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PULMONARY PATHOPHYSIOLOGY AND LUNG MECHANICS IN ANESTHESIOLOGY: A CASE-BASED OVERVIEW

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Abstract

The induction and maintenance of anesthesia, surgical requirements, and patients' unique pathophysiology all combine to create a setting in which our accumulated knowledge of respiratory physiology and lung mechanics take on immediate and central importance in patient management. In this review we will take a case-based approach to illustrate how the complex interactions between anesthesia, surgery, and patient disease impact patient care with respect to pulmonary pathophysiology and clinical decision-making. We will examine two disparate scenarios: a patient with chronic obstructive pulmonary disease undergoing a lung resection, and a patient with coronary artery disease undergoing cardiopulmonary bypass. In each example we will illustrate how important concepts in pulmonary physiology and respiratory mechanics impact clinical management decisions.

Keywords

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

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 ($\dot{V}/\dot{Q}$)

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Dr. Kaczka: Nil

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matching. Blood loss and fluid resuscitation, patient positioning requirements, surgical stress and inflammation, infections and sepsis, cardiopulmonary bypass, regional anesthesia, changing composition of inhaled gases, and many other issues arise during surgery that affect pulmonary function. Moreover, patients present with full spectra of cardiopulmonary pathologies of varying etiologies and severities.

In this review, we take a case-based approach to illustrate such complex interactions affect respiratory physiology and mechanics. First we consider an elderly patient with advanced chronic obstructive pulmonary disease (COPD) requiring a lung resection for cancer. We address preoperative risk stratification and prediction of post-operative 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 post-operative pain control. Next, we use the example of a patient undergoing coronary artery bypass grafting under cardiopulmonary bypass (CPB) to discuss mechanical ventilation, as well as 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, since 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 s (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 post-operative 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 intra- and postoperative respiratory complications. Spirometry in this patient revealed a pattern consistent with severe obstructive disease, as her FEV_1 was markedly reduced. This is due mainly to loss of lung recoil and of 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 resistors¹. In this situation, expiratory flow will become 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 pneumonectomies²⁻⁴. To account for patient age, stature, and gender, these limits are usually compared to predicted normal values. Perioperative risk increases substantially for FEV_1 of 40% to 70% of the predicted normal value^{5, 6}. Similarly, DLCO less than 50% to 60% of predicted is 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. Bronchspirometry 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 ¹³³Xe^{11–15}) or perfusion (as measured with ^{99m}Tc-Macroaggregates^{16–18}) of the lung portion to be resected. PPO FEV₁ has been shown to predict postoperative complications in one large study¹⁹. Perioperative morbidity and mortality may be substantial when PPO FEV₁ is less than 1 L or 40% of predicted^{15, 20, 21}. Operability should be regarded with skepticism when PPO FEV₁ is less than 0.7 L or 30% of predicted^{5, 20}. Long-term disability, as evidenced by the need for home oxygen, is also increased when PPO FEV₁ is less than 40%²². Similarly to FEV₁, PPO DLCO can be calculated from whole lung measurement of DLCO and regional measurements of ventilation or perfusion. Markos et al.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 demonstrated that patients with preoperative FEV₁ of 25–30% of predicted can undergo successful resection under certain conditions^{23, 24}. Finally, preoperative hypercapnia with PaCO₂ > 45 mmHg has been associated with increased risk of postoperative pulmonary complications, thus it is not likely an independent risk factor¹⁹, 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 complications²⁵, as has been 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 very low FEV₁, DLCO lower than 30% of predicted and arterial oxygen desaturation of 8% during mild exercise.

Preoperatively, an epidural catheter is placed between the 6th and 7th thoracic vertebrae for intra and postoperative analgesia. After induction of general anesthesia, the patient is intubated with a left-sided double-lumen endobronchial tube, which allows for independent lung ventilation. After intubation, the ventilator circuit is connected and a continuously rising exhaled CO₂ 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 Figure 1. The patient is ventilated with 100% oxygen, her arterial oxygen saturation is 100%, with plateau airway pressures of 25 cmH₂O. 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 CO₂ concentration rises. 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, resulting in a brisk blood loss of approximately 3 liters. Crystalloid is administered and a phenylephrine infusion is initiated to promote vasoconstriction and counteract the hypotension. Oxygen saturation initially rises to 96%, and then to 100% when the surgeon clamps the right pulmonary artery to control bleeding. In order to repair the vascular tear, the surgeon extends the resection to a bi-lobectomy, 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, due to the small inner diameter and increased length of each channel. This is especially true for the bronchial lumen. This may enhance the effects of increased airway resistance in COPD patients, further slowing expiration and leading to dynamic hyperinflation and air trapping. In this patient, the presence of dynamic hyperinflation can be inferred by the non-zero 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 rising exhaled CO₂ capnograph reflects the sequential emptying of short to long time constant units. Since units with longer time constants have reduced alveolar ventilation and higher local alveolar CO₂ concentrations, Phase III of the capnograph will steadily rise, achieving a final value that reflects truncation of expiration by the subsequent inspiration²⁹.

In the presence of expiratory flow limitation, dynamic hyperinflation occurs even when end-expiratory flow is very 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 due to increased intrathoracic pressure and decreased venous return, it may also have some favorable consequences. For example, increased end-expiratory lung volume allows for higher oxygen reserve, which is advantageous during single-lung ventilation by decreasing the propensity to atelectasis.

Physiological effects of unilateral ventilation and lateral decubitus position—

Unilateral ventilation is accompanied by a reduction of the distribution volume for tidal volume. Normally, the left lung 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 airway pressures for unilateral and bilateral ventilation³⁰, with modest increases in respiratory rate. In patients with expiratory flow limitation, higher rates may not be tolerated or will not improve effective alveolar ventilation³¹.

In the lateral decubitus position, the weight of the mediastinum and cephalad displacement of the lower diaphragm due to increased intra-abdominal pressure reduce FRC and the compliance of the dependent ventilated lung. This may be alleviated by judicious application of 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 will be supported by the higher lung volumes resulting from PEEP, and alveolar ventilation will improve. 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 prior to spontaneous ventilation and emergence.

Unilateral ventilation is also accompanied by shunt in the nonventilated lung, leading to arterial hypoxemia³⁴. Hypoxic pulmonary vasoconstriction (HPV) counteracts this hypoxemia, by increases pulmonary vascular resistance and diverting blood flow to the ventilated lung. Animal studies have shown that such flow diversion occurs within 30 s of unilateral bronchial occlusion, and blood flow to the occluded lung is approximately half that during double lung ventilation by two minutes³⁵. If HPV is intact, shunt fraction during single-lung ventilation may be only 20%–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 due to compression or absorption atelectasis (the latter favored by the use of high FiO₂ during unilateral ventilation). If these hypoxic compartments are substantial (i.e., greater than 70% of the lung), the effectiveness of HPV will be reduced since the normoxic portions of lung are not sufficient to receive diverted blood flow³².

