6
Clinical Management of One-Lung Ventilation

Jens Lohser and Seiji Ishikawa

Key Points

- Ventilation needs to be individualized for the underlying lung pathology.
- Ventilation is a modifiable risk factor for acute lung injury.
- Protective lung ventilation is a combination of small tidal volumes, low peak and plateau pressures, routine PEEP and permissive hypercapnea.
- Hypoxia during one-lung ventilation is rare and often secondary to alveolar de-recruitment in the face of hypoventilation.
- Management of hypoxia requires a structured treatment algorithm.

Introduction

The development of thoracic surgery as a subspecialty only occurred after lung isolation and one-lung ventilation (OLV) had been reported. Prior to the description of endotracheal intubation and the cuffed endotracheal tube, only short intrathoracic procedures had been feasible. Rapid lung movement and quickly developing respiratory distress due to the surgical pneumothorax, made all but minimal procedures impossible. Selective ventilation of one lung was first described in 1931 by Gale and Waters and quickly led to increasingly complex lung resection surgery, with the first published pneumonectomy for cancer in 1933 [1]. Much has since been learnt about the physiology of OLV, particularly the issue of ventilation/perfusion matching (see Chap. 5). Hypoxemia used to be the primary concern during OLV. However, hypoxemia has become less frequent due to more effective lung isolation techniques, particularly the routine use of fiberoptic bronchoscopy (FOB), and the use of anesthetic agents with little or no detrimental effects on hypoxic pulmonary vasoconstriction (HPV). Acute lung injury (ALI) has replaced hypoxia as the chief concern associated with OLV [2].

Acute Lung Injury

Lung injury after lung resection was first recognized in the form of postpneumonectomy pulmonary edema [3], which is now referred to as post-thoracotomy ALI [4]. Pneumonectomy carries a particularly high risk of lung injury, but lesser lung resections and even nonpulmonary intra-thoracic surgery which employs OLV can create the same pathology [5]. Post-thoracotomy ALI is part of a spectrum of disease, which in its most severe form is recognized as acute respiratory distress syndrome (ARDS). Diagnosis is based on the oxygenation index of P_aO_2/F_iO_2 (P/F). Critical care consensus guidelines define ALI as a P/F ratio <300 and ARDS as a P/F ratio <200 [6]. ALI after lung resection is fortunately infrequent, occurring in 2.5–3.1% of all lung resections combined; however, the incidence can be as high as 7.9–10.1% after pneumonectomies. Although infrequent, ALI after lung resection may be associated with significant morbidity in the form of prolonged intubation, hospitalization and death [5]. Mortality, which was reported to be as high as 37–64% amongst patients with ALI [7–9], may be on the decline, as a more recent report indicated a mortality rate of 25–40% [10]. Similarly, Tang et al. reported a decrease in both incidence of (3.2 to 1.6%) and mortality from (72 to 45%) ARDS after pulmonary resection in a single institution cohort over a 10-year period. Their data

P. Slinger (ed.), *Principles and Practice of Anesthesia for Thoracic Surgery*,
DOI 10.1007/978-1-4419-0184-2_6, © Springer Science+Business Media, LLC 2011

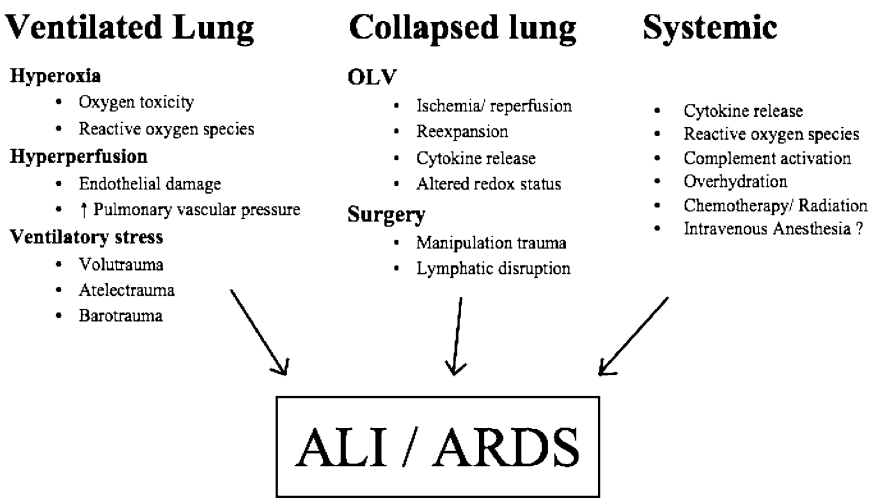

FIG. 6.1. Proposed mechanisms for ALI and ARDS after lung resection surgery.

have to be interpreted with caution, however, as the number of pneumonectomies was drastically higher in the historical cohort (17.4 versus 6.4%), which may explain the higher morbidity and mortality [11].

The etiology of lung injury is likely multifactorial (Fig. 6.1). Early on risk factors were felt to be right-sided surgery and large perioperative fluid loads. However, impaired lymphatic drainage, surgical technique, ventilation, transfusion, aspiration, infection, oxidative stress and ischemia–reperfusion have all since been implicated [12]. The fact that ventilation may have detrimental effects in the critically ill patients in the form of ventilator-induced lung injury has long been recognized. Early animal studies demonstrated that high tidal volumes (45 mL/kg) are particularly injurious to the lung, irrespective of the applied pressure. This has led to the term "volutrauma" and the realization that end-inspiratory stretch plays a dominant role in lung injury [13]. In ARDS patients, application of protective lung ventilation (PLV) with smaller tidal volumes and high positive end-expiratory pressure (PEEP) improved survival [14]. Additionally, protective ventilation was shown to inhibit progression of lung injury compared to high tidal volume ventilation [13]. Whether mechanical ventilation causes lung injury in normal lungs and whether protective ventilation should routinely be applied in anesthesia is being debated. Tidal volume reduction towards 6 mL/kg for patients with risk factors for lung injury, and no higher than 10 mL/kg for the remainder, have been proposed for routine two-lung ventilation (TLV) [15, 16]. Considering that most patients undergoing thoracic surgery have risk factors for lung injury (Table 6.1), tidal volume reduction during TLV, and even more so during OLV should become routine practice.

