The Anesthesiologist's Role in Perioperative Lung Protection

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Potential lung injuries which can occur in the perioperative period and may be influenced by anesthetic management include atelectasis, pneumonia, broncho-pleural fistula, bronchospasm and acute lung injury. Anesthesiologists deal with patients who present with both injured and non-injured lungs in the perioperative period. Non-injured lungs need to be protected from multiple factors in the perioperative period. Injured lungs need to be protected from the Anesthesiologist. This review will look at the relevant issues in both situations.

PATIENTS WITH NONINJURED LUNGS

Management of Patients with Healthy Lungs

Traditionally, anesthesiologists have been taught to ventilate patients in the operative and postoperative periods with relatively large tidal volumes. Volumes as large as 15 mL/kg ideal body weight have been suggested to avoid intraoperative atelectasis.[1] This far exceeds the normal spontaneous tidal volumes (6 mL/kg) common to most mammals.[2] Recently, it has become obvious that these nonphysiologic large tidal volumes can cause a degree of subclinical injury in healthy lungs. Gajic at al.[3] reported that 25% of patients without lung injury ventilated in an ICU setting for 2 days or longer developed acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). The main risk factors associated with the development of lung injury were the use of large tidal volumes, restrictive lung disease, and transfusion of blood products. In a prospective study, the same group have found that tidal volumes >700 mL and peak airway pressures > 30 cm H_2O were independently associated with the development of ARDS.[4] In an intraoperative study of patients having esophageal surgery Michelet et al.[5] compared the use of tidal volumes of 9 mL/kg without positive end-expiratory pressure (PEEP) during two- and one-lung ventilation versus 9 mL/kg during two-lung ventilation and 5 mL/kg during one-lung ventilation with PEEP 5 cm H_2O throughout. They found significantly lower serum makers of inflammation (cytokines IL-1β, -6 and -8) in the lower tidal volume plus PEEP group (see F1 Fig. 1). The study did not find any major difference in postoperative outcome between the two groups, however it was not powered to do this. The study did demonstrate better oxygenation in the lower tidal volume group during and immediately after one-lung ventilation (see Fig. 2) but not after 18 h. In a study of F2 major abdominal surgery patients ventilated for >5 h, Choi et al.[6] compared the use of 12 mL/kg tidal volumes without PEEP versus 6 mL/kg plus PEEP 10 cm H_2O. Bronchiolar lavages were performed before and after 5 h of mechanical ventilation. Lavage fluid from the high tidal volume group showed a pattern of leakage of plasma into the alveoli with increased levels of thrombin-antithrombin complexes (see Fig. 3), soluble tissue factor and factor VIIa. This is the F3 hallmark of alveolar lung injury. A clear pattern seems to be appearing from the clinical research that, even in patients with no lung disease, the use of nonphysiologic patterns of ventilation with large tidal volumes and without PEEP causes a degree of systemic inflammation and lung injury. The severity of this injury seems to be directly related to the duration of mechanical ventilation.

Patients with Chronic Obstructive Pulmonary Disease (COPD)

COPD incorporates three disorders: emphysema, peripheral airways disease, and chronic bronchitis. COPD patients are at an increased risk for lung injury in the perioperative period. Recent advances in the understanding of COPD that are relevant to anesthetic management and perioperative lung injury include:

Dynamic hyperinflation. Emphysema is, almost exclusively, an expiratory disease unlike asthma or chronic bronchitis, which have both inspiratory and expiratory components. As a result, it is easy to get gas into the emphysema patient's lungs during positive pressure ventilation but extremely difficult to get the gas out due to intrinsic PEEP (auto-PEEP). This intrathoracic gas-trapping is referred to as "Dynamic Hyperinflation." .[7] Even seemingly low levels of positive airway pressure in these patients, such as those generated by bag-mask ventilation during induction of anesthesia, can lead to severe hyperinflation with secondary impairment of cardiac venous return leading to hypotension and even cardiac arrest. This hemodynamic effect is exacerbated in the presence of decreased intravascular volume and vasodilating anesthetic agents. Dynamic Hyperinflation is the cause of some of the instances of the "Lazarus Syndrome," in

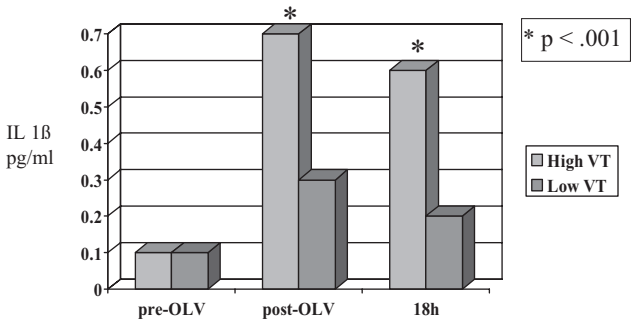

Figure 1. Serum levels of inflammatory cytokine IL 1-β before and after periods of one-lung ventilation (OLV) in patients having esophagectomies. Patients' lungs were ventilated with either a large tidal volume (9 mL/kg) or a small tidal volume (5 mL/kg) plus PEEP (5 cm H_2O) during OLV. Based on data from Michelet et al.[5]

which patients with COPD who have had a cardiorespiratory arrest and have been pronounced dead after failed resuscitation have spontaneously recovered once resuscitation is stopped.[8]

Anesthesiologists must be very aware of the possibility of dynamic hyperinflation whenever general anesthesia is induced in a patient with emphysema. The primary methods to avoid hemodynamic instability in these patients are ventilatory management: thorough preoxygenation prior to induction, then the use of small tidal volumes, slow respiratory rates and long expiratory times and tolerance of hypercarbia until the patient recovers from the vasodepressant effects of induction drugs. Also important for these patients are: large-bore IV access, vasopressors, and inotropes immediately available and IV preloading with colloids or crystalloids.

An extremely difficult differential diagnosis arises when one of these patients "crashes" during positive pressure ventilation. The diagnostic dilemma is to differentiate between tension pneumothorax and dynamic hyperinflation. The choice is not always obvious and the definitive treatments are very different. Unilateral changes in chest auscultation, tracheal deviation and the presence of known bullae favor pneumothorax and the need for decompression. In the absence of these clues, it is best to stop ventilation and let the patient breath out passively to atmosphere while beginning pharmacologic resuscitation. With hyperinflation there will be a gradual return of circulation, but it is not immediate. If there is no improvement after 1 minute of apnea, the assumption should be pnemothorax and chest drains should be placed.

Bullae. Many patients with moderate or severe COPD develop cystic air spaces in the lung parenchyma known as bullae. These bullae will often be asymptomatic unless they occupy more than 50% of the hemithorax, in which case the patient will present with findings of restrictive respiratory disease in addition to their obstructive disease. Previously, it was thought that bullae represented positive pressure areas within the lung that compressed surrounding lung tissue. It is now appreciated that a bulla is actually a localized area of loss of structural support tissue in the lung with elastic recoil of surrounding parenchyma. The pressure in a bulla is actually the mean pressure in the surrounding alveoli averaged over the respiratory cycle. This means that during normal spontaneous ventilation the intrabulla pressure is actually slightly negative in comparison to the surrounding parenchyma.[9] However, whenever positive-pressure ventilation is used the pressure in a bulla will become positive in relation to the adjacent lung tissue and the bulla will expand with the attendant risk of rupture, tension pnuemothorax and bronchopleural fistula. Positive-pressure ventilation can be used safely in patients with bullae provided the airway pressures are kept low and there is adequate expertise and equipment immediately available to insert a chest drain and obtain lung isolation if necessary.

Respiratory drive. Many COPD patients have an elevated $Paco_2$ at rest. Among moderate and severe COPD patients it is not possible to predict from history or physical examination which patients are "CO_2-retainers."[10] Preoperative arterial blood a gases are required to set goals for intra- and postoperative ventilation. This CO_2-retention seems to be primarily related to an inability to maintain the increased work of respiration and not due to an alteration of respiratory control mechanisms.[11] The $Paco_2$ rises in these patients when supplemental oxygen is administered not due to a decrease of minute ventilation,[12] but because a high FiO_2 causes a relative increase in alveolar dead space by the redistribution of lung perfusion and also due to the Haldane effect.[13] However, supplemental oxygen must be administered to these patients postoperatively to prevent hypoxemia. The attendant rise in $Paco_2$ should be anticipated and monitored. Hypercarbia is usually well tolerated in the absence of intracranial pathology and if the vasodepressant effects of acidosis can be managed.[14] In addition to arterial blood gas monitoring, the best monitor of dangerous hypercarbia is the patient's level of consciousness. At levels >80–100 mm|Hg $Paco_2$ carbon dioxide begins to have a sedative and anesthetic effect.

Nocturnal hypoxemia. COPD patients desaturate more frequently and severely than normal patients during sleep. This is related to the shallow rapid pattern of ventilation which occurs in all patients during REM sleep.[15] This tendency to desaturate, combined with the postoperative fall in FRC and opioid analgesia, places these patients at high risk for severe hypoxemia postoperatively during sleep.

Right ventricular (RV) dysfunction. Right ventricular dysfunction occurs in up to 50% of COPD patients.[16] The dysfunctional RV is poorly tolerant of sudden increases in afterload such as the change from spontaneous to controlled ventilation or large pulmonary resections.[17]

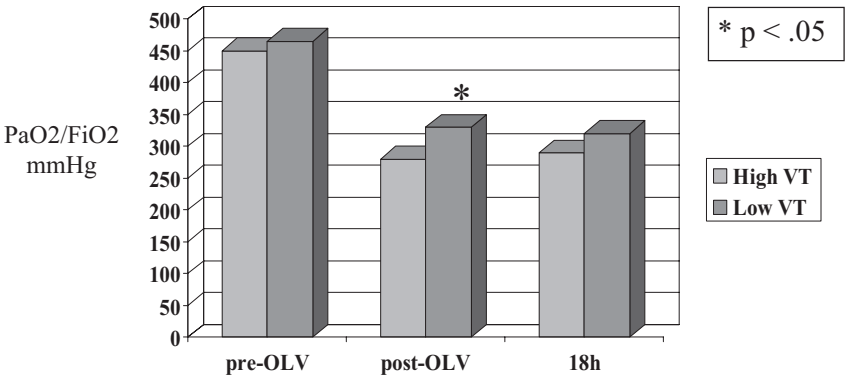

Figure 2. Ratio of arterial oxygen tension to inspired oxygen concentration (PAo_2/FiO_2) in patients ventilated with either a large tidal volume (9 mL/kg) or a small tidal volume (5 mL/kg) plus PEEP (5 cm H_2O) during OLV. Based on data from Michelet et al.[5]

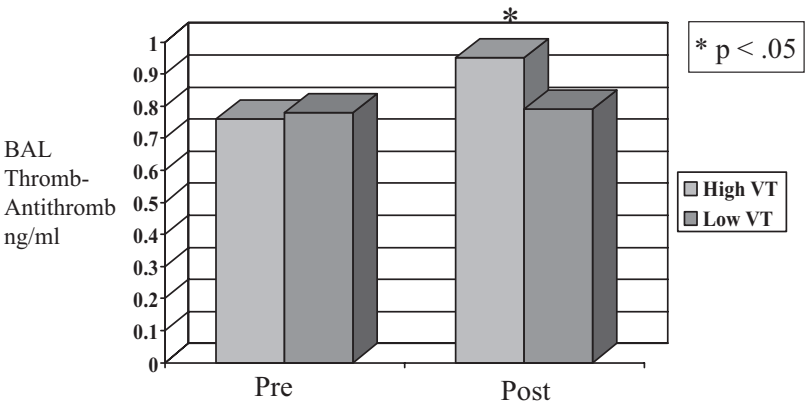

Figure 3. Bronchoalveolar lavage (BAL) levels of thrombin-antithrombin complexes as a marker of lung epithelial injury in patients ventilated for >5 h during abdominal surgery with either a large tidal volume (12 mL/kg) without PEEP vs a small tidal volume (6 mL/kg) with PEEP (10 cm H_2O). Based on data from Choi et al.[6]

Perioperative Therapy of COPD to Decrease Lung Injury

Physiotherapy. It has been clearly shown that patients with COPD have fewer postoperative pulmonary complications when a perioperative program of intensive chest physiotherapy is initiated preoperatively.[18] Even in the most severe COPD patient it is possible to improve exercise tolerance with a physiotherapy program.[19] Little improvement is seen before 1 month. Among COPD patients, those with excessive sputum benefit the most from chest physiotherapy.[20]

Smoking cessation. A preoperative smoking cessation program can significantly decrease the incidence of respiratory complications (4–8 weeks abstinence), wound complications (4 weeks abstinence) and intraoperative myocardial ischemia (48 h abstinence).[21]

Bronchodilation. Bronchoconstriction is assessed by history, physical examination, and evaluation of pulmonary function response to bronchodilators. All asthma/COPD patients should receive maximal bronchodilator therapy as guided by their symptoms. In a patient who is poorly controlled on sympathomimetic and anticholinergic bronchodilators, a trial of corticosteroids may be beneficial.[22] It is not clear if corticosteroids are as beneficial in COPD as they are in asthma.

Are pulmonary function tests needed? Yes. PFTs are not useful as screening tools for all patients, but flow-rates are valuable to assess symptomatic patients, to confirm the diagnosis, and to assess the adequacy of therapy.

Is referral to a chest physician indicated? The anesthesiologist will have to decide if the patient with reactive airways disease is adequately managed preoperatively, i.e., functionally at his or her usual level of exercise tolerance and with flow-rates >80% of stable baseline. If preoperative management of bronchospasm is inadequate or if there is any evidence of current respiratory infection, the patient should be referred to a chest or family physician for therapy preoperatively.