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. Notably, her arterial saturation improved after blood loss and vasoconstrictor therapy. This was most likely due to the reduced shunt fraction associated with decreased cardiac output and pulmonary arterial pressure, since 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 $P\bar{V}O_2$ will result in lower arterial oxygen tension³⁶. Alternatively, 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 atelectasis³³. This 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 occur³⁷. The global effects of PEEP to the dependent lung thus represent the trade-off between these two opposing effects. It is therefore not surprising that some studies have shown PEEP to improve oxygenation during unilateral ventilation³⁴, while 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 cmH₂O 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 that of PEEP to the dependent lung for improving hypoxemia, it must be applied before the nonventilated lung is allowed to deflate completely to be maximally effective⁴⁰. CPAP may also interfere with surgical exposure. Some authors 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 to 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 falls 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 hypoxic pulmonary vasoconstriction

Inhalational anesthetics inhibit HPV because of their vasodilatory effect. This effect, however, appears to be much more pronounced *in vitro* and *ex vivo* than in the intact respiratory system. Domino et al.⁴¹ have shown a dose-response relation between isoflurane concentration and inhibition of HPV in vivo during canine one-lung ventilation. This effect appears to be small, since 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 et al⁴². Intravenous anesthetics, in particular propofol, seem to have even less (if any) of an inhibitory effect on HPV during unilateral ventilation^{42–45}. Consequently, it is 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 appears to be minimal⁴⁶.

Inflammation, as caused by systemic sepsis or localized pneumonia, is another potent inhibitor of HPV^{47–50}, and it exacerbates the hypoxemia due to shunt. Pharmacologic agents such as almitrine (which augments HPV) and inhaled nitric oxide (a selective pulmonary arterial vasodilator) have been demonstrated both separately and in concert to improve oxygenation during one lung ventilation⁵¹, 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 mcg/cc 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 post-thoracotomy pain. Effective pain relief is critical in facilitating deep breathing and coughing to minimize atelectasis and clear secretions. Two potential concerns, however, 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 et al.⁵² have shown that TEA leads to a ~11% decrease of FEV₁ and ~15% decrease of vital capacity (VC) in women with severe COPD or asthma. Because the ratio of FEV₁ to VC increased by 4%, they concluded that the decrease of FEV₁ and VC was due to mild motor blockade of respiratory muscles rather than to increased airway resistance resulting from increased bronchial tone due to 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 et al.⁵³ showed that when TEA was added to general anesthesia during unilateral ventilation for thoracic surgery, PaO₂ and shunt fraction were slightly worse (by ~60 mmHg and 5%, respectively) compared to general anesthesia alone. They hypothesized that this was due to 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 y/o female with history of severe three-vessel coronary artery disease and COPD is scheduled to undergo a 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 “pre-oxygenated” by breathing 100% oxygen through a mask before induction of anesthesia.

Pre-oxygenation and induction of anesthesia

Preoxygenation at the beginning of general anesthesia aims to avoid hypoxemia during the period of apnea required to obtain endotracheal intubation. The increased time constant inequalities present in COPD lungs⁵⁶ require longer preoxygenation times to achieve similar end-expiratory oxygen fractions in COPD than in normal lungs⁵⁷. General anesthesia and muscle paralysis results in decreased functional residual capacity (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 closure⁶⁰ in dependent lung regions due to tissue compression⁶¹, 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 atelectasis⁶⁶ or short term risks of oxygen toxicity⁶². Use of moderate PEEP (i.e., 6–10 cmH₂O) 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 compared to a healthy patient to develop atelectasis and shunt due to the reduced elastic recoil and air trapping in COPD⁶⁹.

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 h is one of the most frequent complications^{73, 74}, although development of acute respiratory distress is rare⁷⁵.

Mechanical ventilation can in itself produce lung injury⁷⁶, and ventilator settings can influence patient morbidity and mortality in intensive care units^{77, 78}. Furthermore a “two-

hit” condition, where the mechanical ventilation insult is accompanied by an inflammatory or other cellular level injurious stimulus, can significantly magnify the lung injury^{79, 80}. Surgical trauma, exposure to cardiopulmonary bypass (CPB)^{81, 82}, endotoxemia^{83, 84}, ischemia-reperfusion of the lung⁸⁵ including reduction of bronchial perfusion^{86–88}, and frequent blood transfusion⁸⁹, are some mechanisms associated with the inflammatory response in cardiac surgery that may amplify lung injury during mechanical ventilation⁹⁰. This is particularly important, since the physiologic mechanisms that produce ventilator associated lung injury (i.e., tidal recruitment and overinflation) are frequently present in patients with and without previous lung disease undergoing cardiac surgery⁹¹.

Previous studies suggest that intraoperative use of protective modes of ventilation, with higher PEEP values (10 cmH₂O) and lower tidal volumes (6–8 ml/kg of predicted body weight), reduce the inflammatory response and improve pulmonary mechanics in postoperative cardiac surgery patients (Figure 2)^{92, 93}. In one of these studies, the protective mode explicitly included a recruitment maneuver by increasing peak inspiratory pressure to 40 cmH₂O for 15 seconds. The inflammatory response for the cases of protective ventilation was characterized by lower levels of IL-6 and IL-8 in plasma and BAL fluid. Interestingly, protective ventilation did not prevent adverse effects of CPB in the lungs in one study⁹⁴, but these authors used a PEEP of 5 cmH₂O in their “protective mode” in contrast to 10 cmH₂O used in other studies. This suggests that low lung volumes may be an important component of VILI during cardiac surgery.

The fraction of inspired oxygen (F_IO₂) during cardiac surgery involves a balance between maximizing oxygenation while minimizing oxidative stress, absorption atelectasis, and ventilator induced lung injury. The use of F_IO₂=1.0 as compared to F_IO₂=0.5 throughout surgery is associated with delayed recovery of oxygenation and increased levels of tumor necrosis factor-alpha in bronchoalveolar lavage⁹⁵. 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 system⁹⁶. This reduction is partial because, in fact, the chest wall is not completely separated from the lungs but instead usually spread at the sternum, with remaining contact of lung and chest wall in dorsal and lateral areas. This may result in increased inflation of the lung FRC⁹⁷, with decreased elastance and resistance of the respiratory system and an inadvertently increased delivered tidal volume if pressure-controlled ventilation is used.

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

The left internal mammary artery (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. Due to its anatomical position, dissection of the LIMA usually involves the opening of the left pleura and packing of the left lung to facilitate exposure. Occasionally, 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}. In fact, 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 postoperatively in the left lung

of CABG patients than patients undergoing mitral valve repair¹⁰³, potentially a result of left internal mammary harvesting.

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

For many decades, pulmonary complications were a major cause of death following CPB¹⁰⁴. 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 parenchymal following CPB usually reveals mild changes. Although data on histopathological changes after CPB are limited due to the difficulty in obtaining samples, microbiopsies performed 20 min following CPB show poorly aerated alveoli, different degrees of alveolar edema, thickening of alveolar septa, alveolar capillaries with perivascular halo, and alveolar flooding¹⁰⁸. Neutrophils can be found in the interstitium and alveolar space, with large alveolar macrophages containing numerous vacuoles indicative of activation. Electron microscopy may demonstrate additional details on injury to the alveolar-capillary barrier. In some cases, only edema of the endothelial cells can be 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 (i.e., airspaces filled with edema fluid). Many PMN are found in blood vessels. Pulmonary surfactant appears to be normal in well-aerated alveoli, although not in fluid filled alveoli¹⁰⁸.