The application of OLV predisposes the patient to ALI. Radiologic density changes in patients with ALI after thoracic surgery are more pronounced in the nonoperative, ventilated lung [17]. An increased duration of OLV was found to be an independent predictor of ALI in a retrospective analysis [7]. In animal models, OLV causes histological changes compatible with lung injury, including vascular congestion, diffuse alveolar wall thickening and damage, as well as a decrease in nitric oxide in the ventilated lung [18, 19]. Re-expansion of lung tissue after short-term OLV incites pro-inflammatory cytokine release in animals [20]. Similar cytokine elevations are found in patients undergoing thoracic surgery [21, 22]. Much of the early attention focused on the use of high tidal volumes during OLV. The analogy to ARDS has been drawn, as both involve ventilation of a so-called "baby lung" with reduced lung capacities [23]. Analogous to ARDS, high tidal volumes may therefore cause excessive end-inspiratory stretch during OLV.

Beyond ventilatory management, even anesthetic agents themselves appear to have the potential to modify the inflammatory response to OLV and surgery. De Conno et al. allocated adult patients undergoing lung resection surgery into propofol or sevoflurane anesthesia, and found that the increase in inflammatory mediators during OLV was significantly less pronounced in the sevoflurane group. Composite adverse events were significantly higher in the propofol group, but the groups differed in OLV duration and the need for surgical re-exploration [24]. The possible benefit of inhalational

TABLE 6.1. Risk factors for ALI after OLV.

Patient
Poor postoperative predicted lung function
Preexisting lung injury
Trauma
Infection
Chemotherapy
EtOH abuse
Female gender
Procedure
Prolonged OLV (>100 min)
Lung transplantation
Larger resections (pneumonectomy > lobectomy)
Esophagectomy
Transfusion
Large perioperative fluid load

anesthesia is not without merit, as volatile anesthetics have been shown to confer attenuating effects in a model of alveolar epithelial injury [25]. In another study, which compared desflurane or propofol anesthesia in thoracic surgery patients, levels of alveolar TNFα and sICAM-1 were significantly higher in the propofol group [26]. These studies indicate that anesthetic agents themselves may influence the pro-inflammatory response to OLV, but the true clinical relevance of that decrease remains to be established. Not surprisingly, however, the true answer as to lung injury avoidance after OLV is likely more complicated than simple tidal volume reduction.

Ventilator Settings

Tidal Volume

Tidal volumes used during TLV (10–12 mL/kg) used to be maintained into the period of OLV [27, 28]. Large tidal volumes were recommended because they had been found to improve oxygenation and decrease shunt fraction, during both TLV [29] and OLV, irrespective of the level of PEEP applied [30]. Large tidal volumes were shown to provide end-inspiratory alveolar recruitment, resulting in improved oxygenation (Fig. 6.2). Excessive tidal volumes (e.g., 15 mL/kg), on the other hand, were shown to worsen oxygenation, secondary to elevations in pulmonary vascular resistance (PVR) resulting in increased shunt flow [31]. Based on the recent literature on ALI, it is becoming increasingly clear that large tidal volumes during OLV expose the patient to undue risk of postoperative respiratory complications.

Two retrospective case series by Van de Werff and Licker identified multiple risk factors among more than 1,000 patients undergoing lung resection surgery. Both studies demonstrated a significant association between high ventilating pressures and ALI, but failed to provide a link to intraoperative tidal volumes [7, 32]. Fernández-Pérez et al., on the other hand, showed a significant association between larger intraoperative tidal volumes (8.3 vs. 6.7 mL/kg) and the development of postoperative respiratory failure in a single institution review of 170 pneumonectomies [33]. The study was criticized for the fact that ventilatory pressures were not analyzed, tidal volumes referred to the largest volume charted on the anesthetic record, with the assumption that they had been carried over to OLV, and patients that developed respiratory failure received a median of 2.2 L of fluid intraoperatively [34]. However, the results were essentially duplicated in another single-institution review of 146 pneumonectomy patients. In that study, larger tidal volumes were independently associated with the development of ALI/ARDS (8.2 vs. 7.7 mL/kg) with an odds ratio (OR) of 3.37 per one mL/kg increase in tidal volume per predicted body weight (95% confidence interval 1.65–6.86). Peak airway pressure was an additional independent risk factor with an OR 2.32 per cm H_2O increase (95% confidence interval 1.46–3.67) [35].

One of the earliest trials of tidal volume reduction during OLV was an animal study published in 2003 [36]. Isolated rabbit lungs were subjected to OLV with either 8 mL/kg – zero end-expiratory pressure (ZEEP) or the "protective" 4 mL/kg – average PEEP 2.1 cmH_2O (based on the dynamic pressure-time curve). OLV was associated with increases in multiple surrogate markers of lung injury (pulmonary artery pressure [PAP], lung weight gain [LWG] and TXB_2 cytokine levels), which occurred to a lesser degree in the protective ventilation group. The protective ventilation group, however, only received half the minute ventilation of the control group, as no compensatory increase in respiratory rate was used in the low tidal volume group. Based on the study design it was therefore not possible to state whether the outcome benefit was due to any one, or all, of minute ventilation reduction, tidal volume reduction and/or application of external PEEP [36]. Kuzkov et al. showed that when comparing equal minute ventilation in anesthetized sheep undergoing pneumonectomies, protective ventilation with 6 mL/kg – PEEP 2 cmH_2O lowered extravascular lung water (a surrogate for lung injury), compared to 12mL/kg – ZEEP [37]. While neither study was able to answer the question whether tidal volume reduction or the addition of PEEP results in improved outcomes, it appears clear that tidal volume reduction alone is not sufficient. This point was well illustrated by an animal study comparing low vs. high tidal volume ventilation with or without PEEP in ALI. While animals with high tidal volume ventilation and ZEEP clearly had significant cytokine elevations, all animals exposed to low tidal volumes and ZEEP died during the experiment [38].