With advances in anesthetic management the incidence of life-threatening intraoperative bronchospasm has become very low.[23] However, the anesthesiologist must always respect the management principles for patients with reactive airways: preoperative optimization of bronchodilation, minimal (or no) instrumentation of the airways, instrument the airways when necessary only after appropriate depth of anesthesia with a bronchodilating anesthetic (propofol, ketamine, sevoflurane), and maintenance of anesthesia with a bronchodilating anesthetic and appropriate warming and humidification of inspired gases.[24] In patients with bronchial hyper-reactivity (FEV1 <70% and >10% increase with bronchodilator) on regular bronchodilator therapy, postintubation wheezing can be significantly reduced by addition of a 5-day preoperative course of corticosteroids (methylprednisolone 40 mg/day p.o.).[25] Inhaled corticosteroids may also be useful in this regard.

Perioperative Surgical Environment Factors

There are multiple factors in the surgical environment that can contribute to lung injury. One of the most obvious is the surgical approach. If major body

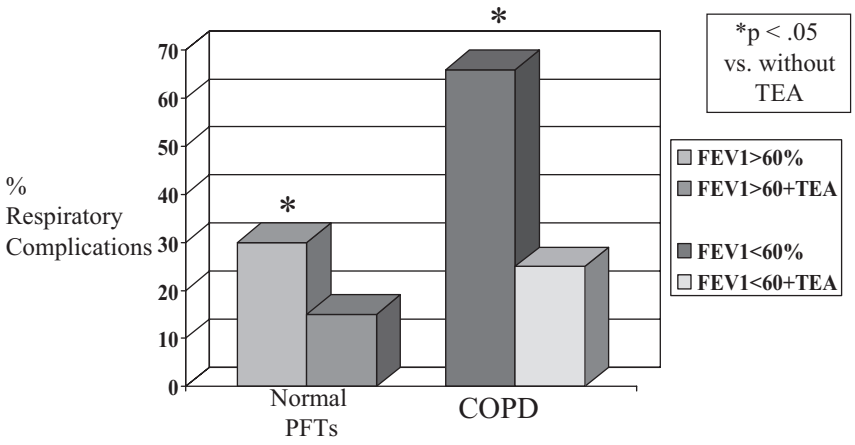

Figure 4. Percent of patients experiencing postoperative respiratory complications in a retrospective study following thoracic surgery for lung cancer. The benefits of thoracic epidural analgesia were more marked in patients with chronic obstructive pulmonary disease (COPD) than in patients with normal preoperative pulmonary function tests (PFTs). Based on data from Licker et al.[39]

cavity procedures can be done with a minimally-invasive versus open technique, the decrease in respiratory complications is well documented.[26]

Atelectasis is a frequent postoperative complication of open surgical procedures. Atelectasis occurs intraoperatively as part of essentially any general anesthetic.[27] Anesthesiologists are aware of this, and techniques to avoid it with air-oxygen mixtures, PEEP, and recruitment maneuvers are used frequently.[28] However, anesthesiologists are often not aware that atelectasis is a pathological state, and if it persists in the postoperative period leads to increased capillary permeability and an inflammatory response with subsequent lung injury.[29] Both retrospective[30] and prospective[31] studies have consistently shown that appropriate thoracic epidural analgesia reduces the incidence of respiratory complications (atelectasis, pneumonia, and respiratory failure) after major abdominal and thoracic surgery. The benefits of epidural analgesia seem to be in direct proportion to the severity of the patients underlying lung disease. Patients with COPD seem to derive the most benefit from epidural analgesia (see Fig. 4). It has also been recently demonstrated that aggressive physiotherapy with CPAP in the postoperative period in patients who develop early desaturation after major abdominal surgery leads to lower rates of major respiratory complications.[32]

PATIENTS WITH INJURED LUNGS

There are situations when the anesthesiologist appreciates that a patient presenting for surgery may have a lung injury (trauma/ARDS, lung transplantation, etc.), however there are many more cases where the lung injury is subclinical and underappreciated in the perioperative period (cardiopulmonary bypass, large pulmonary resections[33]). Acute lung injury following pulmonary resection has been described since the beginning of one-lung ventilation (OLV) for thoracic surgery. The most publicized report is a compilation of 10 cases following pneumonectomy published in 1984[34] which focused on the role of IV overhydration as a cause of post-pneumonectomy pulmonary edema. Subsequently, there have been several reviews of this topic identifying a variety of other potentially causative factors for ALI such as the administration of fresh frozen plasma, mediastinal lymphatic damage, inflammation, and oxygen toxicity.[35] The most thorough study to date[36] is a retrospective survey of 806 pneumonectomies that found 21 cases (2.5%) of post-pneumonectomy pulmonary edema, one of the lowest incidences reported of this complication. There were no differences in perioperative fluid balance between post-pneumonectomy ALI cases (positive fluid balance at 24 h: 10 mL/kg) versus matched pneumonectomy controls (13 mL/kg). These authors used rigorous fluid restriction compared to other reports[37] (e.g., 24 h positive balance: 21 ± 9 mL/kg), suggesting that limiting intraoperative fluids might decrease but not eliminate ALI. Further reports demonstrate improved survival from post-pneumonectomy pulmonary edema is likely due to improved postoperative management of established cases.[38]

ALI after pulmonary resection has been found to have a bimodal distribution of onset. Late cases (10/37, 27%) presented 3–10 days postoperatively and were secondary to obvious causes such as bronchopneumonia, aspiration, etc. "Primary" ALI (27/37, 73% of cases) presented on postoperative days 0–3. Four factors were independent significant predictors of primary ALI: high intraoperative ventilation pressures, excessive IV volume replacement, pneumonectomy, and preoperative alcohol abuse.[39] The known facts about ALI following lung surgery thus include: an incidence of 2–4% following pneumonectomy; greater frequency in right versus left pneumonectomies; symptomatic onset 1–3 days after surgery; high associated mortality (25–50%); and resistance to standard therapies. While ALI occurs following lesser pulmonary resections such as lobectomy, it has a much lower mortality rate. Of interest, in 8 of 9 cases who developed unilateral ALI following lobectomy, the ALI was in the nonoperated (i.e., ventilated) lung.[40]

While there is some association between postoperative ALI and fluid overload, the finding of low/normal pulmonary artery wedge pressures and high-protein edema fluid in affected patients suggests a role

of endothelial damage (low-pressure pulmonary edema). Postoperative increases in lung capillary permeability of the nonoperated lung occur after pneumonectomy but not lobectomy.[41]This capillary-leak injury may be due to an inflammatory cascade affecting even the nonoperative lung that is triggered by lung resection and is proportional to the amount of lung tissue resected.[42,43] Free oxygen radical generation in lung cancer patients is related to the duration of OLV.[44]Nonetheless, there is no single mechanism that can fully explain ALI after lung resection and its etiology is likely multifactorial. A unifying hypothesis is that post-pneumonectomy pulmonary edema is one end of a spectrum of ALI that occurs during all lung resections. The more extensive the resection the more likely there is to be a postoperative injury. The increased dissection and trauma associated with extrapleural pneumonectomy places these patients at high risk to develop postoperative ALI.[45]

Understanding that lung endothelial injury occurs after lung resection supports management strategies similar to other conditions associated with ALI and ARDS. As a general principle, it seems that the lung is least injured when a pattern of ventilation as close as possible to normal spontaneous ventilation can be followed: FiO_2 as low as acceptable, variable tidal volumes,[46]beginning inspiration at FRC, and avoiding atelectasis with frequent recruitment maneuvers.[47] Studies in ARDS demonstrate that ALI is exacerbated by the use of large tidal volumes and that lung-protective ventilation strategies with low tidal volumes and PEEP are less injurious. The most important factor in the etiology of ventilator-induced lung injury is the end-inspiratory lung volume.[48] Many patients, particularly those with emphysema, develop auto-PEEP during one-lung ventilation,[49] thus beginning inspiration at a lung volume above functional residual capacity. It is conceivable that routine use of large tidal volumes (10–12 mL/kg) during OLV in such patients produces end-inspiratory lung volumes close to levels that contribute to ALI.

Changes in respiratory function during OLV in the lateral position with an open nondependent hemithorax are complex. Initial studies of the application of PEEP during OLV suggested that it led to a deterioration of arterial oxygenation.[50] It is now appreciated that the effects of applied PEEP during OLV depend on the lung mechanics of the individual patient. Most patients with COPD develop auto-PEEP during OLV and thus adding external PEEP leads to hyperinflation and increased shunt51 (see Fig. 5). However, patients with normal lung parenchyma or those with restrictive lung diseases tend to fall below their FRC at end-expiration during OLV (see Fig. 6) and benefit from applied external PEEP.[52] Intraoperative atelectasis may contribute to injury in the dependent lung. It is now appreciated that atelectasis is a preinflammatory state predisposing to injury both in the atelectatic

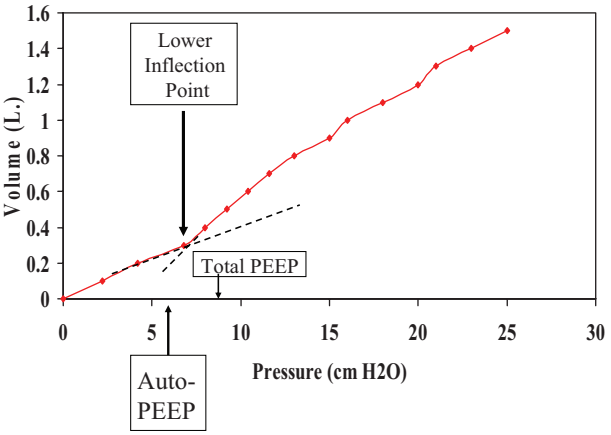

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Figure 5. The inspiratory compliance curve (lung volume vs airway pressure) during one-lung ventilation as the lung is slowly inflated by 100 mL increments in a patient with mild COPD. The lower inflection point of the curve [thought to represent functional residual capacity (FRC)] is at 7 cm H_2O. During OLV this patient developed an intrinsic PEEP (measured by end-expiratory airway occlusion plateau pressure "Auto-PEEP") of 6 cm H_2O. The addition of 5 cm PEEP through the ventilator resulted in a total PEEP in the circuit of 9 cm. The addition of PEEP in this patient raised the end-expiratory lung volume above FRC, thus raising pulmonary vascular resistance in the ventilated lung and caused a deterioration in oxygenation. Based on data from Slinger et al.[51]

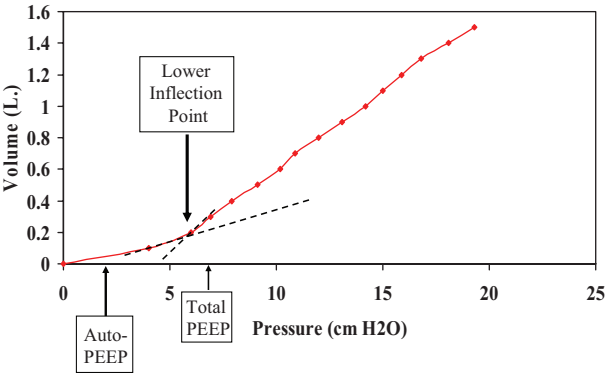

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Figure 6. The inspiratory compliance curve during OLV in a patient with normal pulmonary function. The lower inflection point of the curve is at 6 cm H_2O. During OLV this patient developed an intrinsic PEEP of 2 cm H_2O. The addition of 5 cm PEEP through the ventilator resulted in a total PEEP in the circuit of 7 cm. The addition of PEEP in this patient raised the end-expiratory lung volume to FRC thus decreasing pulmonary vascular resistance in the ventilated lung and caused an improvement in oxygenation. Based on data from Slinger et al.[51]

portion of the lung and in ventilated regions in the same lung, which become hyperinflated.[53]

There is evidence that when an element of lung injury is added to large tidal volume ventilation during OLV, this contributes to ALI. In a rabbit model of OLV during isolated perfusion, large tidal-volume (8 mL/kg) ventilation produced a picture of ALI absent in animals randomized to a lung-protective ventilation pattern (4 mL/kg plus PEEP).[54] In a sheep-pneumonectomy model, the use of large tidal volume

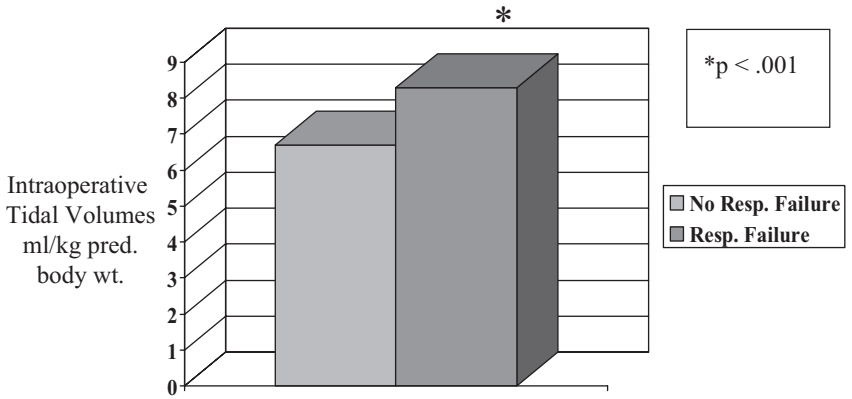


Figure 7. Retrospective analysis of the tidal volumes used during pneumonectomy in patients who developed postoperative respiratory failure vs patients who did not develop respiratory failure. The respiratory failure patients received larger tidal volumes. Based on data from Fernandez-Perez et al.[58]

ventilation (12 mL/kg) was associated with a significant increase in postoperative lung water not seen in animals ventilated with smaller tidal volumes or controls.[55] Another consideration is management of patients who have received preoperative chemotherapy with agents such as cisplatinum and gemcitabine that may affect respiratory function and may increase the risk of postoperative respiratory complications including ALI in some patients.[56] Large pulmonary resections (pneumonectomy or bilobectomy) should be considered to be associated with some degree of ALI. Acute lung injury, diagnosed radiographically, was reported in 42% of pneumonectomy patients who had been ventilated with peak airway pressures >40 cm H_2O.[57] A recent retrospective study found that postpneumonectomy respiratory failure was associated with the use of higher intraoperative tidal volumes (8.3 mL/kg vs 6.7 mL/kg in pneumonectomy patients who did not develop respiratory failure) (see Fig. 7).[58] F7