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 CPB¹⁰⁹. Using inert gases, Loeckinger et al¹¹⁰ showed that 10 cmH₂O 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 was accompanied by improved postoperative oxygenation. In contrast, CPAP of 5 cmH₂O during CPB did not improve lung function when used in patients¹¹¹ or pigs¹¹². More recently, experiments in pigs suggested that a slow ventilatory rate (5 min⁻¹) may lead to even better postoperative outcome due to a reduction in ischemic injury (Figure 3)¹¹³.

Bypass of the pulmonary artery flow produces lung ischemia and respiratory dysfunction⁸⁶. This mechanism has been recently explored with use of pulsatile pulmonary perfusion during experimental CPB, which further reduced the inflammatory response in pigs¹¹⁴. Also potentially contributing to this effect is a reduction of bronchial artery blood flow during CPB, which magnifies 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 flow¹¹⁵.

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 activated⁹⁰. 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 response¹¹⁶. 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”) has been theorized to reduce respiratory impairment postoperatively^{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}.

Whereas some studies report improvement in shunting and hypoxemia¹²⁵, other studies partitioning lung and chest wall mechanics do not support a significant effect of off-pump CABG on respiratory dysfunction¹²⁶. Studies using the forced oscillation technique (FOT) found that off-pump CABG does not affect airway mechanics, but still impairs the parenchymal tissues to degrees similar to those occurring with CPB¹²⁷. While it is hypothesized that off-pump CABG improves outcomes in patients at risk for respiratory dysfunction, such as COPD patients¹²⁸, it is questionable whether off-pump CABG results in better outcomes overall^{107, 120, 129}.

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

Optimal ways to re-expand the lungs have been studied. Based on animal data for CPB¹³⁰ and human data under anesthesia and mechanical ventilation¹³¹, some authors suggest recruiting the lungs using $F_{I}O_2 < 1.0$. For instance, $F_{I}O_2$ of 0.4 has been used aiming at preventing alveolar derecruitment through reabsorption atelectasis following experimental CPB¹³⁰. Expansion to pressures of 35 cmH₂O for 15 s with $F_{I}O_2 = 0.4$ before separation from CPB, combined with a second vital capacity maneuver within 20–30 minutes after arrival in the ICU ($F_{I}O_2 = 0.4$, inflation pressure = 30 cmH₂O for 5 seconds) reduces hypoxemia in the first 24 h postoperatively¹³², and a single vital capacity maneuver post CPB may lead to improved intraoperative oxygenation and shorter times to extubation¹³³.

Following discontinuation of CPB, mechanical ventilation is resumed with settings of $F_{I}O_2 = 1.0$, PEEP = 5 cmH₂O, $V_T = 8$ ml/kg predicted body weight, and a respiratory rate of 12 min⁻¹. After a few minutes of mechanical ventilation, peak inspiratory pressure increases to 35 cmH₂O, plateau pressure to 28 cmH₂O, and the expiratory flow curves show non-zero 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 surgery¹³⁴ and can exacerbate the already compromised respiratory function commonly found in patients undergoing cardiac surgery due to the pre-existing cardiac disease, smoking habits, and other comorbidities¹³⁵. 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 is similar to that observed in seated healthy subjects¹⁴¹. After CABG surgery, lung elastance and resistance markedly decrease with increasing tidal volume while resistance demonstrates a much greater dependence on frequency compared to pre-surgical conditions¹³⁷. Reductions in FRC¹⁴², 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 due to 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 appear 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 modified¹³⁵. 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 resistance¹³⁵. 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 method¹⁴⁰ 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 for the separation of their contributions to total lung impedance^{149–152}. Babik et al. found that cardiac surgery with extracorporeal circulation increased tissue elastance, tissue damping and airway resistance, and significantly reduced airway inertance (Figure 4)¹⁴⁰. Inhomogeneous narrowing of peripheral airways from mucosal thickening or release of inflammatory mediators appears to be the main mechanism producing CPB-induced increase in airways resistance. Restrictive processes due to 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 (Figure 4). Interestingly, these observations appear to be independent from increases in extravascular lung water and in the pulmonary circulation¹⁴⁰.

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 5¹²⁷. Worsening of elastance peaked at postoperative day 2 and persisted higher than baseline levels for the whole first postoperative week. Peak increase in elastance was higher and its elevation lasted longer in patients undergoing CPB than those undergoing off-pump CABG¹²⁷. The total volume of fluids administered to patients appears to also play a role in the respiratory mechanics. In fact, positive fluid balance was associated with worsening in respiratory mechanics and indices of oxygenation¹⁰¹.

Together with the changes in respiratory mechanics, the patient develops hypoxemia with $\text{SaO}_2=90\text{--}92\%$.

During the critical period immediately following discontinuation of CPB, even mild hypoxemia is undesirable since it reduces oxygen transport to the newly revascularized heart, as well as to other tissues. In order 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 membrane¹⁵³, alveolar

collapse^{154, 155}, a decrease in functional residual capacity (FRC)⁹⁷, retention of airway secretion, or insufficient cough as a consequence of pain (postoperatively).

Effects of cardiac surgery and CPB on gas exchange

Increases in venous admixture and physiological dead-space, worsening of blood gas tensions, and reduction in functional residual capacity 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 course¹⁵⁹. 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 upon 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 h after the end of uncomplicated cardiac surgery¹⁶². Indeed, 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 changes in lung recoil from pulmonary edema. The lungs after CPB will exhibit poor $\dot{V}/\dot{Q}$ matching, in addition to the true shunt due to atelectasis. Increases in $\dot{V}/\dot{Q}$ heterogeneity is associated with the inflammatory response to CPB, likely due both to 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 h postoperatively, 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 h after cardiac surgery^{165–167}.

Sequential intraoperative measurements showed that airway dead space increases with sternotomy by 32%¹⁶⁸. Airway dead space will be reduced following extra-corporeal circulation and sternal closure. By the end of surgery, however, alveolar deadspace increases significantly. Airway dead space at this stage can be smaller compared to the preoperative state, and so there is no net change in the physiological dead space fraction at the end of surgery¹⁶⁸. Interestingly, despite such findings, some groups failed to find an increase in the arterial-end tidal gradient of PCO_2 after CPB^{169, 170}.

Although the magnitude of atelectasis has not been found to be different between CABG and mitral valve surgery, it appears that control of regional blood flow may differ in those conditions^{103, 171}. Specifically, 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 cmH₂O for 30 seconds. During this procedure, systemic blood pressure is carefully monitored, as such increased intrathoracic pressure will reduce venous return and cardiac output. Endotracheal suctioning is performed. The inspiratory-to-expiratory ratio in the mechanical ventilator is increased to 1:3.5 and PEEP of 5 cmH₂O is added. Incomplete deflation persists, and a beta agonist (albuterol) is delivered through inhalation. Following these interventions, the SaO_2 increases to 100%.

Perioperative respiratory dysfunction and mechanical ventilation in COPD patients

COPD patients have early changes in the topographic distribution of regional perfusion, which 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 to normal subjects¹⁷⁴. Interestingly, such characteristics appear 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 surgery¹⁷⁶.