Due to the infrequent occurrence of lung injury, prospective clinical studies have focused on cytokine levels as a surrogate marker for potentially harmful ventilation. Cytokine elevations are part of the disease process, as levels of IL-6, IL-8, sICAM-1 and vWF are elevated even prior to intubation in patients with ALI [39] and baseline plasma levels of IL-6, IL-8 and IL-10 are associated with an increased risk of death in patients with ARDS [40]. Wrigge et al. failed to demonstrate a difference in tracheal cytokine levels between patients ventilated with 12–15 mL/kg – ZEEP or 6 mL/kg – PEEP 10 cmH_2O during TLV and OLV for laparotomy or thoracotomy. Cytokine levels before, during and after OLV were no different between the groups [41]. However, tracheal aspirates may not be sensitive enough to detect early alveolar damage. Michelet randomized 52 patients with normal lung functions undergoing esophagectomy to OLV 9 mL/kg – ZEEP or 5 mL/kg – PEEP 5 cmH_2O. In this study, serum cytokine levels (IL-1, IL-6, IL-8) increased perioperatively, but to a lesser degree in the protective ventilation group [22]. The degree of lung injury and cytokine elevation may have been exaggerated by the fact that despite an average of 6 h of mechanical ventilation and 8 L of fluid, only the low tidal volume group received PEEP during OLV and no patient received PEEP during the remainder of the operation [22]. Esophageal surgery may also present a higher risk for lung injury as it is associated with cytokine elevations secondary to intestinal ischemia, potentially acting as a first hit [42].

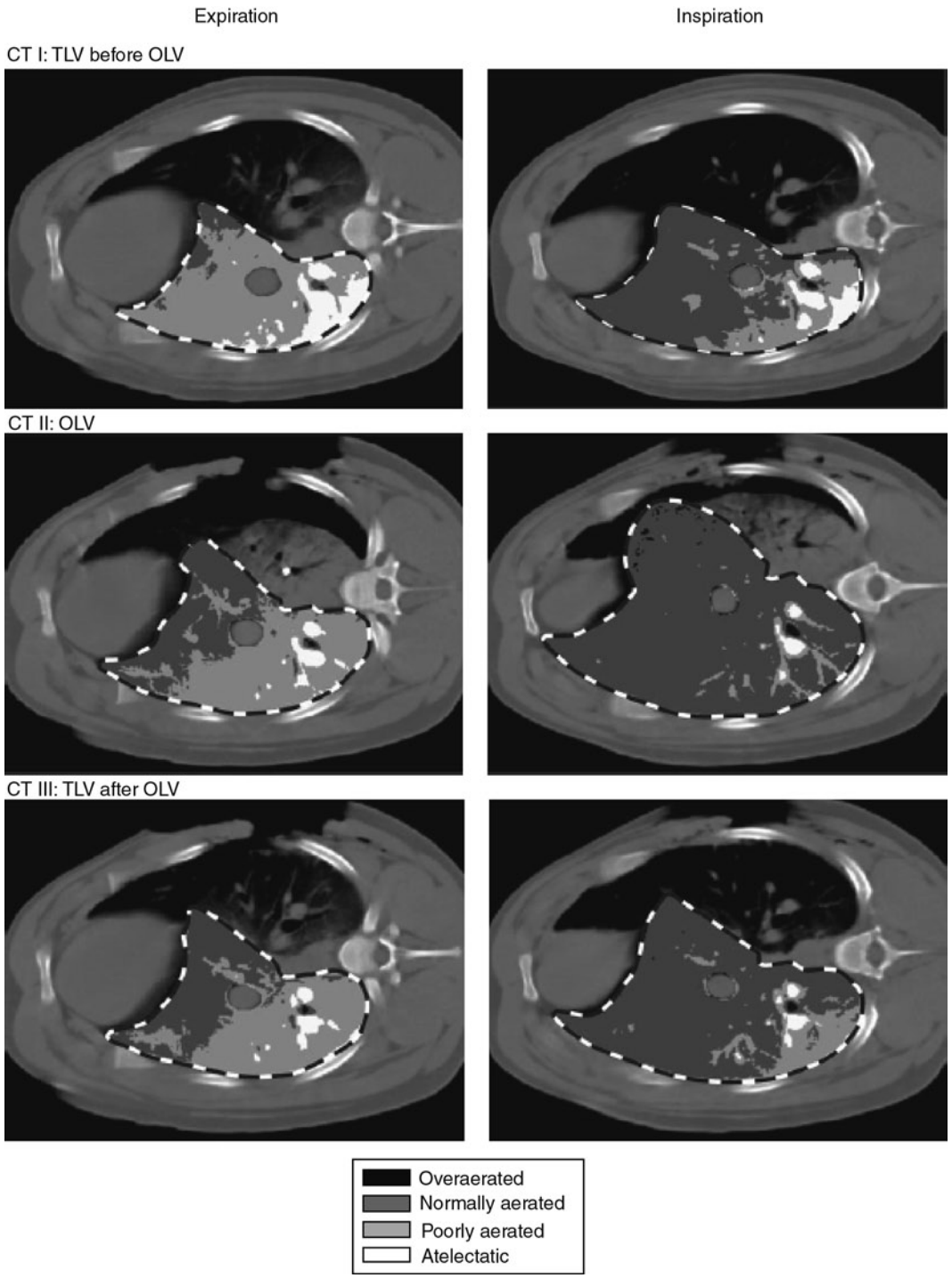

Fig. 6.2. Juxta-diaphragmatic lung CT images of a porcine one-lung ventilation (OLV) model. Scans during two-lung ventilation (TLV) before OLV (CT I), during OLV (CT II), and TLV after OLV (CT III). Lung aeration was defined based on image scaling units (Hounsfield); over-aerated (−1,000 to −900 HU), normally aerated (−900 to −500 HU), poorly aerated (−500 to −100 HU), and atelectatic (−100 to +100 HU) lung regions are coded by *gray scale*. The dependent lung border is outlined by the *dashed line* (reprinted from Kozian et al. [120], with permission).