Since it is not always possible to predict which patient scheduled for a lobectomy may require a pneumonectomy for complete tumor resection, the routine use of several lung protective strategies during OLV seem logical. Overinflation of the nonoperated lung should be avoided using lung-protective ventilation (5–6 mL/kg) adding PEEP to those patients without auto-PEEP and limiting plateau and peak inspiratory pressures to <25 cm H_2O and <35 cm H_2O, respectively. Minimizing pulmonary capillary pressures by avoiding overhydration for patients undergoing pneumonectomy is reasonable, while acknowledging that not all increases in pulmonary artery pressures perioperatively are due to intravascular volume replacement. Other factors such as hypercarbia, hypoxemia, and pain can all increase pulmonary pressures and must be treated. Finally, it must be appreciated that not all hyperinflation of the residual lung occurs in the operating room. Overexpansion of the remaining lung after a pneumonectomy may occur postoperatively either with or without a chest drain in place. The use of a balanced chest drainage system to keep the mediastinum in a neutral position and avoid hyperinflation of the residual lung following a pneumonectomy has been suggested to contribute to a marked decline in this complication in some centers.[59]

Cardiopulmonary bypass causes a subclinical lung injury that can be aggravated by injurious ventilation patterns. Zupancich et al.[60] compared the use of nonprotective high tidal volumes (10–12 mL/kg) plus low PEEP (2–3 cm H_2O) versus lung protective low tidal volumes (8 mL/kg) plus high PEEP (10 cm H_2O) in patients ventilated for 6 h following cardiopulmonary bypass for coronary artery bypass surgery. Serum and bronchiolar lavage levels of the inflammatory cytokines IL-6 and IL–8 were significantly increased at 6 h only in the nonprotective ventilation group (see Fig. 8). F8

TRANSFUSION RELATED ACUTE LUNG INJURY (TRALI)

Over the past 20 years, acute lung injury secondary to transfusion of blood products has become recognized as a distinct clinical entity. It crosses the boundaries between patients with and without lung injury

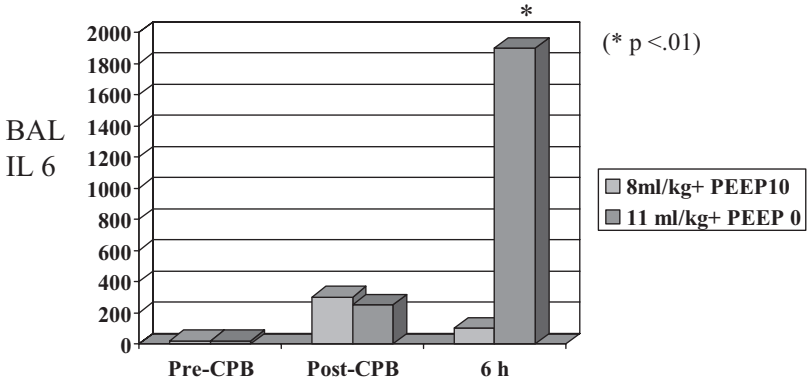


Figure 8. Bronchoalveolar lavage (BAL) levels in patients ventilated for 6 h after cardiopulmonary bypass (CPB) for coronary artery bypass surgery. Patients ventilated with larger tidal volumes (11 mL/kg) without PEEP had increased levels of the inflammatory cytokine IL-6 vs patients ventilated with smaller tidal volumes (8 mL/kg) with PEEP 10 cm H_2O. Based on data from Zupancich et al.[60]

because it can cause injury to healthy lungs or it can exacerbate incipient lung injury.[61] The etiology of TRALI is primarily due anti-white blood cell antibodies in the transfused serum. These antibodies can be to either human leukocyte antigens (HLAs) or human neutrophil antigens (HNAs). HNA antibodies can bind to and trigger neutrophils and leukocytes in the recipient. HLAs are more widespread and these antibodies can react with white blood cells and/or the pulmonary endothelium of the recipient. Neutrophils normally are flexible and are deformed as they pass through the lung, since the diameter of 50% of the pulmonary capillaries is smaller than the neutrophils. Priming of the neutrophils by sepsis, inflammation or immune triggering (as in the case of TRALI) stiffens the neutrophils which then become sequestered in the pulmonary capillary bed. This process can be aggravated by any physical injury to the endothelium which causes the release of intercellular adhesion molecules which then cause transendothelial migration of the sequestered neutrophils into the interstitium of the lung parenchyma, beginning the process of injury. The process seems to be a two-hit phenomenon usually requiring both a degree of lung injury and priming of the circulating neutrophils. Although TRALI can occur unrelated to surgery, a disproportionate number of cases occur in the perioperative period.[62]Some partially preventative measures are open to blood bankers such as the use of washed red cells, leukocyte depleted red cells, and avoiding plasma donations from multiparous females. However the major burden of prevention falls on the anesthesiologist to avoid unnecessary transfusion of blood products and to decrease the potential for perioperative mechanical lung injury.

PREVENTION AND THERAPY FOR THERAPY FOR ACUTE LUNG INJURY

Apart from mechanical ventilation strategies, a number of other therapies have been suggested to prevent or treat acute lung injury. Early reports comparing the use of volatile vs. IV anesthetics[63] have shown mixed results with respect to the ability of anesthetic agents to affect immune responses and lung endothelial injury.[64] Randomized placebo-controlled trials of several different therapies including surfactant, prone positioning, inhaled nitric oxide and anti-inflammatories have not shown significant clinical benefits in patients with established acute lung injury.[65] β-adrenergic agents are currently generating much interest as a potential treatment for acute lung injury.[66] β-agonists increase the rate of alveolar fluid clearance by increasing cellular cyclic adenosine monophophate (cAMP) in the epithelium, also β-agonists have anti-inflammatory properties. In a randomized placebo-controlled study in 40 patients with acute lung injury, Perkins et al. [67] found that the use of IV salbutamol decreased lung water and plateau airway pressure, although there were no significant differences in outcome. A randomized study of inhaled salmeterol has shown that it can reduce the incidence of high altitude pulmonary edema in subjects at risk.[68] Although studies of extracorporeal membrane oxygenation have not shown survival benefits in adults, a pumpless extracorporeal membrane ventilator may be of some benefit.[69]

SUMMARY

There are several evidence-based strategies that can reduce the incidence of perioperative lung injury in patients with noninjured lungs; these include avoidance of bronchospasm, discontinuation of smoking, physiotherapy, and aggressive treatment of atelectasis. The use of epidural analgesia has been demonstrated to reduce respiratory complications in patients with COPD having major surgery. The use of lung-protective mechanical ventilation strategies intraoperatively has not been proven to improve outcomes in this group. However, evidence is accumulating that traditional large-volume tidal volume ventilation without PEEP cases a subclinical lung injury in proportion to the duration of mechanical ventilation in patients with healthy lungs.

There are more patients than commonly appreciated who are at increased risk for acute lung injury during surgery; these include patients with large pulmonary resections and those exposed to cardiopulmonary bypass. Given the low risks, lung protective ventilation strategies, including using low-tidal volumes and the selective use of PEEP, would seem to be a logical choice for ventilation management for these patients in the current era of a low frequency of hypoxemia and continuous arterial oxygen saturation monitoring.

REFERENCES

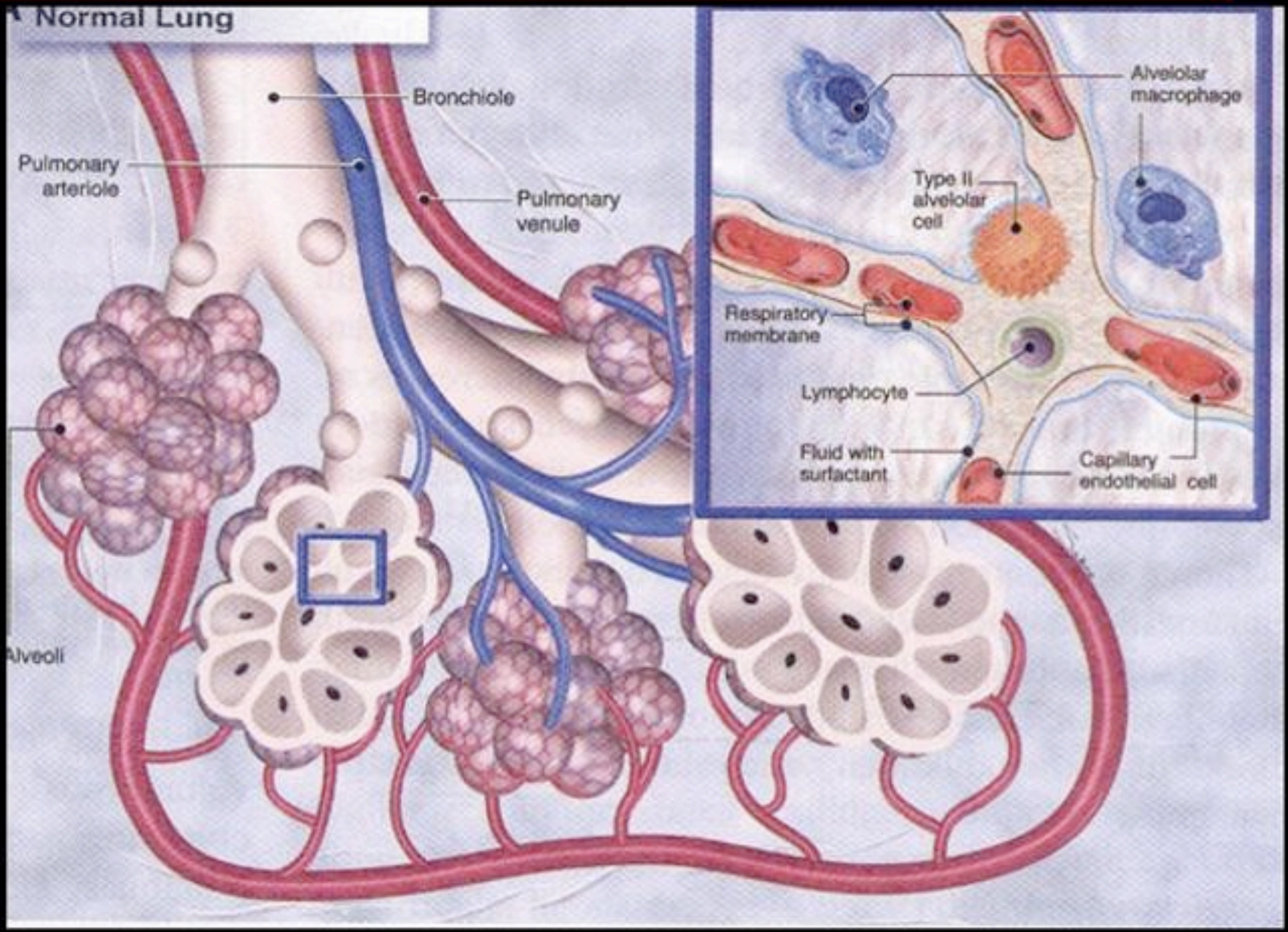
1. Bendixen HH, Hedley-White J, Laver MB. Impaired oxygenation in surgical patients during general anesthesia with controlled ventilation: a concept of atelectasis. N Engl J Med 1963;96:156–66
2. Tenny SM, Remmers JE. Comparative quantitative morphology of the mammalian lung: diff using area. Nature 1963;197:54–6
3. Gajic O, Dara SI, Mendez JL. Ventilator associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. Crit Care Med 2004;32:1817–24
4. Gajic O, Frutos-Vivar F, Esteban A. Ventilator settings as a risk factor for acute respiratory distress syndrome in mechanically ventilated patients. Intensive Care Med 2005;31:922–6
5. Michelet P, D'Jo X-B, Roch A. Protective ventilation influences systemic inflammation after esophagectomy. Anesthesiology 2006;105:911–9
6. Choi G, Wolthuis EK, Bresser P. Mechanical ventilation with lower tidal volumes and positive end-expiratory pressure prevents alveolar coagulation in patients without lung injury. Anesthesiology 2006;105:689–95
7. Myles PE, Madder H, Morgan EB. Intraoperative cardiac arrest after unrecognized dynamic hyperinflation. Br J Anaesth 1995;74:340–1
8. Ben-David B, Stonebraker VC, Hershman R, Frost CL, Williams HK. Survival after failed intraoperative resuscitation: a case of "Lazarus syndrome." Anesth Analg 2001;92:690–1