Although use of PEEP during mechanical ventilation of COPD patients 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 constants¹⁷⁷. The presence of sticky airway closure, alterations in intraparenchymal tethering forces, and increases in airway wall rigidity due to PEEP are possible mechanisms. *A priori* information regarding disease, respiratory mechanics, or ventilatory settings is not predictive of the response. As a consequence, an empirical PEEP trial investigating plateau pressure response was suggested as a strategy to guide use of PEEP in COPD patients during mechanical ventilation¹⁷⁸.

Occasionally, significant bronchoconstriction is observed at the end of the CPB period^{179, 180}. Because COPD patients have a chronic lung inflammation and higher airway resistances, bronchoconstriction in these patients can be particularly critical. Bronchodilators, such as beta 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}. Use of inhaled nitric oxide in COPD patients can, however, lead to deterioration of gas exchange. This is caused by $\dot{V}/\dot{Q}$ imbalances rather than by shunt, likely because of impaired hypoxic regulation of the matching between ventilation and perfusion¹⁸⁴.

Finally, it has been recognized that COPD patients 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 COPD¹⁸⁵. 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 cmH₂O. Arterial blood gas at the end of the case shows that PaO₂/F_IO₂=287 mmHg. The patient is transferred to the intensive care unit while still intubated. Respiratory mechanics and gas exchange are still marginal at ICU arrival but improved 16 h postoperatively allowing for 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 due to increased derecruitment of dependent and subdiaphragmatic lung regions. Resistance is increased due to the chest wall contribution and likely, at least partially, due to interdependence, where the collapse of alveolar units reduces traction on the small airways allowing for reduction in their diameter. FRC after chest closure can be lower than that at the beginning of surgery⁹⁷. The observed PaO₂/F_IO₂ 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 intensive care unit^{106, 145}.

CONCLUSION

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 impact critical respiratory function and mechanics. Instrumentation of the airway, inhalation of halogenated hydrocarbon anesthetics, motor block resulting from neuraxial anesthesia, cardiopulmonary bypass, 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 the face of 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.

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References

1. Bates, JHT. Physiologic Basis of Respiratory Disease. Hamilton, Ontario: BC Decker Inc; 2005. Physics of Expiratory Flow Limitation; p. 55-60.
2. Bolliger CT, Perruchoud AP. Functional evaluation of the lung resection candidate. *Eur Respir J*. 1998; 11(1):198–212. [PubMed: 9543294]
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. [PubMed: 8088100]
4. Beckles MA, Spiro SG, Colice GL, Rudd RM. The physiologic evaluation of patients with lung cancer being considered for resectional surgery. *Chest*. 2003; 123(1 Suppl):105S–114S. [PubMed: 12527570]
5. Pate P, Tenholder MF, Griffin JP, Eastridge CE, Weiman DS. Preoperative assessment of the high-risk patient for lung resection. *Ann Thorac Surg*. 1996; 61(5):1494–1500. [PubMed: 8633965]
6. Mittman C. Assessment of operative risk in thoracic surgery. *Am Rev Respir Dis*. 1961; 84:197–207. [PubMed: 13771442]
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. [PubMed: 3193801]
8. Nagasaki F, Flehinger BJ, Martini N. Complications of surgery in the treatment of carcinoma of the lung. *Chest*. 1982; 82(1):25–29. [PubMed: 7083931]
9. Carlens E. A new flexible double-lumen catheter for bronchspirometry. *J Thorac Surg*. 1949; 18(5):742–746. [PubMed: 18149050]
10. Jacobaeus HC, Frenckner P, Björkman S. Some attempts at determining the volume and function of each lung separately. *Acta Medica Scandinavica*. 1932; 79:174–215.

11. Neuhaus H, Cherniack NS. A bronchspirometric method of estimating the effect of pneumonectomy on the maximum breathing capacity. *J Thorac Cardiovasc Surg.* 1968; 55:144–148. [PubMed: 5638325]
12. Ali MK, Mountain CF, Ewer MS, Johnston D, Haynie TP. Predicting loss of pulmonary function after pulmonary resection for bronchogenic carcinoma. *Chest.* 1980; 77(3):337–342. [PubMed: 7357934]
13. Tonnesen KH, Dige-Petersen H, Lund JO, Nielsen SL, Lauridsen F. Lung split function test and pneumonectomy. A lower limit for operability. *Scand J Thorac Cardiovasc Surg.* 1978; 12(2):133–136. [PubMed: 715397]
14. Kristersson S, Arborelius M Jr, Jungquist G, Lilja B, Svanberg L. Prediction of ventilatory capacity after lobectomy. *Scand J Respir Dis.* 1973; 54(6):315–325. [PubMed: 4773702]
15. Kristersson S, Lindell SE, Svanberg L. Prediction of pulmonary function loss due to pneumonectomy using 133 Xe-radiospirometry. *Chest.* 1972; 62(6):694–698. [PubMed: 4635418]
16. Ellis DA, Hawkins T, Gibson GJ, Nariman S. Role of lung scanning in assessing the resectability of bronchial carcinoma. *Thorax.* 1983; 38(4):261–266. [PubMed: 6867977]
17. Boysen PG, Harris JO, Block AJ, Olsen GN. Prospective evaluation for pneumonectomy using perfusion scanning: follow-up beyond one year. *Chest.* 1981; 80(2):163–166. [PubMed: 7249760]
18. Olsen GN, Block AJ, Tobias JA. Prediction of postpneumonectomy pulmonary function using quantitative macroaggregate lung scanning. *Chest.* 1974; 66(1):13–16. [PubMed: 4846113]
19. Kearney DJ, Lee TH, Reilly JJ, DeCamp MM, Sugarbaker DJ. Assessment of operative risk in patients undergoing lung resection. Importance of predicted pulmonary function. *Chest.* 1994; 105(3):753–759. [PubMed: 8131537]
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):902–910. [PubMed: 2930068]
21. Olsen GN, Block AJ, Swenson EW, Castle JR, Wynne JW. Pulmonary function evaluation of the lung resection candidate: a prospective study. *Am Rev Respir Dis.* 1975; 111(4):379–387. [PubMed: 1124884]
22. Cerfolio RJ, Allen MS, Trastek VF, Deschamps C, Scanlon PD, Pairolero PC. Lung resection in patients with compromised pulmonary function. *Ann Thorac Surg.* 1996; 62(2):348–351. [PubMed: 8694589]
23. Edwards MA, Hazelrigg S, Naunheim KS. The National Emphysema Treatment Trial: summary and update. *Thorac Surg Clin.* 2009; 19(2):169–185. [PubMed: 19662959]
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):1181–1185. [PubMed: 9554858]
25. Ninan M, Sommers KE, Landreneau RJ, et al. Standardized exercise oximetry predicts postpneumonectomy outcome. *Ann Thorac Surg.* 1997; 64(2):328–333. [PubMed: 9262569]
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):1429–1435. [PubMed: 9877504]
27. Pierce RJ, Copland JM, Sharpe K, Barter CE. 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):947–955. [PubMed: 7921468]
28. BTS guidelines: guidelines on the selection of patients with lung cancer for surgery. *Thorax.* 2001; 56(2):89–108. [PubMed: 11209097]
29. Gravenstein, JS.; Paulus, DA.; Hayes, TJ. *Capnography in Clinical Practice.* Boston: Butterworth Publishers; 1989.
30. Fernandez-Perez ER, Keegan MT, Brown DR, Hubmayr RD, Gajic O. Intraoperative tidal volume as a risk factor for respiratory failure after pneumonectomy. *Anesthesiology.* 2006; 105(1):14–18. [PubMed: 16809989]
31. Musch G, Foti G, Cereda M, Pelosi P, Poppi D, Pesenti A. Lung and chest wall mechanics in normal anaesthetized subjects and in patients with COPD at different PEEP levels. *Eur Respir J.* 1997; 10(11):2545–2552. [PubMed: 9426093]
32. Benumof JL. One-lung ventilation and hypoxic pulmonary vasoconstriction: implications for anesthetic management. *Anesth Analg.* 1985; 64(8):821–833. [PubMed: 3893223]