The most compelling experimental evidence that tidal volumes per se are linked to the etiology of ALI after lung surgery comes from a randomized trial, which investigated 32 patients scheduled for OLV and thoracotomy. Patients received OLV with 10 or 5 mL/kg, both without PEEP but identical minute ventilation. While OLV increased cytokine levels (TNF-α, sICAM-1) in both groups, levels were lower in the low tidal volume ventilation group [21].

More important than cytokine elevations, clinically significant outcomes of ALI, ICU admission and hospital stay were shown to be reduced in a cohort analysis of patients who routinely received PLV (2003–2008), as compared to historical controls (1998–2003) [44]. While historical controls are fraught with limitations due to concomitant developments and improvements in medical care, this analysis by Licker et al. showed a dramatic reduction in adverse postoperative respiratory outcomes after the routine implementation of a PLV strategy. The ventilation strategy consisted of an open lung concept, with tidal volumes <8 mL/kg, routine PEEP, pressure-control ventilation (PCV) and frequent recruitment maneuvers. The statistically averaged ventilation parameters among the 558 patients in their protective ventilation group consisted of a tidal volume of 5.3 mL/kg (standard deviation [SD] 1.1), plateau pressure of 15 cmH_2O (SD 6), PEEP of 6.2 cmH_2O (SD 2.4) and respiratory rate of 15 bpm (SD 2). While the historical control already had a mean tidal volume of 7.1 mL/kg, only 24% of patients received tidal volumes less than 8 mL/kg, compared to the 92% compliance with low tidal volumes in the PLV cohort. As mentioned above, historical comparisons of ICU admission and length of hospitalization are difficult to interpret as criteria change and moves towards fast-tracking of patients are established. However, the definition of ALI has been consistent during the study period and the authors were able to show a significant reduction in ALI from 3.8 to 0.9% [44].

While the benefits of protective ventilation for lung injury prevention are becoming clearer, its impact on oxygenation is uncertain. Two studies that investigated PLV (lower tidal volume and PEEP) during OLV reported improved oxygenation and shunt fraction as compared to traditional high tidal volume OLV [22, 37]. However, with inadequate or no PEEP, low tidal volume ventilation may be associated with worse oxygenation and shunt fraction [21]. Recruitment studies performed during protective OLV have shown that despite a PEEP of 8 cmH_2O patient ventilated with a tidal volume of 6 mL/kg showed significant recruitability of the ventilated lung, suggesting relative hypoventilation and atelectasis formation. Despite the presence of atelectatic lung prior to the recruitment maneuver, however, oxygenation was adequate in all patients [43]. Postoperative arterial oxygenation was not affected in a historical cohort analysis of patients undergoing lung cancer surgery with a PLV protocol incorporating lower tidal volumes [44].

PEEP

Positive-end expiratory pressure minimizes alveolar collapse and atelectasis formation by providing resistance to mechanical exhalation. Applied PEEP should therefore be routine for all ventilated patients during TLV [15]. Klingstedt et al. demonstrated that the mediastinal weight results in significant compression of the dependent lung in the lateral position during TLV. They were able to show that resulting *V*/*Q* mismatch can be resolved with the application of selective PEEP to the dependent lung (Fig. 6.3) [45].

PEEP does attenuate lung injury, both in the setting of high and low tidal volumes [13]. Intrinsic or auto-PEEP, on the other hand, occurs if expiratory time is too short to allow lung units to empty towards their resting volume. Lung areas with high compliance, characteristically found in patients with emphysema, are particularly prone due to their poor elastic recoil. Auto-PEEP is inhomogeneous throughout the lung and can therefore not be relied upon for effective avoidance of de-recruitment [46]. The total PEEP after application of external PEEP is also unpredictable, due to the heterogeneous nature of auto-PEEP [47].

Endotracheal intubation prevents glottic closure, resulting in complete absence of auto-PEEP in patients without obstructive lung disease on TLV. However, initiation of OLV with 10 mL/kg ZEEP has been shown to create auto-PEEP and air trapping. Measured auto-PEEP was minimal in patients without obstructive lung disease, but patients with severe COPD developed auto-PEEP levels up to 16 cmH_2O, which was associated with air trapping of 284 mL [46]. Patients with preexisting auto-PEEP have an unpredictable response to the application of extrinsic PEEP. In a study of ICU patients on TLV, application of PEEP changed total PEEP up, down or not at all [48]. In a small study of patients during OLV the additive effect of applied PEEP to auto-PEEP was inversely related to the preexisting auto-PEEP level. In other words, extrinsic PEEP contributed less to total PEEP in patients with already high auto-PEEP than patients with low auto-PEEP; however, the extent of the response was not predictable [47]. Excessive total PEEP and dynamic hyperinflation are clearly undesirable as they may cause cardiovascular depression and may require fluid loading and/or inotropic support [16].