9. Morgan MDL, Edwards CW, Morris J, Matthews HR. Origin and behavior o f emphysematous bullae. Thorax: 1989;44:533–6
10. Parot S, Saunier C, Gauthier H, Milic-Emile J, Sadoul P. Breathing pattern and hypercapnia in patients with obstructive pulmonary disease. Am Rev Resp ir Dis 1980;121:985–91
11. Levetown M. Oxygen-induced hypercapnia in chronic obstructive pulmonary disease: what's the problem? Critic Care Med 2002;30:258–9
12. Aubier M, Murciano D, Milic-Emili J. Effects of the administration of O_2 on ventilation and blood gases in patients with chronic obstructive pulmonary disease during acute respiratory failure. Am Rev Respir Dis 1980;122:747–54
13. Hanson CW III, Marshall BE, Frasch HF, Marshall C. Causes of hypercarbia in patients with chronic obstructive pulmonary disease. Crit Care Med 1996;24:23–8
14. Slinger P, Blundell P, Metcalf I. Management of massive grain a spiration. Anesthesiology 1997;87:993–5
15. Douglas NJ, Flenley DC. Breathing during sleep in patients with obstructive lung disease. Am Rev Respir Dis 1990;141:1055–70
16. Klinger JR, Hill NS. Right ventricular dysfunction in chronic obstructive pulmonary disease. Chest 1991;99:715–23
17. Schulman DS, Mathony RA. The right ventricle in pulmonary disease. Cardiol Clin 1992;10:111–35
18. Warner DO. Preventing postoperative pulmonary complications. Anesthesiology 2000;92:1467–72
19. Niederman MS, Clemente P, Fein AM. Benefits of a multidisciplinary pulmonary rehabilitation program. Chest 1991; 99:798–801
20. Selsby D, Jones JG. Some physiological and clinical aspects of chest ph ysiotherapy. Br J Anaesth 1990;64:621–26
21. Warner DO. Helping surgical patients quit smoking: why, when and how. Anesth Analg 2005;101:481–7
22. Nisar M, Eoris JE, Pearson MG, Calverly PMA. Acute bronchodilator trials in chronic obstructive pulmonary disease. Am Rev Respir Dis 1992;146:555–9
23. Bishop M, Cheny F. Anesthesia for patients with asthma: low risk but not no risk. Anesthesiology 1996;85:455–6
24. Hurford W. The bronchospastic patient. Int Anesthesiol Clin 2000;38:77–90
25. Silvanus MT, Groeben H, Peters J. Corticosteroids and inhaled salbutamol in patients with reversible airway obstruction markedly decrease the incidence of bronchospasm after tracheal intubation. Anesthesiology 2004;100:1052–7
26. Ramivohan SM, Kaman L, Jindal R. Postoperative pulmonary function in laparoscopic versus open cholecystectomy. Indian J Gastroenterol 2005;24:6–8
27. Lindberg P, Gunnarsson L, Tokics L. Atelectasis and lung function in the postoperative period. Acta Anaesthesiol Scand 1992;36:546–53
28. Tusman G Bohm SH. Suarez-Sipmann F. Alveolar recruitment improves ventilatory efficiency of the lungs during anesthesia. Can J Anaesth 2004;51:723–7
29. D uggan M, Kavanagh B. Pulmonary atelectasis a pathological perioperative entity. Anesthesiology 2005;102:838–54
30. Ballantyne JC, Carr DB, deFerranti S. The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta-analysis of randomized, controlled trials. Anesth Analg 1998;86:598–612
31. Rigg J, Jamrozik K, Myles P. Epidural anaesthesia and analgesia and outcome of major surgery: a randomized trial. Lancet 2002;359:1276–82
32. Squadrone V, Coha M, Cerutti E. Continuous positive airway pressure for treatment of postoperative hypoxemia. JAMA 2005;293:589–95
33. Grichnik KP, D'Amico TA. Acute lung injury and acute respiratory distress syndrome after pulmonary resection. Sem Cardiothorac Vasc Anesth 2004;8:317–34
34. Zeldin RA, Normadin D, Landtwing BS, Peters RM. Postpneumonectomy pulmonary edema. J Thorac Cardiovasc Surg 1984;87:359–65
35. Slinger P. Post-pneumonectomy pulmonary edema: is anesthesia to blame? Curr Opin Anesthesiol 1999;12:49–54
36. Turnage WS, Lunn JL. Postpneumonectomy pulmonary edema: a retrospective analysis of associated variables. Chest 1993;103:1646–50
37. Waller DA, Gebitekin C, Saundres NR, Walker DR. Noncardiogenic pulmonary edema complicating lung resection. Ann Thorac Surg 1993;55:140–3
38. Keegan MT, Harrison BA, De Ruyter ML, Deschamps C. Postpneumonectomy pulmonary edema are we making progress? Anesthesiology 2004;101:A431
39. Licker M, De Perrot M, Spiliopoulos A. Risk factors for acute lung injury after thoracic surgery for lung cancer. Anesth Analg 2003;97:1558–65
40. Padley SPG, Jordan SJ, Goldstraw P. Asymmetric ARDS following pulmonary resection. Radiology 2002;223:468–73
41. Waller DA, Keavey P, Woodfine L, Dark JH. Pulmonary endothelial permeability changes after major resection. Ann Thorac Surg 1996;61:1435–40
42. Williams EA, Quinlan GJ, Goldstraw P. Postoperative lung injury and oxidative damage in patients undergoing pulmonary resection. Eur Respir J 1998;11:1028–34
43. Tayama K, Takamori S, Mitsuoka M. Natriuretic peptides after pulmonary resection. Ann Thorac Surg 2002;73:1582–6
44. Misthos P, Katsaragikis A, Milingos N. Postresectional pulmonary oxidative stress in lung cancer patients: the role of one-lung ventilation. Eur J Cardiothorac Surg 2005;27:379–83
45. Stewart DJ, Martin-Uncar AE, Edwards JG. Extra-pleural pneumonectomy for malignant mesothelioma: the risks of induction chemotherapy, right-sided procedures and prolonged operations. Eur J Cardiothorac Surg 2005;27:373–8
46. Boker A, Haberman C, Girling L. Variable ventilation improves perioperative lung function in patients undergoing abdominal aortic aneurysmectom y. Anesthesiology 2004; 100:608–16
47. Mols G, Priebe H-J, Guttmann. Alveolar recruitment in acute lung injury. Br J Anaesth 2006;96:156–66
48. Dreyfuss D, Soler P, Basset G. High Inflation pressure pulmonary edema. Am Rev Respir Dis 1988;137:1159–64
49. Slinger P, Hickey DR. The interaction between applied PEEP and auto-PEEP during one-lung ventilation. J Thorac Cardiovasc Anesth 1998;12:133–6
50. Capan LM, Turndorf H, Patel C. Optimization of arterial oxygenation during one-lung anesthesia. Anesth Analg 1980;59:847–51
51. Slinger P, Kruger M, McRae K, Winton T. Relation of the static compliance curve and positive end-expiratory pressure to oxygenation during one-lung. Anesthesiology 2001;95:1096–102
52. 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 Anesthesia 2001;13:473–7
53. Tsuchida S, Engleberts D, Peltekova V. Atelectais causes alveolar injury in nonatelectatic lung regions. AJRCCM 2006; 174:279–89
54. Gama de Abreu M, Heintz M, Heller A. One-lung ventilation with high tidal volumes and zero positive end-expiratory pressure is injurious in the isolated rabbit lung model. Anesth Analg 2003;96:220–8
55. Kuzkov V, Suborov E, Kirov M. Extravascular lung water after pneumonectomy and one-lung ventilation in sheep. Crit Care Med 2007;35:1550–9
56. Leo F, Solli P, Spaggiari L. Respiratory function changes after chemotherapy: an additional risk for post-operative respiratory complications? Ann Thorac Surg 2004;77:260–5
57. Van der Werff YD, van der Houwen HK, Heilmans PJM. Postpneumonectomy pulmonary edema: a retrospective analysis of incidence and possible risk factors. Chest 1997; 111:1278–84
58. Fernandez-Perez E, Keegan M, Brown DR. Intraoperative tidal volume as a risk factor for respiratory failure after pneumonectomy. Anesthesiology 2006;105:14–18
59. Alvarez JM, Panda RK, Newman MAJ. Postpneumonectomy pulmonary edema. J Cardiothorac Vasc Anesth 2003; 17:388–95
60. Zupancich E, Paparella D, Turani F. Mechanical ventilation affects inflammatory mediators in patients undergoing cardiopulmonary bypass for cardiac surgery: a randomized controlled trial. J Thorac Cardiovasc Surg 2005;130:378–83
61. Bux J, Sachs UJH. The pathogenesis of transfusion related lung injury (TRALI). Br J Haem atol 2007;136:788–99
62. Popovsky MA, Moore SB. Diagnostic and pathogenic considerations in transfusion-related acute lung injury. Transfusion 1985;25:573–77

63. Schilling T, Kozian A, Kretzschmar M. Effects of desflurane or propofol on pulmonary and systemic immune responses to one-lung ve ntilation. Anesthesiology 2006;105:A15
64. Balyasnikova I, Vistinine D, Gunnerson H. Propofol attenuates lung endothelial injury induced by ischemia-reperfusion and oxida tive stress. Anesth Analg 2005;100:929–36
65. Bernard GR. Acute respiratory distress syndrome. Am J Respir Crit Care Med 20 05;171:1125–8
66. Matthay M. β-adrenergic agonist therapy as apotential treatment for acute lung injury. Am J Respir Crit Care Med 2006;173:254–5
67. Perkins GD, McAuley DF, Thickett DR. The β-agonist lung injury trial. Am J Respir Crit Care Med 2006;173:281–7
68. Sartori C, Allemann Y, Duplain H. Salmeterol for the prevention of high altitude pulmonary edema. New Engl J Med 2002;346:1631–6
69. Iglesias M, Martinez E, Badia JR. Extrapulmonary venti lation for unresponsive severe acute respiratory distress syndrome after pulmonary resection. Ann Thorac Surg 2008;85:237–44

Pulmonary Atelectasis

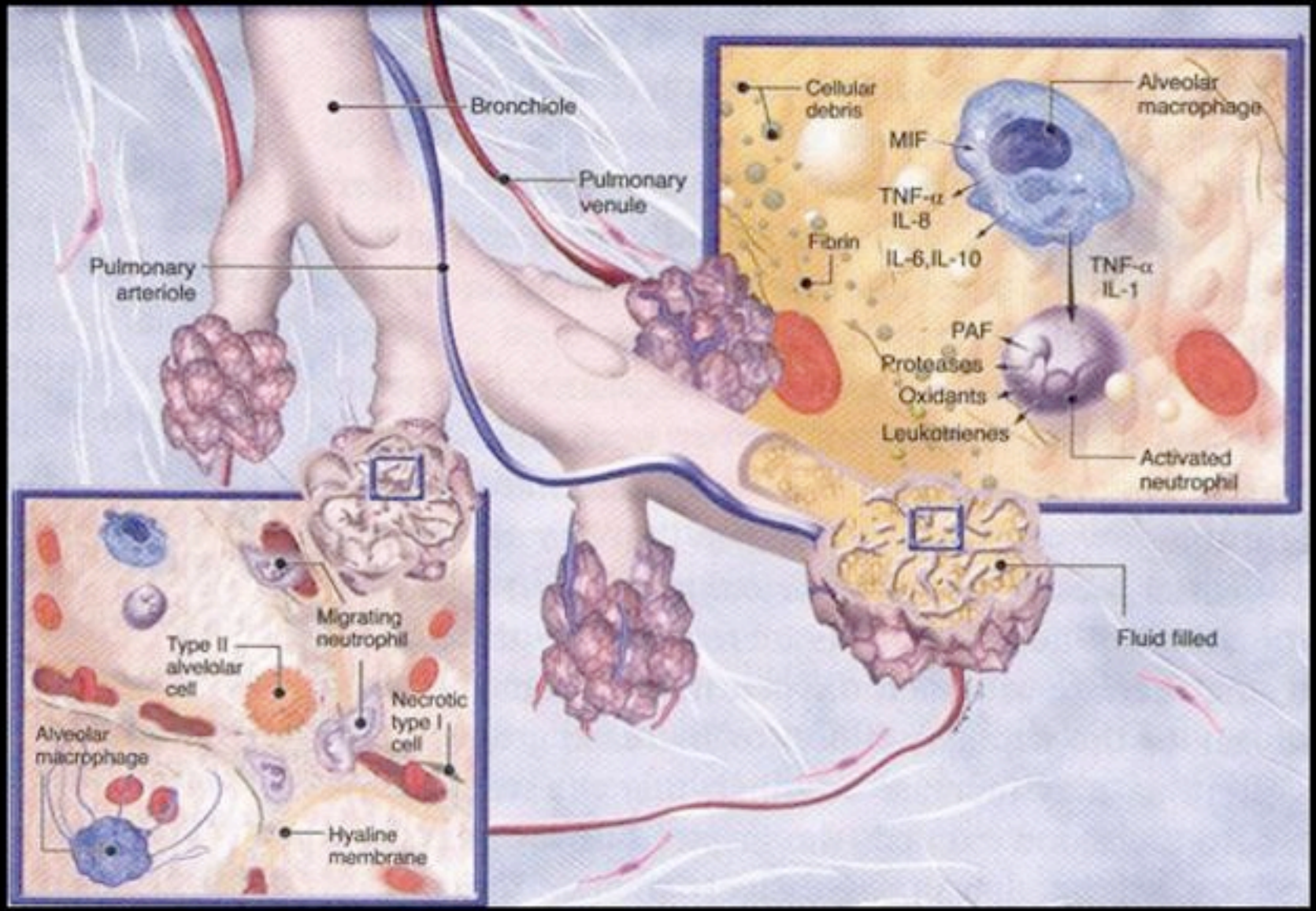
Duggan M, Kavanagh B. Anesthesiology 2005, 102: 838-54



Pulmonary Atelectasis

Duggan M, Kavanagh B. Anesthesiology 2005, 102: 838-54

Atelectasis

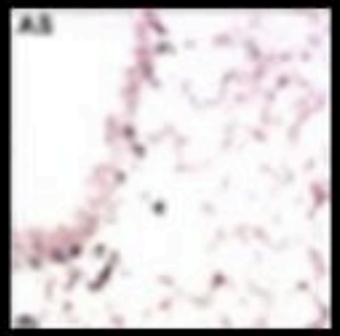


Atelectasis Causes Lung Injury in Non-Atelectatic Lung Regions

Tschudia S, et al. AJRCCM 2006: 174: 279-89

Non-Dependent

Dependent



- Rat lung injury model
- Lg. Vol. Vent.
- Distal airway injury all regions
- Alveolar injury more severe in non-dependent, non-atelectatic regions

Helping Surgical Patients Quit Smoking

Warner DO, Anesth Analg 2005; 101: 481-7

Surgical Benefits:

- Decrease ST changes intraop.: 2 days
- Decrease wound complic's: ≥4wk.
- Decrease Resp. Complications :
  - Cardiac: ≥8 wk.
  - Thoracic: Anytime

Abstinence @ 1yr:

- Angiography: 14%
- Angioplasty : 25%
- After ACB: 55%

Preoperative Physiotherapy

- Particularly in patients with excessive secretions
- No proven superior modality
- Proven decrease in pulmonary complications in COPD

Warner DO, Anesthesiology 2000, 92: 1467

The Comparative Effects of Analgesia on Pulmonary Outcomes : Meta-Analysis

Ballantyne JC, et al. Anesth Analg 1998, 86: 598

- Atelectasis decreased: Epidural opioid/LA vs. Systemic opioid
- Pulmonary Infections decreased Epidural opioid/LA vs. Systemic opioid
- Pain VAS movement (not PFTs) correlate with outcome

Epidural Anaesthesia and Analgesia and Outcome of Major Surgery (MASTER)

n =888, random., ASA >/=3, Abd./Esoph. Surg.,
225/ 447 Epidural > 72h.