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):938–943. [PubMed: 15719856]
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):473–477. [PubMed: 11704442]
35. Johansen B, Melsom MN, Flatebo T, Nicolaysen G. Time course and pattern of pulmonary flow distribution following unilateral airway occlusion in sheep. *Clin Sci (Lond).* 1998; 94(4):453–460. [PubMed: 9640352]
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. [PubMed: 9776547]
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):323–330. [PubMed: 14739807]
38. Katz JA, Laverne RG, Fairley HB, Thomas AN. Pulmonary oxygen exchange during endobronchial anesthesia: effect of tidal volume and PEEP. *Anesthesiology.* 1982; 56(3):164–171. [PubMed: 7036798]
39. Cohen E, Eisenkraft JB, Thys DM, Kirschner PA, Kaplan JA. Oxygenation and hemodynamic changes during one-lung ventilation: effects of CPAP10, PEEP10, and CPAP10/PEEP10. *J Cardiothorac Anesth.* 1988; 2(1):34–40. [PubMed: 2979130]
40. Slinger P, Triolet W, Wilson J. Improving arterial oxygenation during one-lung ventilation. *Anesthesiology.* 1988; 68(2):291–295. [PubMed: 3277487]
41. Domino KB, Borowec L, Alexander CM, et al. Influence of isoflurane on hypoxic pulmonary vasoconstriction in dogs. *Anesthesiology.* 1986; 64(4):423–429. [PubMed: 3963450]
42. Spies C, Zaune U, Pauli MH, Boeden G, Martin E. A comparison of enflurane and propofol in thoracic surgery. *Anaesthesist.* 1991; 40(1):14–18. [PubMed: 2006722]
43. Benumof JL, Wahrenbrock EA. Local effects of anesthetics on regional hypoxic pulmonary vasoconstriction. *Anesthesiology.* 1975; 43(5):525–532. [PubMed: 1190522]
44. Kellow NH, Scott AD, White SA, Feneck RO. 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):578–582. [PubMed: 7577284]
45. Abe K, Shimizu T, Takashina M, Shiozaki H, Yoshiya I. The effects of propofol, isoflurane, and sevoflurane on oxygenation and shunt fraction during one-lung ventilation. *Anesth Analg.* 1998; 87(5):1164–1169. [PubMed: 9806702]
46. Satoh D, Sato M, Kaise A, Hagiwara Y, Saishu T, Hashimoto Y. Effects of isoflurane on oxygenation during one-lung ventilation in pulmonary emphysema patients. *Acta Anaesthesiol Scand.* 1998; 42(10):1145–1148. [PubMed: 9834795]
47. Easley R, Mulreany D, Lancaster C, et al. Redistribution of Pulmonary Blood Flow Impacts Thermolulution-based Extravascular Lung Water Measurements in a Model of Acute Lung Injury. *Anesthesiology.* 2009; 111(5):1065–1074. [PubMed: 19809280]
48. Easley RB, Fuld MK, Fernandez-Bustamante A, Hoffman EA, Simon BA. Mechanism of hypoxemia in acute lung injury evaluated by multidetector-row CT. *Acad Radiol.* 2006; 13(7):916–921. [PubMed: 16777566]
49. Gust R, Kozlowski J, Stephenson AH, Schuster DP. Synergistic hemodynamic effects of low-dose endotoxin and acute lung injury. *Am J Respir Crit Care Med.* 1998; 157(6 Pt 1):1919–1926. [PubMed: 9620928]
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):832–838. [PubMed: 11325876]
51. Silva-Costa-Gomes T, Gallart L, Vallès J, Trillo L, Minguella J, Puig M. Low- vs high-dose almitrine combined with nitric oxide to prevent hypoxia during open-chest one-lung ventilation. *Br J Anaesth.* 2005; 95(3):410–416. [PubMed: 16024585]
52. Groeben H, Schafer B, Pavlakovic G, Silvanus MT, Peters J. 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):536–541. [PubMed: 11873024]
53. Garutti I, Quintana B, Olmedilla L, Cruz A, Barranco M, Garcia de Lucas E. Arterial oxygenation during one-lung ventilation: combined versus general anesthesia. *Anesth Analg*. 1999; 88(3):494–499. [PubMed: 10071993]
 54. Brister N, Barnette R, Kim V, Keresztury M. Anesthetic considerations in candidates for lung volume reduction surgery. *Proc Am Thorac Soc*. 2008; 5(4):432–437. [PubMed: 18453351]
 55. Hillier J, Gillbe C. Anaesthesia for lung volume reduction surgery. *Anaesthesia*. 2003; 58(12): 1210–1219. [PubMed: 14705686]
 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):1570–1580. [PubMed: 8514671]
 57. Samain E, Biard M, Farah E, Holtzer S, Delefosse D, Marty J. Monitoring expired oxygen fraction in preoxygenation of patients with chronic obstructive pulmonary disease. *Ann Fr Anesth Reanim*. 2002; 21(1):14–19. [PubMed: 11878116]
 58. Hedenstierna G, Strandberg A, Brismar B, Lundquist H, Svensson L, Tokics L. Functional residual capacity, thoracoabdominal dimensions, and central blood volume during general anesthesia with muscle paralysis and mechanical ventilation. *Anesthesiology*. 1985; 62(3):247–254. [PubMed: 3977112]
 59. Hedenstierna G, Strandberg A, Brismar B, Lundquist H, Tokics L. What causes the lowered FRC during anaesthesia? *Clin Physiol*. 1985; 5 (Suppl 3):133–141. [PubMed: 3888500]
 60. Rothen HU, Sporre B, Engberg G, Wegenius G, Hedenstierna G. Airway closure, atelectasis and gas exchange during general anaesthesia. *Br J Anaesth*. 1998; 81(5):681–686. [PubMed: 10193276]
 61. Brismar B, Hedenstierna G, Lundquist H, Strandberg A, Svensson L, Tokics L. Pulmonary densities during anesthesia with muscular relaxation--a proposal of atelectasis. *Anesthesiology*. 1985; 62(4):422–428. [PubMed: 3885791]
 62. Davis WB, Rennard SI, Bitterman PB, Crystal RG. Pulmonary oxygen toxicity. Early reversible changes in human alveolar structures induced by hyperoxia. *N Engl J Med*. 1983; 309(15):878–883. [PubMed: 6888481]
 63. Edmark L, Kostova-Aherdan K, Enlund M, Hedenstierna Gr. Optimal oxygen concentration during induction of general anesthesia. *Anesthesiology*. 2003; 98(1):28–33. [PubMed: 12502975]
 64. Tokics L, Hedenstierna G, Strandberg A, Brismar B, Lundquist H. Lung collapse and gas exchange during general anesthesia: effects of spontaneous breathing, muscle paralysis, and positive end-expiratory pressure. *Anesthesiology*. 1987; 66(2):157–167. [PubMed: 3813078]
 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):1822–1833. [PubMed: 8904605]
 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):1491–1495. [PubMed: 15105237]
 68. Rusca M, Proietti S, Schnyder P, et al. Prevention of atelectasis formation during induction of general anesthesia. *Anesth Analg*. 2003; 97(6):1835–1839. [PubMed: 14633570]
 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):1106–1116. [PubMed: 1756845]
 70. Athanasiou T, Al-Ruzzeh S, Del Stanbridge R, Casula RP, Glenville BE, Amrani M. Is the female gender an independent predictor of adverse outcome after off-pump coronary artery bypass grafting? *Ann Thorac Surg*. 2003; 75(4):1153–1160. [PubMed: 12683554]
 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):1285–1289. [PubMed: 9596307]

