best bypass surgery trial. Circulation 2010;121(4):498–504.
130. Magnusson L, Zemgulis V, Tenling A, et al. Use of a vital capacity maneuver to prevent atelectasis after cardiopulmonary bypass: an experimental study. Anesthesiology 1998;88(1):134–42.
131. Rothen HU, Sporre B, Engberg G, et al. Influence of gas composition on recurrence of atelectasis after a reexpansion maneuver during general anesthesia. Anesthesiology 1995;82(4):832–42.
132. Minkovich L, Djaiani G, Katznelson R, et al. Effects of alveolar recruitment on arterial oxygenation in patients after cardiac surgery: a prospective, randomized, controlled clinical trial. J Cardiothorac Vasc Anesth 2007;21(3):375–8.
133. Murphy GS, Szokol JW, Curran RD, et al. Influence of a vital capacity maneuver on pulmonary gas exchange after cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2001;15(3):336–40.
134. Prakash O, Meij S, Bos E, et al. Lung mechanics in patients undergoing mitral valve replacement. The value of monitoring of compliance and resistance. Crit Care Med 1978;6(6):370–2.
135. Auler JO Jr, Zin WA, Caldeira MP, et al. Pre- and postoperative inspiratory mechanics in ischemic and valvular heart disease. Chest 1987;92(6):984–90.
136. Andersen NB, Ghia J. Pulmonary function, cardiac status, and postoperative course in relation to cardiopulmonary bypass. J Thorac Cardiovasc Surg 1970;59(4):474–83.
137. Barnas GM, Watson RJ, Green MD, et al. Lung and chest wall mechanical properties before and after cardiac surgery with cardiopulmonary bypass. J Appl Physiol 1994;76(1):166–75.
138. Ghia J, Andersen NB. Pulmonary function and cardiopulmonary bypass. JAMA 1970;212(4):593–7.
139. Prakash O, Meij S, v d Borden B, et al. Cardiorespiratory monitoring during open heart surgery. Crit Care Med 1981;9(7):530–5.
140. Babik B, Asztalos T, Petak F, et al. Changes in respiratory mechanics during cardiac surgery. Anesth Analg 2003;96(5):1280–7.
141. Barnas GM, Mills PJ, Mackenzie CF, et al. Dependencies of respiratory system resistance and elastance on amplitude and frequency in the normal range of breathing. Am Rev Respir Dis 1991;143(2):240–4.
142. Heldt GP, Peters RM. A simplified method to determine functional residual capacity during mechanical ventilation. Chest 1978;74(5):492–6.
143. Kaczka DW, Hager DN, Hawley ML, et al. Quantifying mechanical heterogeneity in canine acute lung injury: impact of mean airway pressure. Anesthesiology 2005;103(2):306–17.
144. Kaczka DW, Brown RH, Mitzner W. Assessment of heterogeneous airway constriction in dogs: a structure-function analysis. J Appl Physiol 2009;106(2):520–30.
145. Ranieri VM, Vitale N, Grasso S, et al. Time-course of impairment of respiratory mechanics after cardiac surgery and cardiopulmonary bypass. Crit Care Med 1999;27(8):1454–60.
146. Zin WA, Caldeira MP, Cardoso WV, et al. Expiratory mechanics before and after uncomplicated heart surgery. Chest 1989;95(1):21–8.
147. Garzon AA, Seltzer B, Lichtenstein S, et al. Influence of open-heart surgery on respiratory work. Dis Chest 1967;52(3):392–6.

148. Habre W, Schutz N, Pellegrini M, et al. Preoperative pulmonary hemodynamics determines changes in airway and tissue mechanics following surgical repair of congenital heart diseases. Pediatr Pulmonol 2004;38(6):470–6.
149. Hantos Z, Daroczy B, Suki B, et al. Input impedance and peripheral inhomogeneity of dog lungs. J Appl Physiol 1992;72(1):168–78.
150. Hantos Z, Petak F, Adamicza A, et al. Differential responses of global airway, terminal airway, and tissue impedances to histamine. J Appl Physiol 1995; 79(5):1440–8.
151. Lutchen KR, Hantos Z, Petak F, et al. Airway inhomogeneities contribute to apparent lung tissue mechanics during constriction. J Appl Physiol 1996; 80(5):1841–9.
152. Suki B, Petak F, Adamicza A, et al. Airway and tissue constrictions are greater in closed than in open-chest conditions. Respir Physiol 1997;108(2):129–41.
153. Royston D, Minty BD, Higenbottam TW, et al. The effect of surgery with cardiopulmonary bypass on alveolar-capillary barrier function in human beings. Ann Thorac Surg 1985;40(2):139–43.
154. Hachenberg T, Lundquist H, Tokics L, et al. Analysis of lung density by computed tomography before and during general anaesthesia. Acta Anaesthesiol Scand 1993;37(6):549–55.
155. Magnusson L, Zemgulis V, Wicky S, et al. Atelectasis is a major cause of hypoxemia and shunt after cardiopulmonary bypass: an experimental study. Anesthesiology 1997;87(5):1153–63.
156. Nahas RA, Melrose DG, Sykes MK, et al. Post-perfusion lung syndrome: effect of homologous blood. Lancet 1965;2(7406):254–6.
157. Nahas RA, Melrose DG, Sykes MK, et al. Post-perfusion lung syndrome: role of circulatory exclusion. Lancet 1965;2(7406):251–4.
158. Rea HH, Harris EA, Seelye ER, et al. The effects of cardiopulmonary bypass upon pulmonary gas exchange. J Thorac Cardiovasc Surg 1978;75(1):104–20.