- Mortality Epidural vs. IV: ns.
- Cardiac/Renal/GI/ Sepsis: ns.
- Analgesia: Epid. vs. IV @ rest n.s.,
  with cough <.001
- Resp. Fail. Epid. vs. IV: 23% vs. 30% (.02)

Rigg JRA, et al. Lancet 359: 1276-82, 2002

CPAP Treatment of Post-op. Hypoxemia

Squadrone V, et al. JAMA 2005, 293: 589-95

Patients:

- n= 209
- Major Abd. Surg.
- PaO2/FiO2<300 post-op. in Rec. Room
- FiO2 0.5 by mask or CPAP until PaO2/FiO2 stable >300 (19-28h)

Results:

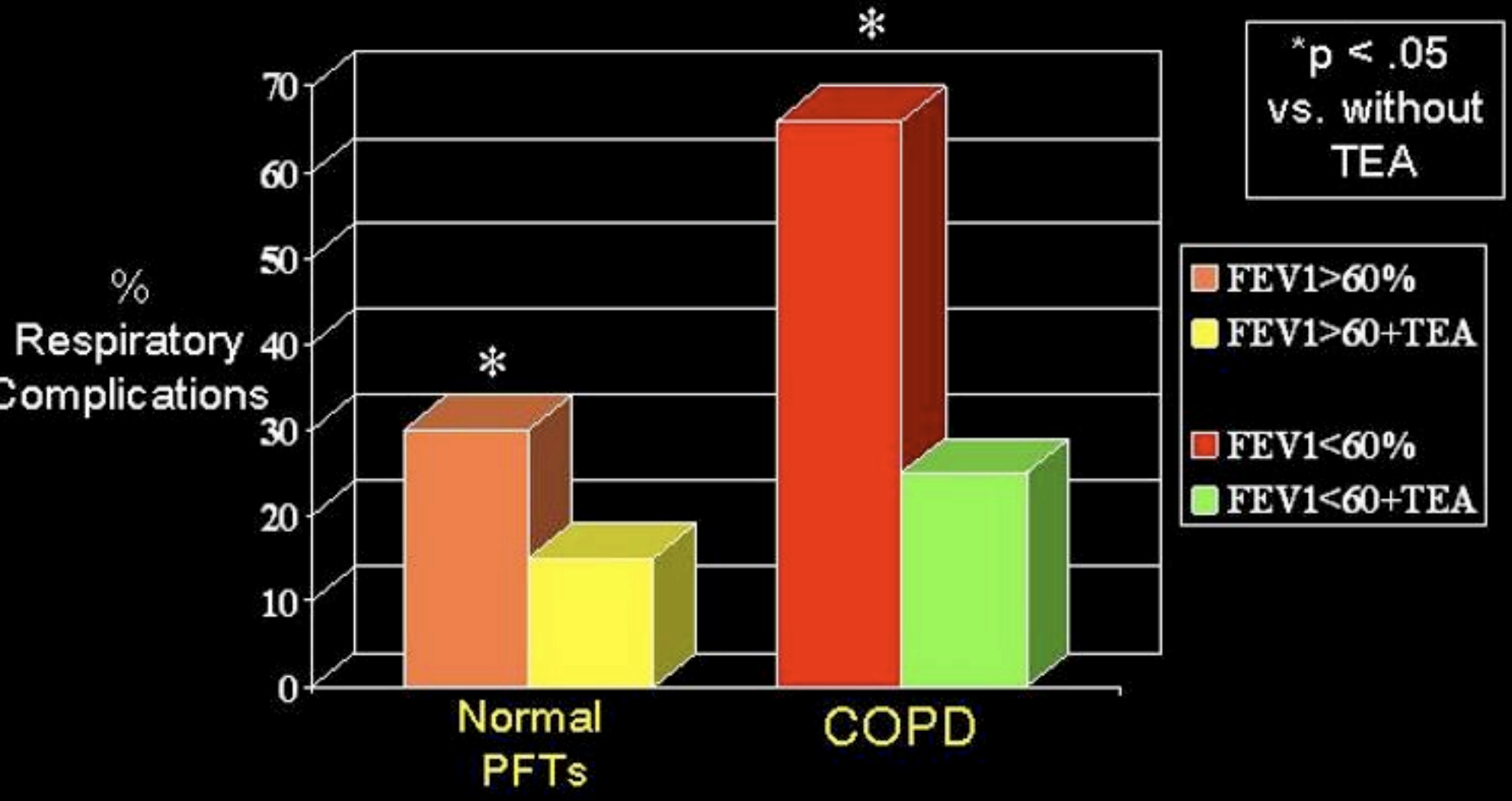
- CPAP decreased Sepsis (p= .03)
- Decreased Pneumonia (p= .02)
- Decreased Re-intubation (p< .01)

Post-Pneumonectomy Pulmonary Edema

Turnage WS, Lunn JL. Chest 103: 1646-50, 1993

- 806 Pneumonectomies, 21 cases
- Right Pneumectomy 16 vs. Left 5
- Mortality 21/21 (ARDS)
- Cases vs. Controls:
  - Fluid Balance (n.s.)
  - Fluid Administration (n.s.)
  - mean PAOP: initial 10, final 13 (n.s.)

Reduction of Respiratory Complications in Lung Resection by Thoracic Epidural



Licker M, et al. Ann Thorac Surg 2006; 81: 1830-8

Pulmonary Endothelial Permeability Changes after Major Lung Resection

Pneumx. =24, Lobx. =11, rad-labl. Alb., 8h post-op.

- Permeability Pneumx. > Lobx. ($p<.01$)
  (Low-Press., hi-Prot. PE fluid)
- Increase Perm. $\propto$ Increase PVR
- Increase MPAP $\propto$ 1/ pre MPAP

Waller DA, et al. Ann Thorac Surg 1996, 61: 1435-40

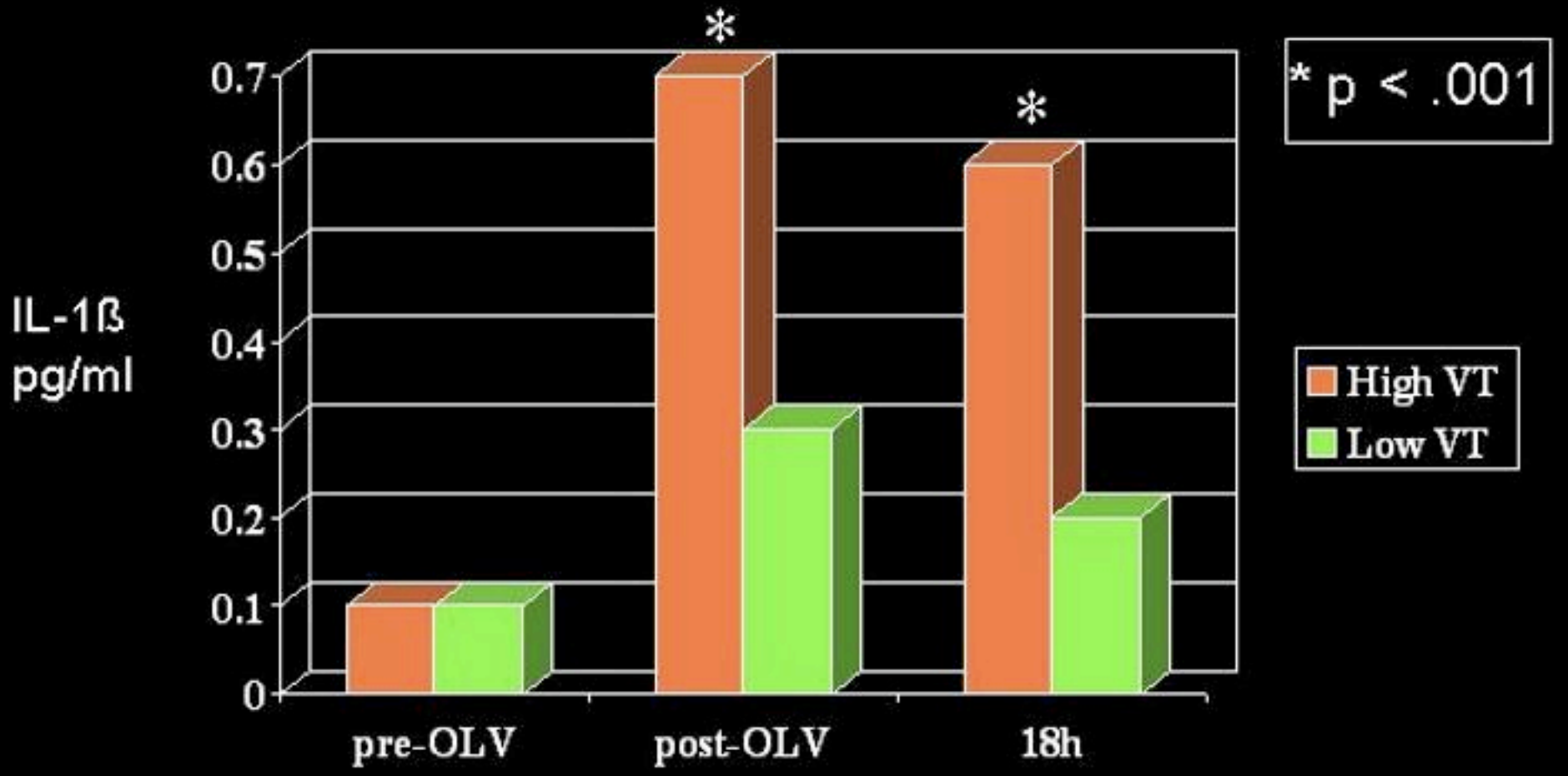
Post-operative Lung Injury and Oxidative Damage

Williams EA, et al. Eur Resp J 1998, 11: 1028-34

Operation	Increase Plasma Protein Carbonyl %
Pneumonectomy	26 ($p<.05$)
Bi-lobectomy	10
Lobectomy	5
Wedge/Biopsy	0
Abdominal Surgery	0

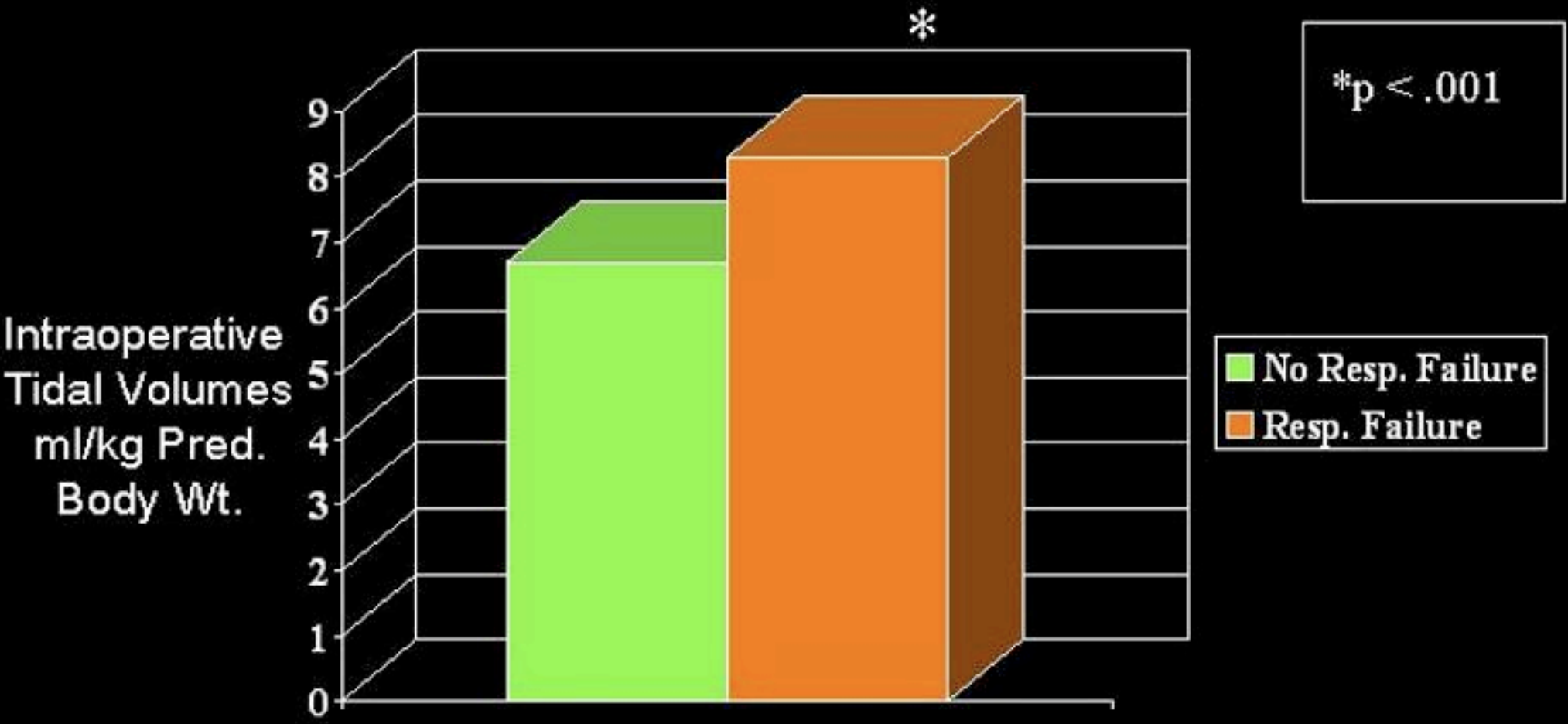
(n= 8/group)