72. Taggart DP, el-Fiky M, Carter R, Bowman A, Wheatley DJ. Respiratory dysfunction after uncomplicated cardiopulmonary bypass. *Ann Thorac Surg.* 1993; 56(5):1123–1128. [PubMed: 8239811]
73. Hammermeister KE, Burchfiel C, Johnson R, Grover FL. Identification of patients at greatest risk for developing major complications at cardiac surgery. *Circulation.* 1990; 82(5 Suppl):IV380–389. [PubMed: 2225429]
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):1102–1110. [PubMed: 21430518]
75. Milot J, Perron J, Lacasse Y, Letourneau L, Cartier PC, Maltais F. Incidence and predictors of ARDS after cardiac surgery. *Chest.* 2001; 119(3):884–888. [PubMed: 11243972]
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):556–565. [PubMed: 4611290]
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):347–354. [PubMed: 9449727]
78. Brower RG, Network ACT. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med.* 2000; 342(18):1301–1308. [PubMed: 10793162]
79. Altmeier 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):L533–542. [PubMed: 15145786]
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):658–669. [PubMed: 20179503]
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):3542–3548. [PubMed: 9396453]
82. Massoudy P, Zahler S, Becker BF, Braun SL, Barankay A, Meisner H. Evidence for inflammatory responses of the lungs during coronary artery bypass grafting with cardiopulmonary bypass. *Chest.* 2001; 119(1):31–36. [PubMed: 11157581]
83. Andersen LW, Baek L, Degn H, Lehd J, Krasnik M, Rasmussen JP. Presence of circulating endotoxins during cardiac operations. *J Thorac Cardiovasc Surg.* 1987; 93(1):115–119. [PubMed: 3025527]
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):1007–1012. [PubMed: 8596232]
85. Kuratani T, Matsuda H, Sawa Y, Kaneko M, Nakano S, Kawashima Y. Experimental study in a rabbit model of ischemia-reperfusion lung injury during cardiopulmonary bypass. *J Thorac Cardiovasc Surg.* 1992; 103(3):564–568. [PubMed: 1545556]
86. Chai PJ, Williamson JA, Lodge AJ, et al. Effects of ischemia on pulmonary dysfunction after cardiopulmonary bypass. *Ann Thorac Surg.* 1999; 67(3):731–735. [PubMed: 10215218]
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. [PubMed: 14563666]
88. Schlensak C, Doenst T, Preusser S, Wunderlich M, Kleinschmidt M, Beyersdorf F. 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):1199–1205. [PubMed: 12063469]
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):1229–1239. [PubMed: 18354101]

90. Laffey JG, Boylan JF, Cheng DC. The systemic inflammatory response to cardiac surgery: implications for the anesthesiologist. *Anesthesiology*. 2002; 97(1):215–252. [PubMed: 12131125]
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. [PubMed: 21952833]
92. Chaney MA, Nikolov MP, Blakeman BP, Bakhos M. Protective ventilation attenuates postoperative pulmonary dysfunction in patients undergoing cardiopulmonary bypass. *J Cardiothorac Vasc Anesth*. 2000; 14(5):514–518. [PubMed: 11052430]
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):378–383. [PubMed: 16077402]
94. Koner O, Celebi S, Balci H, Cetin G, Karaoglu K, Cakar N. Effects of protective and conventional mechanical ventilation on pulmonary function and systemic cytokine release after cardiopulmonary bypass. *Intensive Care Med*. 2004; 30(4):620–626. [PubMed: 14722635]
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):519–523. [PubMed: 11052431]
96. Barnas GM, Gilbert TB, Watson RJ, Sequeira AJ, Roitman K, Nooroni RJ. Respiratory mechanics in the open chest: effects of parietal pleurae. *Respir Physiol*. 1996; 104(1):63–70. [PubMed: 8865383]
97. Jonmarker C, Nordstrom L, Werner O. Changes in functional residual capacity during cardiac surgery. *Br J Anaesth*. 1986; 58(4):428–432. [PubMed: 3485439]
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):817–822. [PubMed: 17720381]
99. Peng MJ, Vargas FS, Cukier A, Terra-Filho M, Teixeira LR, Light RW. Postoperative pleural changes after coronary revascularization. Comparison between saphenous vein and internal mammary artery grafting. *Chest*. 1992; 101(2):327–330. [PubMed: 1735249]
100. Singh NP, Vargas FS, Cukier A, Terra-Filho M, Teixeira LR, Light RW. Arterial blood gases after coronary artery bypass surgery. *Chest*. 1992; 102(5):1337–1341. [PubMed: 1424847]
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):844–849. [PubMed: 8969388]
102. Gullu AU, Ekinici A, Sensoz Y, et al. Preserved pleural integrity provides better respiratory function and pain score after coronary surgery. *J Card Surg*. 2009; 24(4):374–378. [PubMed: 19178610]
103. Hachenberg T, Tenling A, Hansson HE, Tyden H, Hedenstierna G. 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):809–817. [PubMed: 9105225]
104. Pennock JL, Pierce WS, Waldhausen JA. The management of the lungs during cardiopulmonary bypass. *Surg Gynecol Obstet*. 1977; 145(6):917–927. [PubMed: 337541]
105. Messent M, Sullivan K, Keogh BF, Morgan CJ, Evans TW. Adult respiratory distress syndrome following cardiopulmonary bypass: incidence and prediction. *Anaesthesia*. 1992; 47(3):267–268. [PubMed: 1566999]
106. Apostolakis E, Filos KS, Koletsis E, Dougenis D. Lung dysfunction following cardiopulmonary bypass. *J Card Surg*. 2010; 25(1):47–55. [PubMed: 19549041]
107. Ng CS, Wan S, Yim AP, Arifi AA. Pulmonary dysfunction after cardiac surgery. *Chest*. 2002; 121(4):1269–1277. [PubMed: 11948063]
108. Wasowicz M, Sobczynski P, Drwila R, Marszalek A, Biczysko W, Andres J. 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):216–221. [PubMed: 12944210]