Traditionally OLV has been performed with ZEEP, with selective application of PEEP to the nonoperative lung as part of a hypoxemia treatment algorithm. The effect of PEEP on oxygenation during OLV is variable. It is beneficial in patients whose intrinsic PEEP is well below the lower inflection point (LIP) of the compliance curve, more commonly the patient with normal lung function. In that scenario application of external PEEP will increase the total PEEP towards the LIP of the pressure–volume curve, resulting in more open (recruited) lung and improved oxygenation. Oxygenation is worse, however, if total PEEP is increased well above the LIP, likely due to alveolar over-distention and increases in PVR resulting in an increased shunt fraction (Fig. 6.4) [49]. Neither intrinsic PEEP nor the compliance curve is routinely or easily acquired during thoracic surgery, which is why preoperative prediction of PEEP responders would be ideal. Valenza et al. showed that patients with relatively normal lung function ($FEV_1 > 72\%$) exhibited improved oxygenation on application of PEEP 10 cmH_2O during OLV [50].

Whether applied PEEP is able to decrease ALI after OLV is unclear, as it has not been studied in isolation. PEEP application as part of a "protective" ventilation regime has

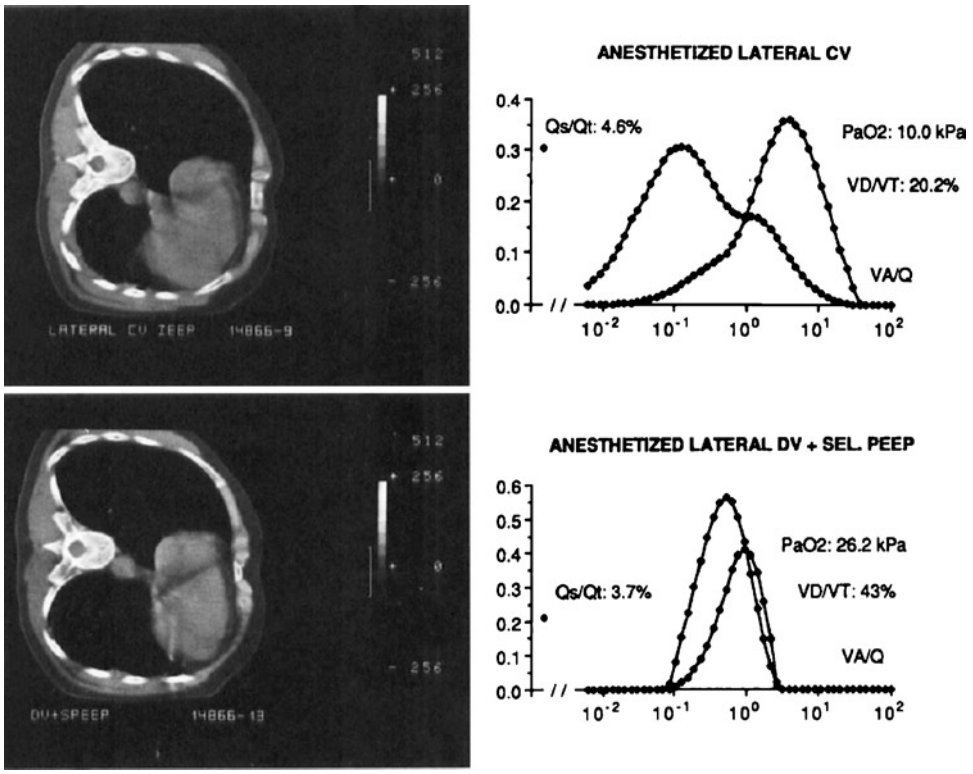

FIG. 6.3. Mediastinal weight causes significant dependent lung compression and secondary ventilation/perfusion (*V*/*Q*) mismatch during two-lung conventional ventilation (CV). Application of differential ventilation (DV) and selective PEEP (SPEEP) to the dependent lung restores *V*/*Q* matching. For comparison see Fig. 4.7a for a normal awake *V*/*Q* scan (reprinted from Klingstedt et al. [45], with permission).

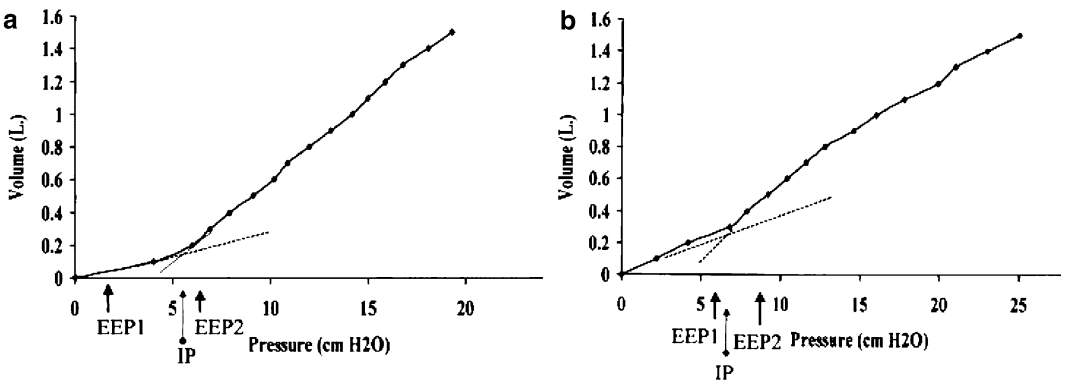

FIG. 6.4. Effect of applied PEEP on total PEEP and oxygenation during OLV. Static compliance curves of patients undergoing OLV. End-expiratory pressure before (EEP1) and after application of 5 cmH_2O PEEP (EEP2) as well as lower inflection points (IP) are indicated. Patients with normal pulmonary function and low EEP1 (**a**), in whom EEP2 moved closer to IP were more likely to show oxygenation benefits after PEEP application, than patients with poor lung function and intrinsic PEEP (**b**). See text for details (reprinted from Slinger et al. [49], with permission).

been shown to decrease surrogate markers of lung injury [22, 36, 37]. Additionally, routine PEEP in patients with or without COPD as part of a PLV strategy was shown to be associated with a significant decrease in the incidence of ALI and atelectasis after OLV [44].