Protective Ventilation Influences Systemic Inflammation after Esophagectomy



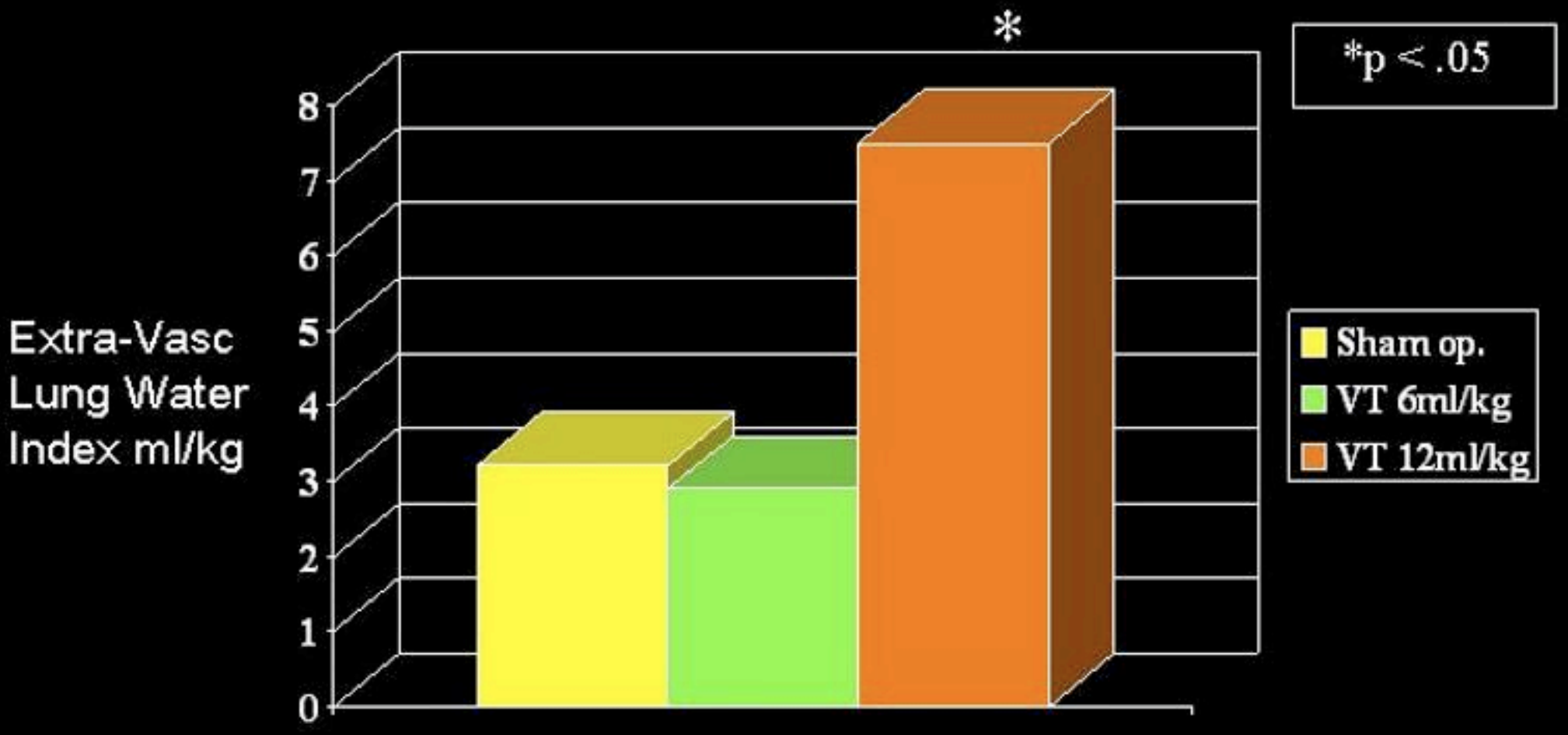
Michelet P, et al. Anesthesiology 2006; 105: 911-9

Intra-operative Tidal Volumes vs. Post-Pneumonectomy Respiratory Failure



Fernandez-Perez ER, et al. Anesthesiology 2006, 105:14-18

Extravascular Lung Water after Pneumonectomy in Sheep



Kuzkov V, et al. Crit Care Med 35: 1550-9, 2007

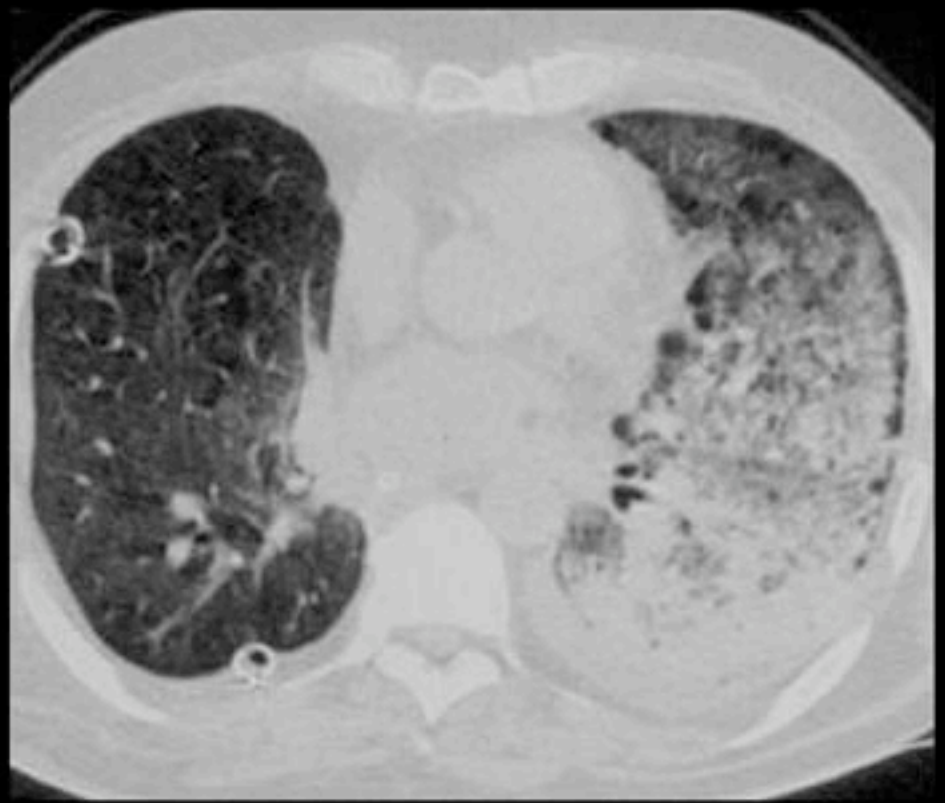
Principles of Lung-Protective Ventilation:

- Mimic normal spontaneous ventilation
- FiO_2 as low as safe
- Tidal volumes 4-6 ml/kg
- Frequent recruitment maneuvers
- Vary position / vary tidal volume
- PEEP to maintain FRC

Fan E, et al. JAMA. 2005; 294:2889-96

Asymmetric ARDS Following Pulmonary Resection

Padley S, et al. Radiology 223: 468-73, 2002

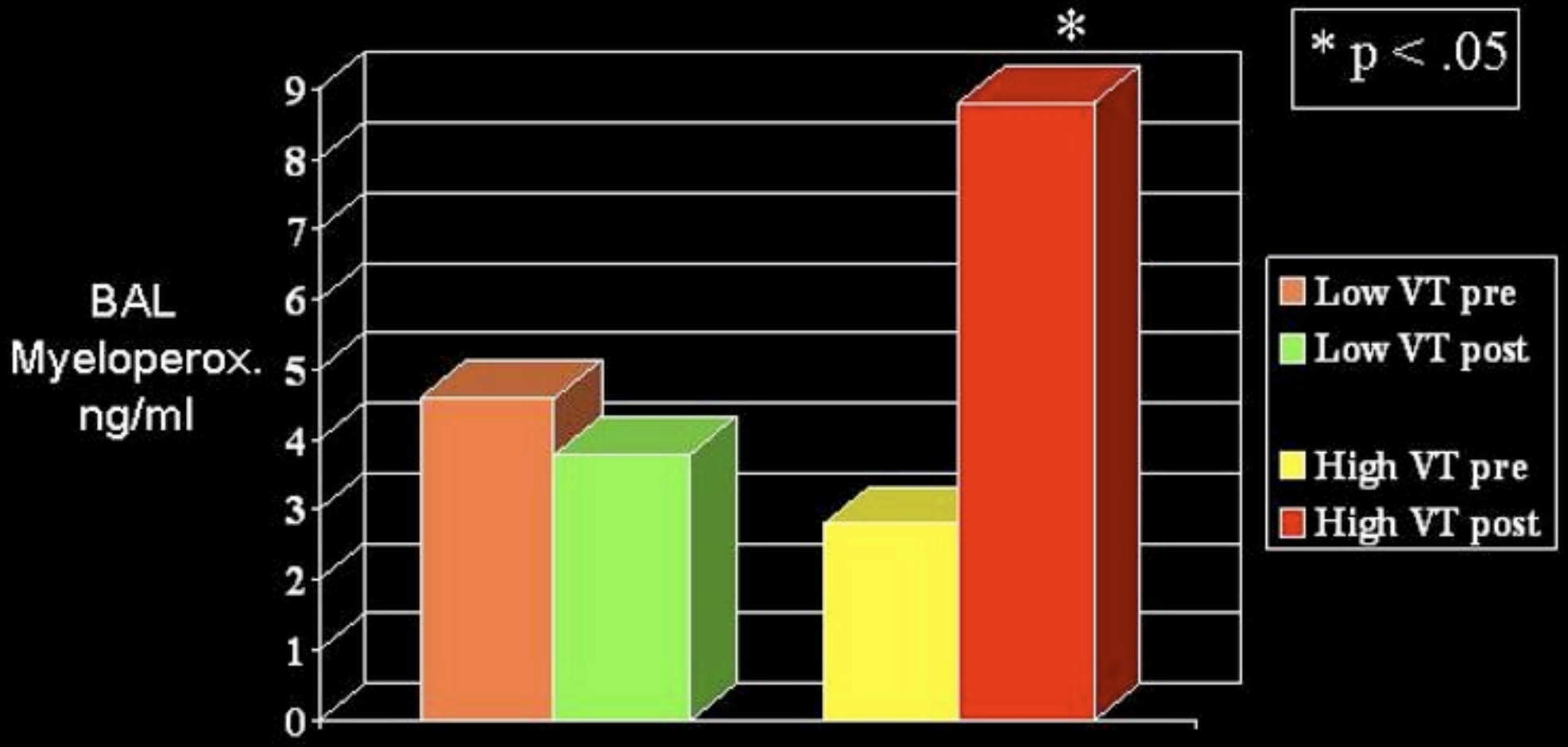


- 17/ 583 (3%) lobectomies ARDS
- 9/17 CT scans
- 8/9 ARDS in Non-operated lung

Individualizing One-lung Ventilation:

		Exceptions:
Tidal Vol.	4-5 ml/kg	Pk. a/w P<35 Plat. a/w P<25
PEEP	Total 5 cm.	Not added if COPD
FiO2	1.0 initial	Decrease as tol.
Resp. Rate	12	Maint. Norm. PaCO2
Mode	Vol-C Vent.	P-C V: COPD, LTx, Pneumnx

Low Tidal Vol. + PEEP Prevents Pulmonary Inflammation in Patients Without Lung Injury