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): 391–395. [PubMed: 324319]
110. Loeckinger A, Kleinsasser A, Lindner KH, Margreiter J, Keller C, Hoermann C. Continuous positive airway pressure at 10 cm H₂O during cardiopulmonary bypass improves postoperative gas exchange. *Anesth Analg*. 2000; 91(3):522–527. [PubMed: 10960369]
111. Berry CB, Butler PJ, Myles PS. Lung management during cardiopulmonary bypass: is continuous positive airways pressure beneficial? *Br J Anaesth*. 1993; 71(6):864–868. [PubMed: 8280555]
112. Magnusson L, Zemgulis V, Wicky S, Tyden H, Hedenstierna G. Effect of CPAP during cardiopulmonary bypass on postoperative lung function. An experimental study. *Acta Anaesthesiol Scand*. 1998; 42(10):1133–1138. [PubMed: 9834793]
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):1530–1537. [PubMed: 19464476]
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):115–122. [PubMed: 18573409]
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):882–891. [PubMed: 9074978]
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):2912–2920. [PubMed: 16275880]
117. Friedman M, Sellke FW, Wang SY, Weintraub RM, Johnson RG. Parameters of pulmonary injury after total or partial cardiopulmonary bypass. *Circulation*. 1994; 90(5 Pt 2):II262–268. [PubMed: 7955263]
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. *The Heart Surgery Forum*. 2003; 6(2):89–93. [PubMed: 14640133]
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):50–55. [PubMed: 12493504]
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. [PubMed: 15764773]
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):843–848. [PubMed: 12698147]
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):562–567. [PubMed: 16427852]
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):90–96. [PubMed: 15209550]
124. Wan S, Izzat MB, Lee TW, Wan IY, Tang NL, Yim AP. Avoiding cardiopulmonary bypass in multivessel CABG reduces cytokine response and myocardial injury. *Ann Thorac Surg*. 1999; 68(1):52–56. discussion 56–57. [PubMed: 10421114]
125. Tschernko EM, Bambazek A, Wissner 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):732–738. [PubMed: 12324731]
126. Roosens C, Heerman J, De Somer F, Caes F, Van Belleghem Y, Poelaert JI. 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):2430–2437. [PubMed: 12441750]

127. Albu G, Babik B, Kesmarky K, Balazs M, Hantos Z, Petak F. Changes in airway and respiratory tissue mechanics after cardiac surgery. *Ann Thorac Surg.* 2010; 89(4):1218–1226. [PubMed: 20338338]
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):152–157. [PubMed: 11216737]
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. [PubMed: 20083683]
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): 134–142. [PubMed: 9447866]
131. Rothen HU, Sporre B, Engberg G, Wegenius G, Hogman M, Hedenstierna G. Influence of gas composition on recurrence of atelectasis after a reexpansion maneuver during general anesthesia. *Anesthesiology.* 1995; 82(4):832–842. [PubMed: 7717553]
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):375–378. [PubMed: 17544889]
133. Murphy GS, Szokol JW, Curran RD, Votapka TV, Vender JS. Influence of a vital capacity maneuver on pulmonary gas exchange after cardiopulmonary bypass. *J Cardiothorac Vasc Anesth.* 2001; 15(3):336–340. [PubMed: 11426365]
134. Prakash O, Meij S, Bos E, Frederiksz PA, Hekman W, Jonson B. Lung mechanics in patients undergoing mitral valve replacement. The value of monitoring of compliance and resistance. *Crit Care Med.* 1978; 6(6):370–372. [PubMed: 720098]
135. Auler JO Jr, Zin WA, Caldeira MP, Cardoso WV, Saldiva PH. Pre- and postoperative inspiratory mechanics in ischemic and valvular heart disease. *Chest.* 1987; 92(6):984–990. [PubMed: 3677843]
136. Andersen NB, Ghia J. Pulmonary function, cardiac status, and postoperative course in relation to cardiopulmonary bypass. *J Thorac Cardiovasc Surg.* 1970; 59(4):474–483. [PubMed: 5439358]
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):166–175. [PubMed: 8175502]
138. Ghia J, Andersen NB. Pulmonary function and cardiopulmonary bypass. *JAMA.* 1970; 212(4): 593–597. [PubMed: 5467358]
139. Prakash O, Meij S, vd Borden B, Saxena PR. Cardiorespiratory monitoring during open heart surgery. *Crit Care Med.* 1981; 9(7):530–535. [PubMed: 6940690]
140. Babik B, Asztalos T, Petak F, Deak ZI, Hantos Z. Changes in respiratory mechanics during cardiac surgery. *Anesth Analg.* 2003; 96(5):1280–1287. [PubMed: 12707120]
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):240–244. [PubMed: 1990935]
142. Heldt GP, Peters RM. A simplified method to determine functional residual capacity during mechanical ventilation. *Chest.* 1978; 74(5):492–496. [PubMed: 738086]
143. Kaczka DW, Hager DN, Hawley ML, Simon BA. Quantifying mechanical heterogeneity in canine acute lung injury: impact of mean airway pressure. *Anesthesiology.* 2005; 103(2):306–317. [PubMed: 16052113]
144. Kaczka DW, Brown RH, Mitzner W. Assessment of heterogeneous airway constriction in dogs: a structure-function analysis. *J Appl Physiol.* 2009; 106(2):520–530. [PubMed: 18927269]
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):1454–1460. [PubMed: 10470749]
146. Zin WA, Caldeira MP, Cardoso WV, Auler JO Jr, Saldiva PH. Expiratory mechanics before and after uncomplicated heart surgery. *Chest.* 1989; 95(1):21–28. [PubMed: 2909337]
147. Garzon AA, Seltzer B, Lichtenstein S, Karlson KE. Influence of open-heart surgery on respiratory work. *Dis Chest.* 1967; 52(3):392–396. [PubMed: 6039703]