Use of "protective" OLV with low tidal volumes but no PEEP does not appear sensible, as de-recruitment is harmful and auto-PEEP unreliable in terms of homogeneous lung recruitment. Lack of PEEP in the setting of low tidal volume OLV has been shown to worsen oxygenation [21].

Low levels of PEEP are safe, likely beneficial for lung injury avoidance and should be used in all patients. The only true contraindication to PEEP application would be the presence of a broncho-pleural fistula. PEEP levels, however, need to be adjusted to the individual and their respiratory mechanics. Patients with normal lung function or restrictive lung disease should benefit from, and will tolerate, 5–10 cmH_2O PEEP. Patients with severe obstructive lung disease, as evidenced by preoperative hyperinflation (RV/TLC>>140%) exhibit significant air trapping during OLV, but as previously stated may not exhibit a significant increase in total PEEP with the application of external PEEP. Low levels of extrinsic PEEP 2–5 cmH_2O are likely well tolerated and should routinely be applied. Clearly dynamic hyperinflation must be considered in the differential for intraoperative hypotensive episodes in patients at risk. However, based on the static compliance analysis by Licker et al., who used routine PEEP in all patients as part of their PLV strategy, hyperinflation (and secondary decrease in static compliance) does not appear to be a significant concern, as the compliance actually increased in their cohort exposed to PLV with routine PEEP [44]. Early, routine application of PEEP helps to prevent atelectasis and shunt formation and thereby improves oxygenation during OLV [51].

Clearly it would be best to measure total PEEP for each patient in order to rationally apply external PEEP [47]. This, however, is difficult or impossible in most intraoperative settings due to the inability of anesthetic ventilators to perform an end-expiratory hold maneuver. The simplest approximation of intrinsic PEEP can be derived from inline spirometry where interruptions of the end-expiratory flow curve indicate the presence of auto-PEEP (Fig. 6.5) [52]. Alternatively, compliance can be approximated by simple calculation (compliance = tidal volume/driving pressure), which may serve as an indicator of potential air-trapping, realizing that hyperinflation is only one of the possible explanations for a decrease in compliance.

F_iO_2

One hundred percent oxygen used to be a routine component of OLV, as hypoxia was its most feared complication. However, with the decline in the incidence of hypoxemia and the realization that high F_iO_2 may be detrimental, even this practice has been questioned. Oxygen toxicity is a well-recognized consequence of prolonged exposure to high F_iO_2, characterized by histopathologic changes similar to ALI. Oxygen toxicity occurs during OLV and involves ischemia–reperfusion injury and oxidative stress [12]. Collapse of the operative lung and surgical manipulation results in relative organ ischemia, and reperfusion at the time of lung expansion leads to the production of radical oxygen species. Increasing durations of OLV and the presence of tumor result in increased markers of oxidative stress, which after 120 min are associated with significant increases in the rates of respiratory failure and death [53]. Lung re-expansion should likely occur at a lower F_iO_2, as hypoxemic reperfusion has been shown to attenuate the reperfusion syndrome [54]. This is of particular relevance after lung transplantation. Even short-term exposure to high F_iO_2 during the induction of anesthesia has been shown to cause significant absorption atelectasis [55]. Studies have shown that an F_iO_2 as low as 0.4 may provide adequate oxygenation for OLV in the lateral decubitus position [56]. Due to the potential for lung injury, particularly in the high-risk patient, after adjuvant therapy or undergoing lung transplantation, F_iO_2 should be titrated to effect. At the initiation of OLV a F_iO_2 of 0.8 may be appropriate, but 15–20 min later, when the nadir of oxygenation has occurred, the F_iO_2 should be gradually decreased to the minimum that is required to maintain a stable saturation level above 92–94%. During lung resection surgery further reductions in F_iO_2 are possible once the vasculature to the resected lobe or lung has been disrupted. Stapling of the vasculature effectively reduces, or, in the setting of a pneumonectomy, essentially eliminates the shunt flow.

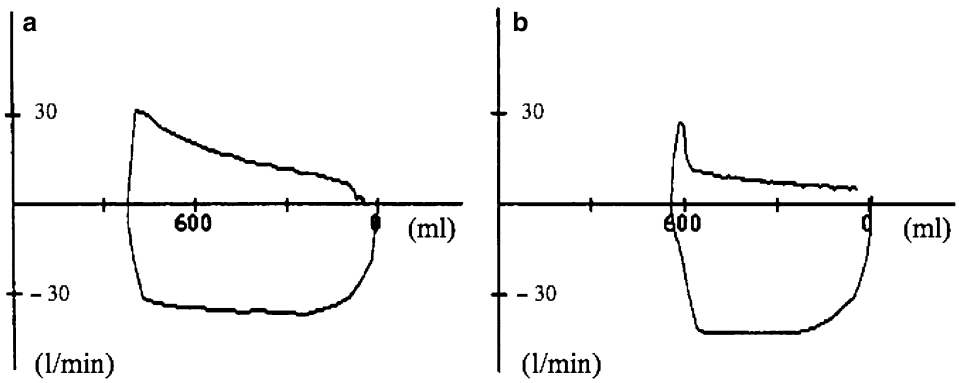

Fig. 6.5. Auto-PEEP detection by in-line spirometry. Flow volume curves with expiration above and inspiration below the line. Expiratory flow normally returns to zero prior to inspiration (**a**), interrupted air-flow at end-expiration indicates the presence of auto-PEEP (**b**) (reprinted from Dueck et al. [121] with permission).