N=40, Abd. Surg. 5h PPV,
VT= 12ml/kg vs. 6 ml/kg -/+ 10cmH2O PEEP

Wolthuis EK, et al. Anesthesiology 2008; 108: 46-54

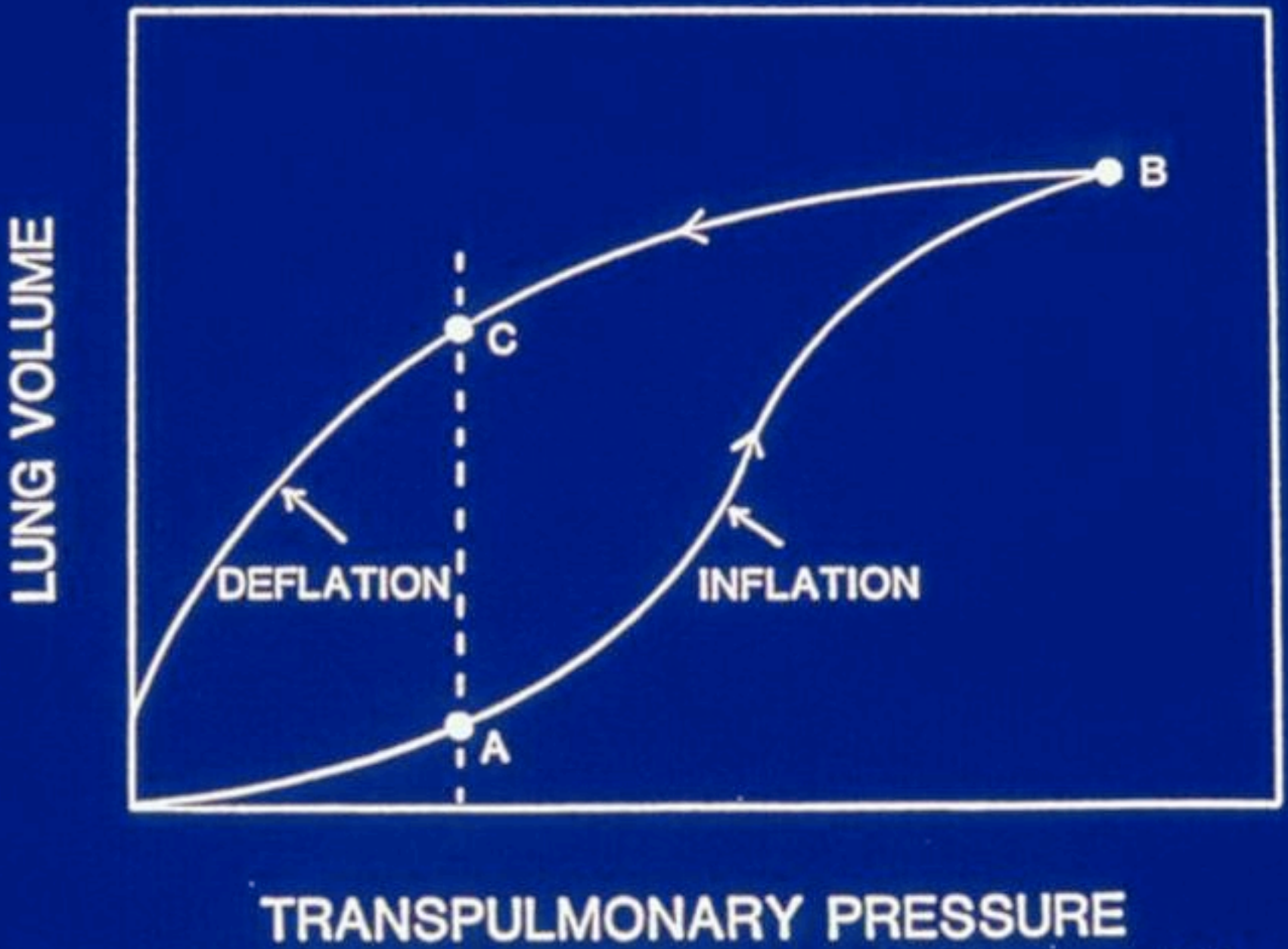
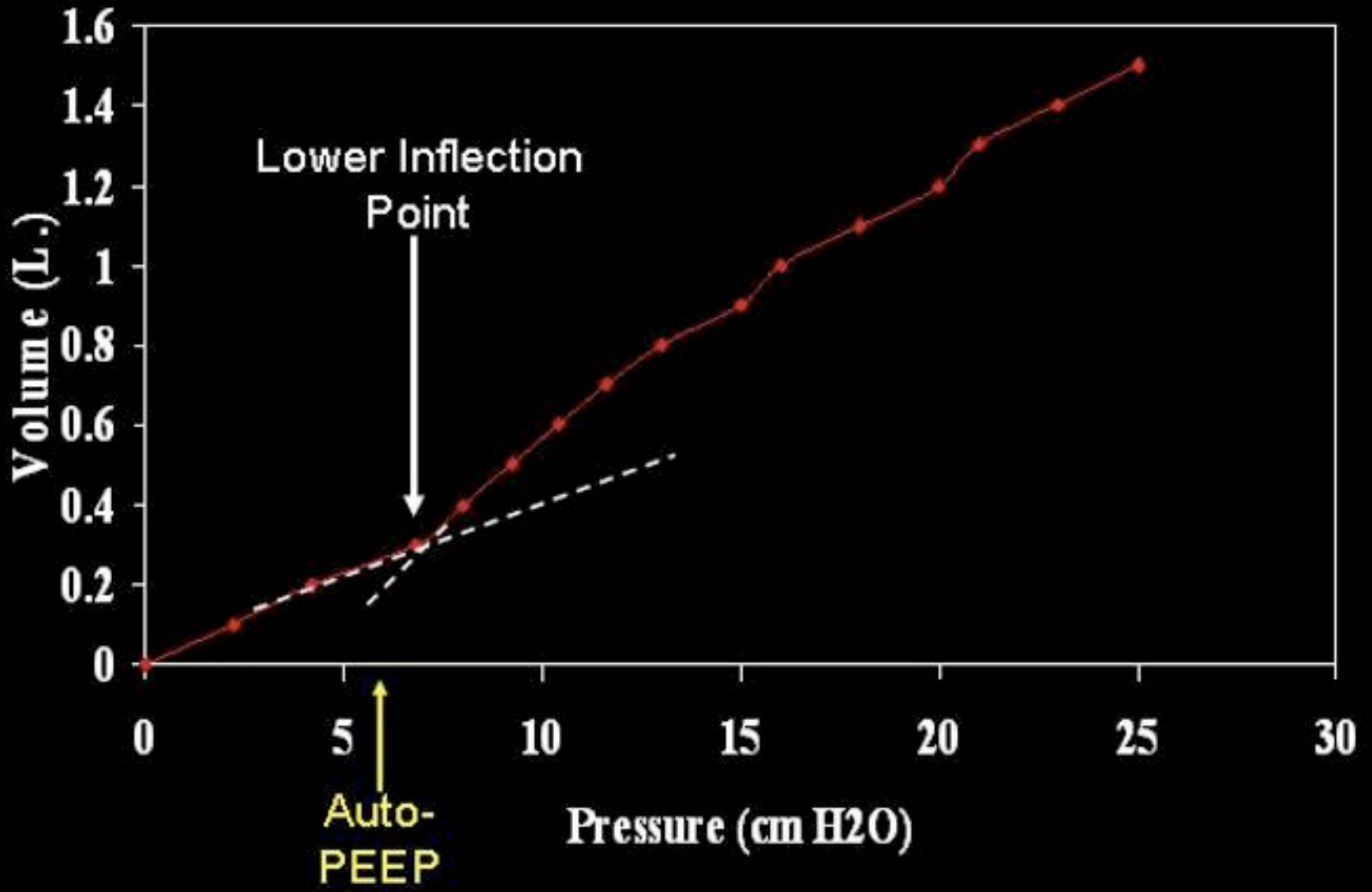


Fig. 1. Classical static pressure-volume curve of the lung. Volume for a given pressure is much greater on the deflation limb than on the inflation portion. Symbols are referenced in the text.

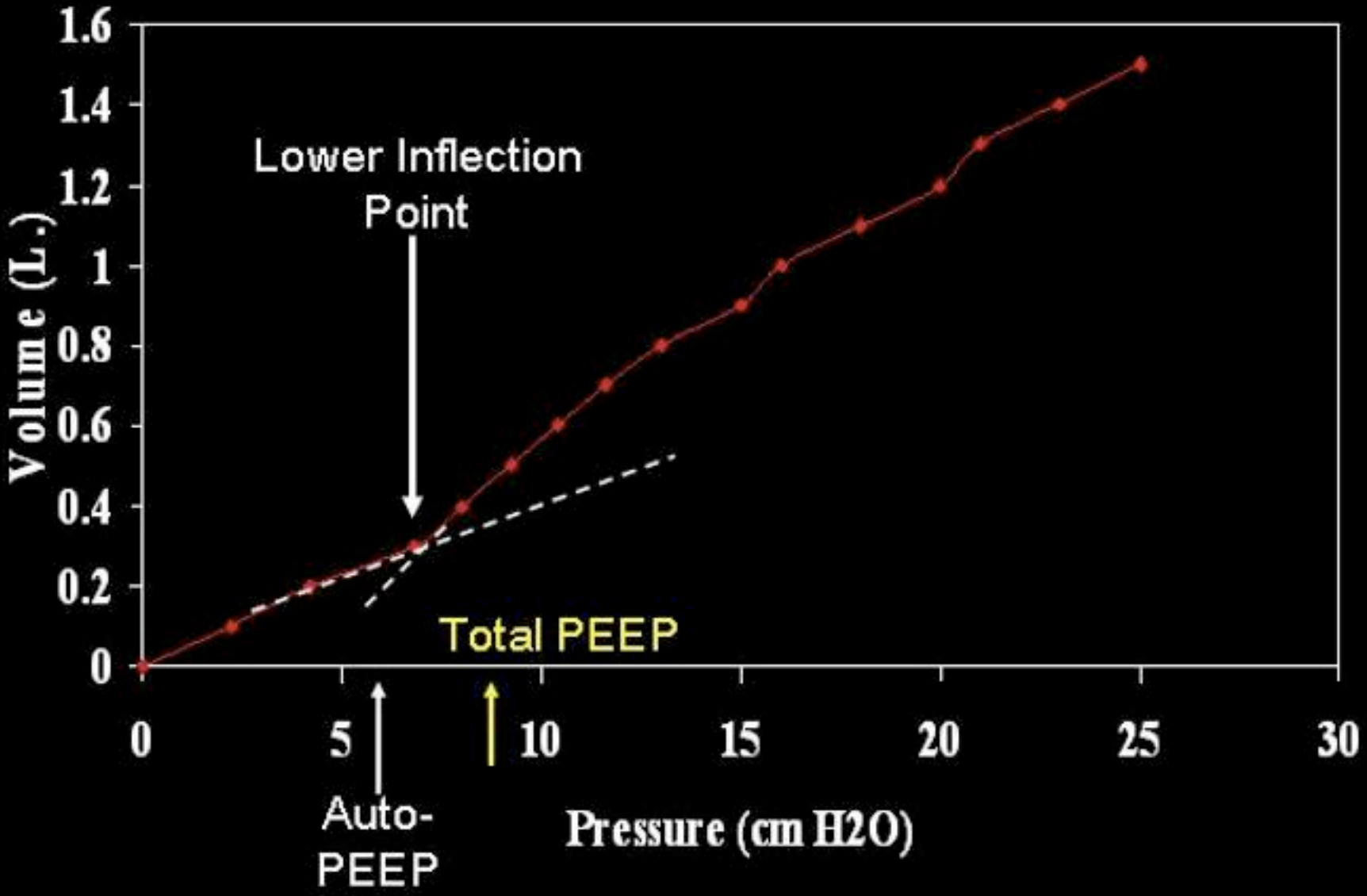
Static Compliance Curve of the Ventilated (dependent) Lung, 57 y.o. Female, FEV1= 72%

Slinger P, et al. Anesthesiology 95:1096, 2001



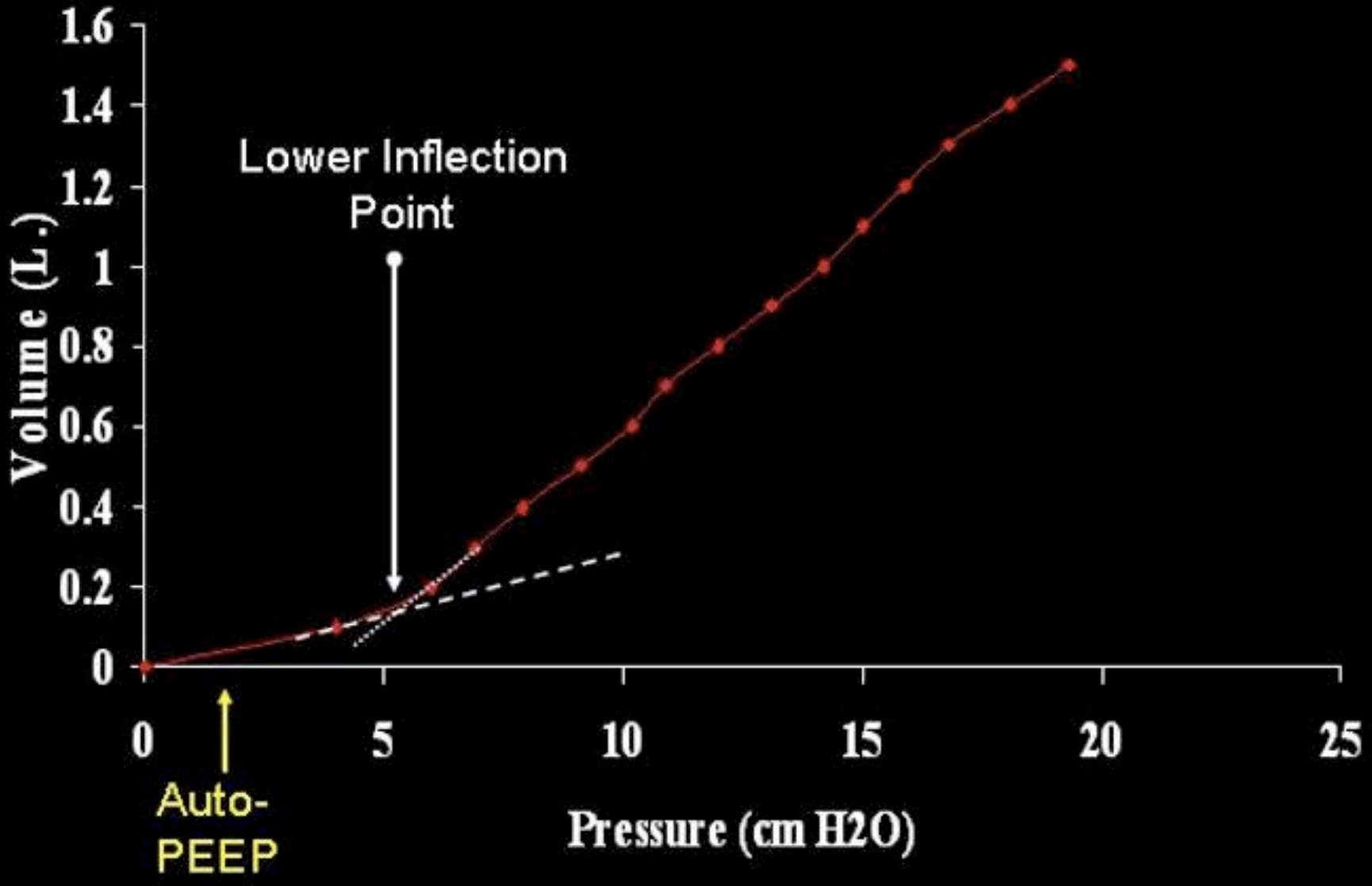
Static Compliance Curve of the Ventilated (dependent) Lung, 57 y.o. Female, FEV1= 72%