159. Weiss YG, Merin G, Koganov E, et al. Postcardiopulmonary bypass hypoxemia: a prospective study on incidence, risk factors, and clinical significance. J Cardiothorac Vasc Anesth 2000;14(5):506–13.
160. Apostolakis EE, Koletsis EN, Baikoussis NG, et al. Strategies to prevent intraoperative lung injury during cardiopulmonary bypass. J Cardiothorac Surg 2010; 5(1):1.
161. Groeneveld AB, Jansen EK, Verheij J. Mechanisms of pulmonary dysfunction after on-pump and off-pump cardiac surgery: a prospective cohort study. J Cardiothorac Surg 2007;2:11.
162. Hachenberg T, Tenling A, Nystrom SO, et al. Ventilation-perfusion inequality in patients undergoing cardiac surgery. Anesthesiology 1994;80(3):509–19.
163. Lindberg P, Gunnarsson L, Tokics L, et al. Atelectasis and lung function in the postoperative period. Acta Anaesthesiol Scand 1992;36(6):546–53.
164. Strandberg A, Tokics L, Brismar B, et al. Atelectasis during anaesthesia and in the postoperative period. Acta Anaesthesiol Scand 1986;30(2):154–8.
165. Anjou-Lindskog E, Broman L, Broman M, et al. Effects of oxygen on central haemodynamics and VA/Q distribution after coronary bypass surgery. Acta Anaesthesiol Scand 1983;27(5):378–84.
166. Anjou-Lindskog E, Broman L, Broman M, et al. Effects of nitroglycerin on central haemodynamics and VA/Q distribution during ventilation with FIO2 = 1.0 in patients after coronary bypass surgery. Acta Anaesthesiol Scand 1984;28(1): 27–33.

167. Anjou-Lindskog E, Broman L, Holmgren A. Effects of nitroglycerin on central haemodynamics and VA/Q distribution early after coronary bypass surgery. Acta Anaesthesiol Scand 1982;26(5):489–97.
168. Fletcher R, Malmkvist G, Niklason L, et al. On-line measurement of gas-exchange during cardiac surgery. Acta Anaesthesiol Scand 1986;30(4):295–9.
169. Fletcher R, Veintemilla F. Changes in the arterial to end-tidal PCO_2 differences during coronary artery bypass grafting. Acta Anaesthesiol Scand 1989;33(8): 656–9.
170. Myles PS, Story DA, Higgs MA, et al. Continuous measurement of arterial and end-tidal carbon dioxide during cardiac surgery: Pa-ETCO2 gradient. Anaesth Intensive Care 1997;25(5):459–63.
171. Tenling A, Hachenberg T, Tyden H, et al. Atelectasis and gas exchange after cardiac surgery. Anesthesiology 1998;89(2):371–8.
172. Barbera JA, Ramirez J, Roca J, et al. Lung structure and gas exchange in mild chronic obstructive pulmonary disease. Am Rev Respir Dis 1990;141(4 Pt 1): 895–901.
173. Peinado VI, Barbera JA, Ramirez J, et al. Endothelial dysfunction in pulmonary arteries of patients with mild COPD. Am J Physiol 1998;274(6 Pt 1):L908–13.
174. Vidal Melo MF, Winkler T, Harris RS, et al. Spatial heterogeneity of lung perfusion assessed with (13)N PET as a vascular biomarker in chronic obstructive pulmonary disease. J Nucl Med 2010;51(1):57–65.
175. Wagner PD, Dantzker DR, Dueck R, et al. Ventilation-perfusion inequality in chronic obstructive pulmonary disease. J Clin Invest 1977;59(2):203–16.
176. Vidal Melo MF, Ichinose F, Walker J, et al. Intraoperative changes in respiratory function during on-pump CABG in COPD patients. Anesthesiology 2006;105: A1221.
177. Kaczka DW, Ingenito EP, Body SC, et al. Inspiratory lung impedance in COPD: effects of PEEP and immediate impact of lung volume reduction surgery. J Appl Physiol 2001;90(5):1833–41.
178. Caramez MP, Borges JB, Tucci MR, et al. Paradoxical responses to positive end-expiratory pressure in patients with airway obstruction during controlled ventilation. Crit Care Med 2005;33(7):1519–28.
179. Kawahito S, Kitahata H, Tanaka K, et al. Bronchospasm induced by cardiopulmonary bypass. Ann Thorac Cardiovasc Surg 2001;7(1):49–51.
180. Morel DR, Zapol WM, Thomas SJ, et al. C5a and thromboxane generation associated with pulmonary vaso- and broncho-constriction during protamine reversal of heparin. Anesthesiology 1987;66(5):597–604.
181. Gwyn DR, Lindeman KS, Hirshman CA. Inhaled nitric oxide attenuates bronchoconstriction in canine peripheral airways. Am J Respir Crit Care Med 1996; 153(2):604–9.
182. Lindeman KS, Aryana A, Hirshman CA. Direct effects of inhaled nitric oxide on canine peripheral airways. J Appl Physiol 1995;78(5):1898–903.
183. Matera MG. Nitric oxide and airways. Pulm Pharmacol Ther 1998;11(5–6): 341–8.
184. Barbera JA, Roger N, Roca J, et al. Worsening of pulmonary gas exchange with nitric oxide inhalation in chronic obstructive pulmonary disease. Lancet 1996; 347(8999):436–40.
185. de Prost N, El-Karak C, Avila M, et al. Changes in cysteinyl leukotrienes during and after cardiac surgery with cardiopulmonary bypass in patients with and without chronic obstructive pulmonary disease. J Thorac Cardiovasc Surg 2011;141(6): 1496–502.