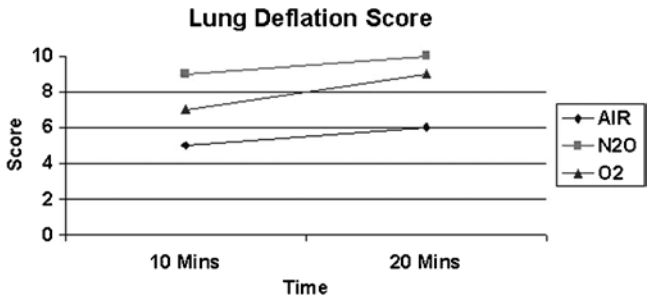

FIG. 6.6. Lung deflation is significantly impaired when nitrogen is part of the gas mixture pre-OLV (reprinted from Ko et al. [57], with permission).

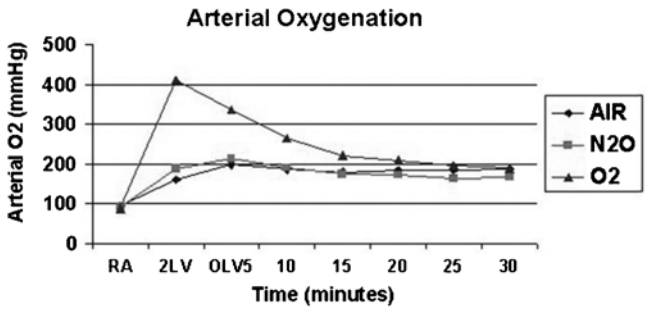

FIG. 6.7. Use of 100% O_2 pre-OLV confers a transient oxygenation benefit, which is lost by 15 min of OLV (reprinted from Ko et al. [57] with permission).

The oxygen content and gas mixture are not only important for oxygenation, but also for the speed of nonventilated lung collapse during OLV. This is of particular importance for surgical exposure during video-assisted thoracoscopic surgery. Ko et al. compared three different gas mixtures during TLV immediately prior to OLV (air/O_2, N_2O/O_2, O_2) and investigated which gas mixture would best collapse the operative lung while maintaining arterial oxygenation in patients undergoing lung resection surgery [57]. F_iO_2 was 0.4 in the air/O_2 and N_2O/O_2 group, and 1.0 in the O_2 group during TLV. All groups received 100% oxygen on initiation of OLV. Not surprisingly, lung deflation was worse if nitrogen (i.e., air) was administered prior to lung collapse, due to the poor solubility of nitrogen in blood (Fig. 6.6). A nitrous oxide/O_2 mixture was superior to oxygen alone for lung collapse, but nitrous oxide is contraindicated in many thoracic patients. Administering 100% oxygen pre-OLV temporarily improved OLV oxygenation, but only until the nonventilated lung becomes atelectatic. Once the operative lung has collapsed at around 15 min of OLV that oxygen reservoir and any benefit from it has disappeared (Fig. 6.7) [57].

Minute Ventilation/Permissive Hypercapnea

Permissive hypercapnea has been a key component of the critical care management for ALI/ARDS. Reduction of the minute ventilation allows for a decrease in tidal volumes and ventilatory pressures, thereby minimizing mechanical stress and secondary volu- or barotrauma. Beyond the reduction in minute ventilation and mechanical trauma, the actual elevated CO_2 level itself may be beneficial [58], as hypercapnea appears to attenuate the cytokine response [59].

Permissive hypercapnea has been investigated in the OLV setting. In the previously mentioned study by Gama de Abreu et al., isolated rabbit lungs were exposed to OLV with 8 mL/kg – ZEEP or 4 mL/kg – PEEP 2.1 cmH_2O (based on the dynamic pressure–time curve), without respiratory rate compensation. The protective ventilation group, which received half the minute ventilation, exhibited a reduction in surrogate markers for lung injury (PAP, LWG, cytokine levels) [36]. Similar ventilatory parameters were studied during OLV in thoracotomy patients. Sticher et al. ventilated patients with 7 mL/kg – PEEP 2 cmH_2O or 3.5 mL/kg – PEEP 2 cmH_2O, again without respiratory rate compensation, effectively halving minute ventilation similar to Gama de Abreu. P_aCO_2 values rose from 42 to 64 mmHg, which was associated with a 42% increase in PVR, but no change in oxygenation. Hypercapnea was well tolerated, however, higher risk patients with pulmonary hypertension or major cardiac rhythm disturbances were excluded [60]. In a case series of 24 patients undergoing volume reduction surgery for advanced emphysema, permissive hypercapnea was used electively as part of a barotrauma avoidance strategy. The mean P_aCO_2 value was 56 mmHg with a peak of 86 mmHg, resulting in pH values between 7.11 and 7.41 (mean 7.29). The authors state that hypercapnea was well tolerated, however, inotropic support was required in over 50% of patients [61]. Even higher P_aCO_2 levels have been described in a small series of ten patients with severe emphysema that were again managed with elective hypoventilation for barotrauma avoidance. P_aCO_2 values rose to peak levels of 70–135 mmHg, resulting in pH values as low as 7.03 (despite bicarbonate administration). Hypercapnea was poorly tolerated at these high levels. All patients required inotropic support during anesthesia. Four patients developed ventricular dysrhythmias and three patients required tracheal gas insufflation for treatment of hypoxemia [62]. Significant hypercapnea can cause increased intracranial pressure, pulmonary hypertension, decreased myocardial contractility, decreased renal blood flow and release of endogenous catecholamines. At extremely high levels, CO_2 can be lethal due to excessive sympathetic stimulation, cardiac rhythm disturbances and/or cardiac collapse [16, 62]. Moderate hypercapnea potentiates the HPV response and is therefore unlikely to adversely affect oxygenation [63]; however, the same may not hold true for extreme CO_2 elevations [62]. A protective ventilation strategy including permissive hypercapnea has been shown to reduce the incidence of ALI in a cohort analysis by Licker et al. While not explicitly discussed in the manuscript, permissive hypercapnea clearly was part of their strategy. The PLV group had significantly lower tidal volumes with only marginal rate compensation. Based on the

manuscript, the minute ventilation of the historical cohort was 92 vs. 80 mL/kg/min in the PLV group. The PLV group therefore had smaller minute ventilation and increased anatomic dead space ventilation (increased respiratory rate), resulting in decreased CO_2 elimination [44]. Permissive hypercapnea should be considered a routine component of a PLV strategy for OLV. Assuming a reasonable cardiovascular reserve, and in particular right ventricular function, P_aCO_2 levels up to 70 mmHg are well tolerated in the short term and clearly beneficial in terms of lung injury avoidance and attenuation. Higher levels should be avoided in the majority of patients due to the risk of hemodynamic instability.