Slinger P, et al. Anesthesiology 95:1096, 2001



One-Lung, Static Compliance Curve

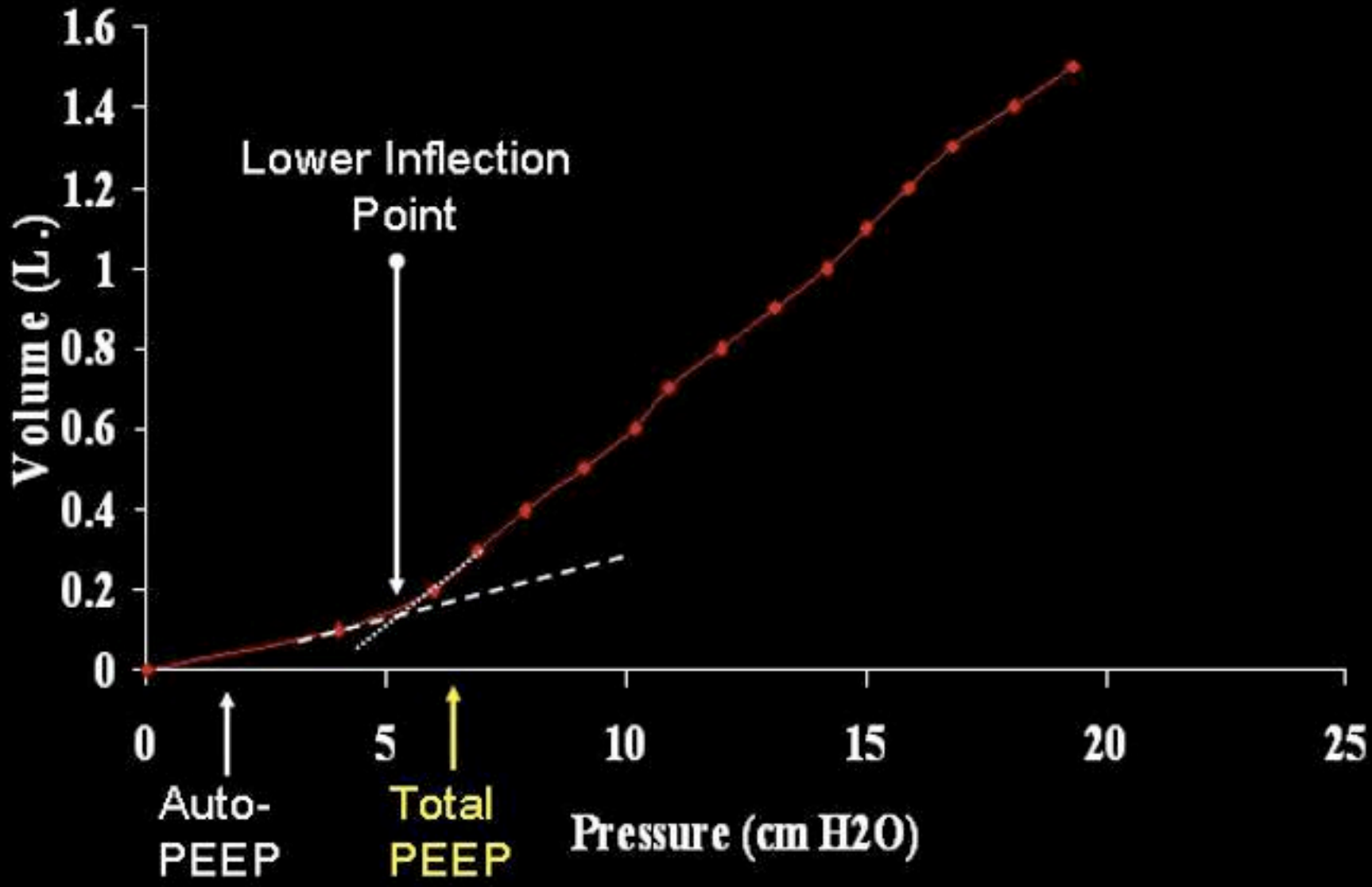
Slinger P, et al. Anesthesiology 2001, 95: 1096



32 y.o. Male, FEV1= 102%

One-Lung, Static Compliance Curve

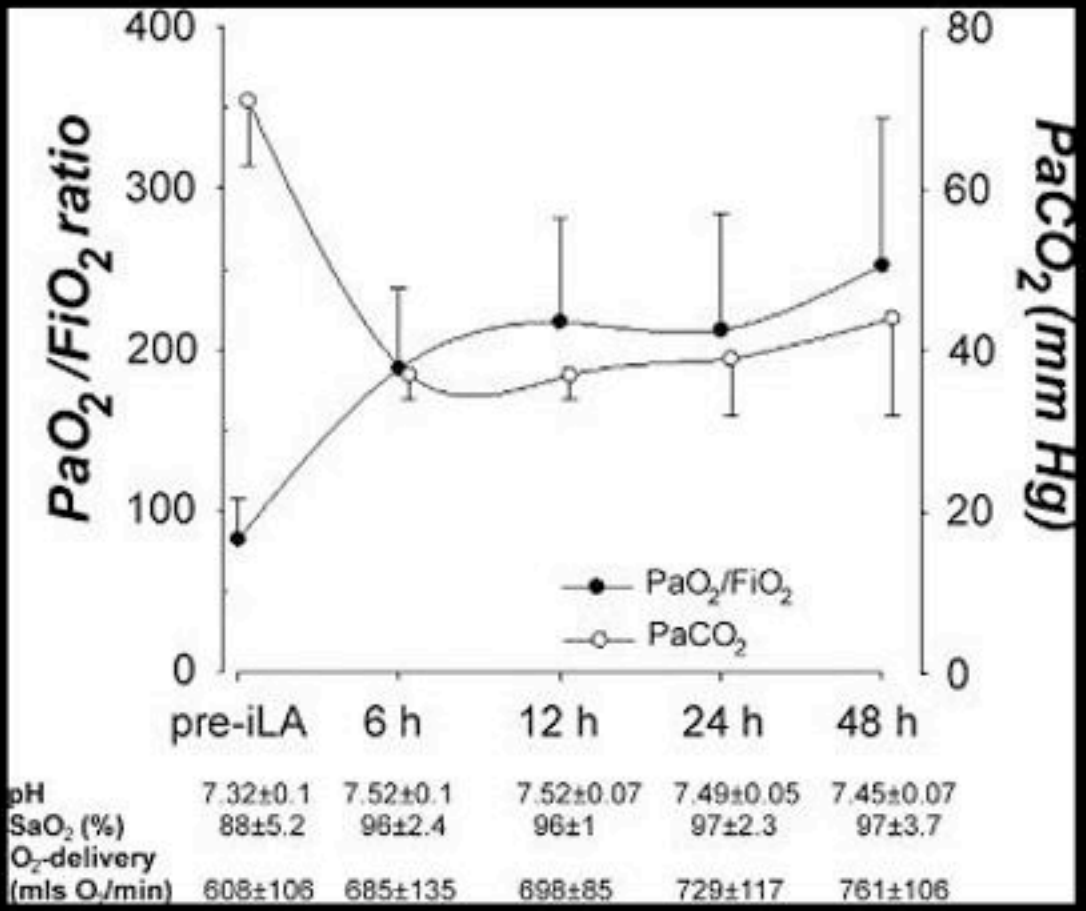
Slinger P, et al. Anesthesiology 2001, 95: 1096



32 y.o. Male, FEV1= 102%

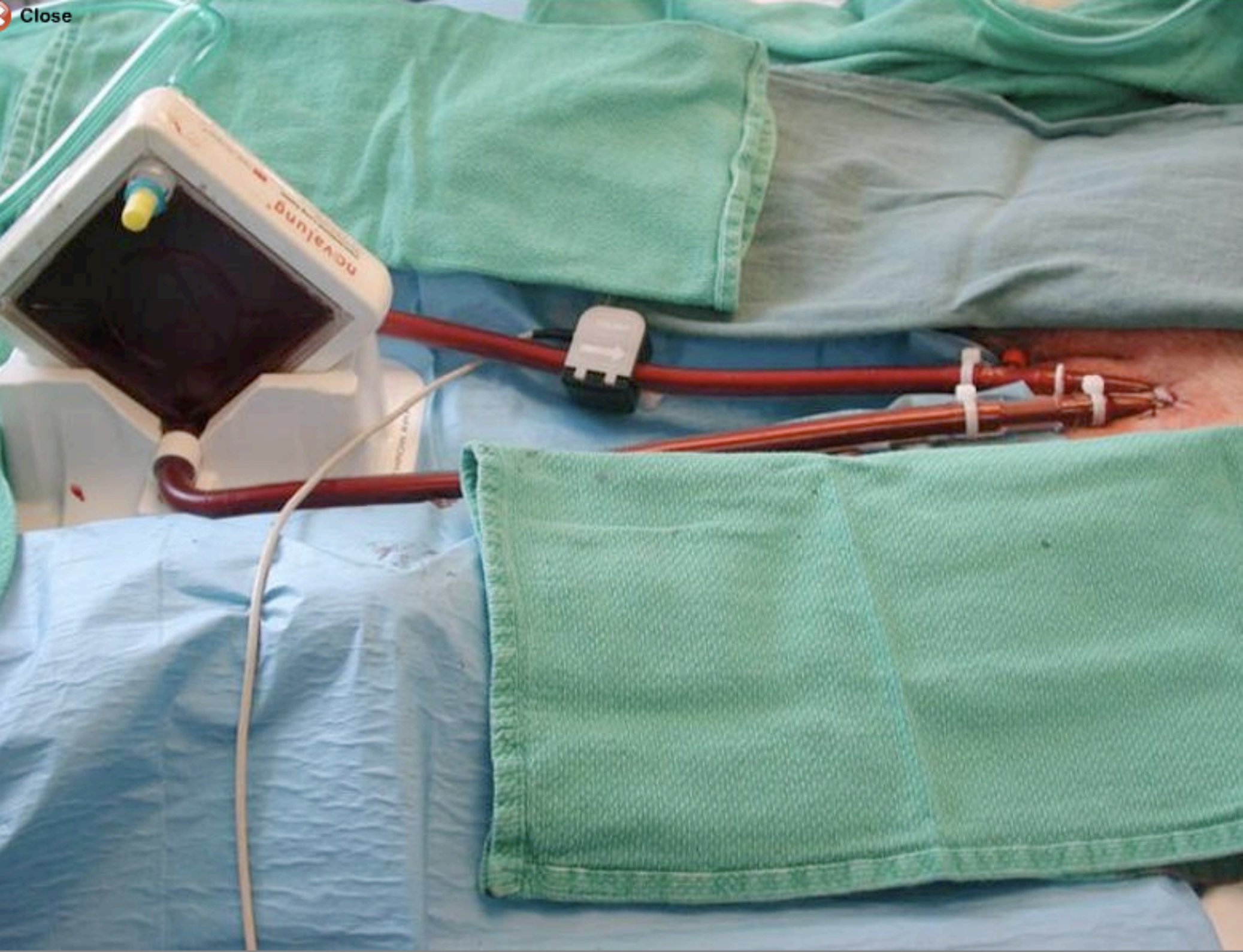
Extrapulmonary Ventilation for ARDS after Pulmonary Resection

Iglesias M, et al. Ann Thorac Surg 85: 237-44, 2008

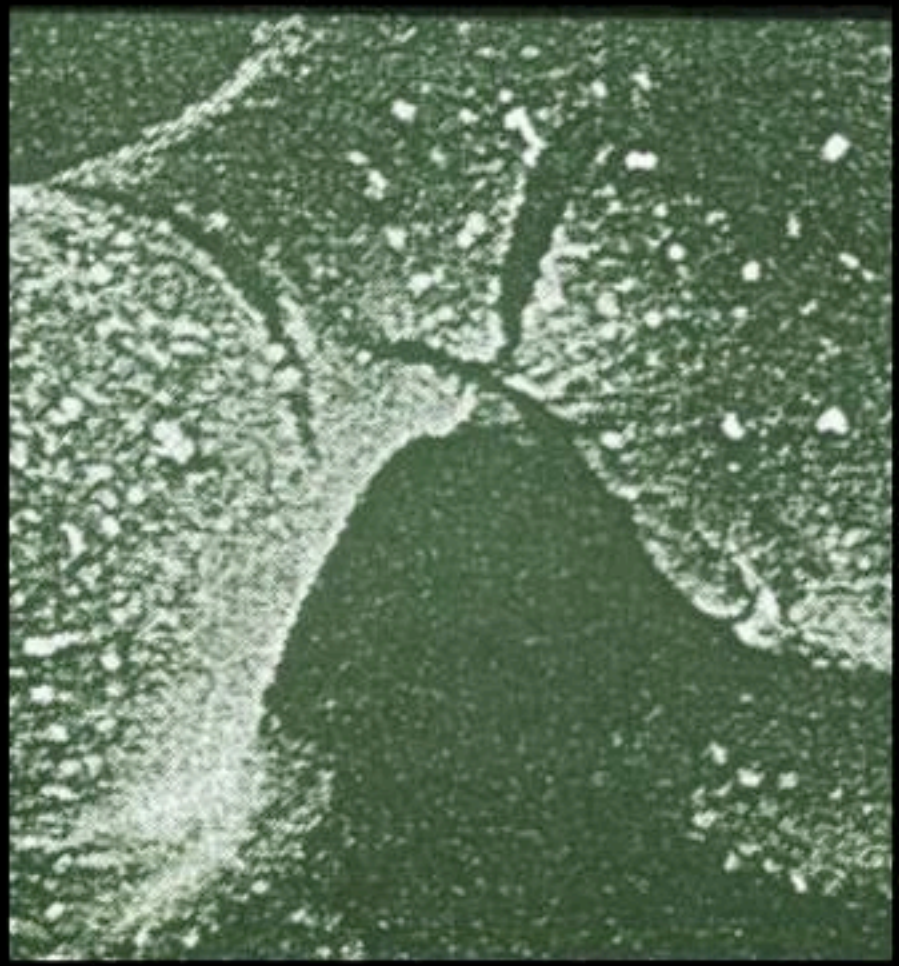


	pre-iLA	6 h	12 h	24 h	48 h
pH	7.32±0.1	7.52±0.1	7.52±0.07	7.49±0.05	7.45±0.07
SaO_2 (%)	88±5.2	96±2.4	96±1	97±2.3	97±3.7
O_2-delivery (mls O_2/min)	608±106	685±135	698±85	729±117	761±106

- n=7/239 (3%) resections
  7 Pneumonx, 2 lobex
- Novalung 4.3 (=/- 2 days)
- Flow 1.4 (+/- 0.4 l/min)
- Mean Vent settings: Vt 3ml/kg, RR 6, Pa/w peak 19, PEEP 12, FiO2 0.5
- 6/7 (86%) survive to discharge


Close

Patients with Lung Injury:



- ARDS/ALI
- Lung Transplantation
- Major Pulmonary Resection