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):470–476. [PubMed: 15514973]
149. Hantos Z, Daroczy B, Suki B, Nagy S, Fredberg JJ. Input impedance and peripheral inhomogeneity of dog lungs. *J Appl Physiol*. 1992; 72(1):168–178. [PubMed: 1537711]
150. Hantos Z, Petak F, Adamicza A, Daroczy B, Fredberg JJ. Differential responses of global airway, terminal airway, and tissue impedances to histamine. *J Appl Physiol*. 1995; 79(5):1440–1448. [PubMed: 8593999]
151. Lutchen KR, Hantos Z, Petak F, Adamicza A, Suki B. Airway inhomogeneities contribute to apparent lung tissue mechanics during constriction. *J Appl Physiol*. 1996; 80(5):1841–1849. [PubMed: 8727575]
152. Suki B, Petak F, Adamicza A, Daroczy B, Lutchen KR, Hantos Z. Airway and tissue constrictions are greater in closed than in open-chest conditions. *Respir Physiol*. 1997; 108(2):129–141. [PubMed: 9232686]
153. Royston D, Minty BD, Higenbottam TW, Wallwork J, Jones GJ. The effect of surgery with cardiopulmonary bypass on alveolar-capillary barrier function in human beings. *Ann Thorac Surg*. 1985; 40(2):139–143. [PubMed: 3896173]
154. Hachenberg T, Lundquist H, Tokics L, Brismar B, Hedenstierna G. Analysis of lung density by computed tomography before and during general anaesthesia. *Acta Anaesthesiol Scand*. 1993; 37(6):549–555. [PubMed: 8213018]
155. Magnusson L, Zemgulis V, Wicky S, Tyden H, Thelin S, Hedenstierna G. Atelectasis is a major cause of hypoxemia and shunt after cardiopulmonary bypass: an experimental study. *Anesthesiology*. 1997; 87(5):1153–1163. [PubMed: 9366468]
156. Nahas RA, Melrose DG, Sykes MK, Robinson B. Post-Perfusion Lung Syndrome: Effect of Homologous Blood. *Lancet*. 1965; 2(7406):254–256. [PubMed: 14330057]
157. Nahas RA, Melrose DG, Sykes MK, Robinson B. Post-Perfusion Lung Syndrome: Role of Circulatory Exclusion. *Lancet*. 1965; 2(7406):251–254. [PubMed: 14330056]
158. Rea HH, Harris EA, Seelye ER, Whitlock RM, Withy SJ. The effects of cardiopulmonary bypass upon pulmonary gas exchange. *J Thorac Cardiovasc Surg*. 1978; 75(1):104–120. [PubMed: 339001]
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):506–513. [PubMed: 11052429]
160. Apostolakis EE, Koletsis EN, Baikoussis NG, Siminelakis SN, Papadopoulos GS. Strategies to prevent intraoperative lung injury during cardiopulmonary bypass. *Journal of Cardiothorac Surgery*. 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. [PubMed: 17300720]
162. Hachenberg T, Tenling A, Nystrom SO, Tyden H, Hedenstierna G. Ventilation-perfusion inequality in patients undergoing cardiac surgery. *Anesthesiology*. 1994; 80(3):509–519. [PubMed: 8141447]
163. Lindberg P, Gunnarsson L, Tokics L, et al. Atelectasis and lung function in the postoperative period. *Acta Anaesthesiol Scand*. 1992; 36(6):546–553. [PubMed: 1514340]
164. Strandberg A, Tokics L, Brismar B, Lundquist H, Hedenstierna G. Atelectasis during anaesthesia and in the postoperative period. *Acta Anaesthesiol Scand*. 1986; 30(2):154–158. [PubMed: 3705902]
165. Anjou-Lindskog E, Broman L, Broman M, Holmgren A. Effects of oxygen on central haemodynamics and VA/Q distribution after coronary bypass surgery. *Acta Anaesthesiol Scand*. 1983; 27(5):378–384. [PubMed: 6605644]
166. Anjou-Lindskog E, Broman L, Broman M, Holmgren A. 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. [PubMed: 6424390]

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):489–497. [PubMed: 6815975]
168. Fletcher R, Malmkvist G, Niklason L, Jonson B. On-line measurement of gas-exchange during cardiac surgery. *Acta Anaesthesiol Scand*. 1986; 30(4):295–299. [PubMed: 3488633]
169. Fletcher R, Veintemilla F. Changes in the arterial to end-tidal PCO₂ differences during coronary artery bypass grafting. *Acta Anaesthesiol Scand*. 1989; 33(8):656–659. [PubMed: 2511727]
170. Myles PS, Story DA, Higgs MA, Buckland MR. Continuous measurement of arterial and end-tidal carbon dioxide during cardiac surgery: Pa-ETCO₂ gradient. *Anaesth Intensive Care*. 1997; 25(5):459–463. [PubMed: 9352755]
171. Tenling A, Hachenberg T, Tyden H, Wegenius G, Hedenstierna G. Atelectasis and gas exchange after cardiac surgery. *Anesthesiology*. 1998; 89(2):371–378. [PubMed: 9710395]
172. Barbera JA, Ramirez J, Roca J, Wagner PD, Sanchez-Lloret J, Rodriguez-Roisin R. Lung structure and gas exchange in mild chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1990; 141(4 Pt 1):895–901. [PubMed: 2327653]
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):L908–913. [PubMed: 9609729]
174. Vidal Melo MF, Winkler T, Harris RS, Musch G, Greene RE, Venegas JG. 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. [PubMed: 20008987]
175. Wagner PD, Dantzker DR, Dueck R, Clausen JL, West JB. Ventilation-perfusion inequality in chronic obstructive pulmonary disease. *J Clin Invest*. 1977; 59(2):203–216. [PubMed: 833271]
176. Vidal Melo MF, Ichinose F, Walker J, MacGillivray T, Hess D. 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):1833–1841. [PubMed: 11299274]
178. Caramaz 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):1519–1528. [PubMed: 16003057]
179. Kawahito S, Kitahata H, Tanaka K, Nozaki J, Oshita S. Bronchospasm induced by cardiopulmonary bypass. *Ann Thorac Cardiovasc Surg*. 2001; 7(1):49–51. [PubMed: 11343567]
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. [PubMed: 3495208]
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):604–609. [PubMed: 8564105]
182. Lindeman KS, Aryana A, Hirshman CA. Direct effects of inhaled nitric oxide on canine peripheral airways. *J Appl Physiol*. 1995; 78(5):1898–1903. [PubMed: 7649928]
183. Matera MG. Nitric oxide and airways. *Pulm Pharmacol Ther*. 1998; 11(5–6):341–348.
184. Barbera JA, Roger N, Roca J, Rovira I, Higenbottam TW, Rodriguez-Roisin R. Worsening of pulmonary gas exchange with nitric oxide inhalation in chronic obstructive pulmonary disease. *Lancet*. 1996; 347(8999):436–440. [PubMed: 8618485]
185. de Prost N, El-Karak C, Avila M, Ichinose F, Vidal Melo MF. 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):1496–1502. [PubMed: 21377695]

KEY POINTS

- Alterations in patient condition and unpredictable requirements of surgery impact 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.

Figure 1.

Expiratory flow-volume curve of an anesthetized mechanically ventilated patient with severe chronic obstructive pulmonary disease. Note the marked upper concavity and an end-expiratory flow of approximately 0.1 L/s. Both these features are indicative of 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 rising exhaled CO₂ 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 et al., *European Respiratory Journal*, 1997³¹, permission pending.

Figure 2.

The effect of high V_T /low PEEP vs. low V_T /high PEEP ventilation strategies on lung inflammation as indicated by BAL fluid IL-6 and IL-8 concentrations at three 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 et al., *Journal of Thoracic and Cardiovascular Surgery*, 2005⁹³, with permission.

Figure 3.

Lung tissue light micrographs depicting alveolar regions 90 minutes after CPB: (A) When the lung was either open to atmosphere or received 5 cmH₂O CPAP there was significant atelectasis and pulmonary edema. (B) Low frequency ventilation (5 breaths per minute) lead to normal appearing lung tissue. Modified from Imura et al., *Journal of Thoracic and Cardiovascular Surgery*, 2009¹¹³, with permission.

Figure 4.

Changes in airway and lung tissue mechanical properties in patients undergoing CABG surgery performed “off pump” (OPCAB), or with cardiopulmonary bypass (CPB). Group CPB-DA also had intravenous dopamine administered. R_{aw} , airways resistance; I_{aw} , airways inertance; G , tissue damping coefficient; H , tissue elastance coefficient; η , tissue hysteresivity. Reprinted from Babik et al., *Anesthesia and Analgesia*, 2003¹⁴⁰, with permission.