I:E Ratio and Respiratory Rate

Each ventilatory cycle consists of time spent in inspiration and expiration. The appropriate ratio of inspiratory to expiratory (I:E) time depends on underlying lung mechanics. Restrictive lung disease is characterized by poorly compliant lungs, which resist passive lung expansion, but rapidly recoil to FRC. Increasing the I:E ratio to 1:1 (or using inverse ratio ventilation) maximizes the time spent in inspiration, thereby reducing peak and plateau ventilatory pressures. For illustration, at a respiratory rate of 15 bpm and an I:E ratio of 1:1, each respiratory cycle lasts 4 s, with 2 s spent in each of inspiration and expiration, respectively. Obstructive lung disease, on the other hand, is characterized by lungs, which have difficulty to empty towards FRC, due to poor elastic recoil and conducting airway collapse. Decreasing the I:E ratio towards 1:4 allows for more expiratory time, and helps to minimize the risk of auto-PEEP and dynamic hyperinflation. For illustration, at a respiratory rate of 15 bpm, now with the I:E ratio to 1:4, each respiratory cycle is still 4 s, however, expiration now takes up 3.2 s of the entire cycle.

Respiratory rate modification may be equally necessary depending on the underlying lung mechanics. Extreme airflow obstruction may require very long expiratory times. After reducing the I:E ratio to the minimum of 1:4 this can only be achieved by increasing the overall cycle length, i.e., reducing the respiratory rate. Clinical examples, such as the patient with severe cystic fibrosis requiring a respiratory rate of 4–6 to allow for complete exhalation have been reported [64]. In restrictive lung disease, on the other hand, dividing a given minute volume by a higher respiratory frequency may be beneficial in reducing peak and plateau ventilatory pressures. It has to be realized, however, that as anatomic dead space remains unchanged, dividing the minute volume by a higher respiratory rate results in reduced CO_2 elimination as the unchanged size of the anatomic dead space makes up a larger component of the tidal volume [65]. For illustration, a patient ventilated at 400 mL – 20 bpm receives the identical minute ventilation as a patient ventilated at 800 mL – 10 bpm. However, dead space ventilation, which occupies about 150 mL of each breath, has doubled from 1,500 mL at 10 bpm to 3,000 mL at 20 bpm. Alveolar ventilation has therefore been reduced from 6,500 mL (8,000–1,500) to 5,000 mL (8,000–3,000). Additionally, OLV with small tidal volume and rapid respiratory rate results in statistically higher auto-PEEP [65]. While auto-PEEP elevations in this study were unlikely to be clinically significant, they serve as a reminder that rapid, shallow ventilation has the potential to increase dynamic hyperinflation.

Peak/Plateau Pressure

The peak inspiratory pressure is a reflection of the dynamic compliance of the respiratory system and depends on tidal volume, inspiratory time, endotracheal size and airway tone (bronchospasm). Plateau pressure, on the other hand, relates to the static compliance of the respiratory system, i.e., chest wall and lung compliance. Double-lumen endobronchial tubes have small internal diameters resulting in increased resistance to air flow [66]. Application of the full TLV minute volume to a single lumen of the double lumen tube (DLT) results in a 55% increase in peak inspiratory pressure and 42% increase in plateau pressure [67]. While plateau pressure reflects alveolar pressure, peak pressure is unlikely to be fully applied to the alveolus. A retrospective study of 197 pneumonectomy patients did, however, show that peak ventilation pressures above 40 cmH_2O were associated with the development of PPPE [32]. Recently, Fernández-Pérez et al. reviewed 4,420 consecutive patients without preexisting lung injury undergoing high-risk elective surgeries for postoperative pulmonary complications and demonstrated that mean first hour airway pressure (OR 1.07; 95% CI 1.02–1.15 cmH_2O) but not tidal volume, PEEP or F_iO_2, were associated with ALI after adjusting for nonventilatory parameters [68]. Similarly, patients exposed to a plateau pressure of 29 cmH_2O were at significantly higher risk of developing ALI after lung resection surgery than those with a plateau pressure of 14 cmH_2O [7]. Based on the critical care literature there does not appear to be a critical plateau pressure level above which injury occurs, but rather any elevation in plateau pressure increases the relative risk of lung injury. With the implementation of permissive hypoventilation, peak pressure levels well less than 35–40 cmH_2O and plateau pressures less than 25 cmH_2O should therefore be achievable in the majority of patients during OLV. This was confirmed in the cohort study by Licker et al. who showed that implementation of a PLV strategy for OLV resulted in mean plateau pressures of 15 cmH_2O [44].

Ventilatory Mode

Volume-control ventilation (VCV) has been the dominant ventilatory mode both in the intensive care and operating room. VCV uses a constant inspired flow (square wave), creating a progressive increase in airway pressure towards the peak inspiratory pressure, which is reached as the full tidal volume has been delivered. Inspiratory pressure during VCV depends on the set tidal volume and PEEP, gas flow rates and resistance, as well as respiratory system compliance. The set

tidal volume will be delivered unless the inspiratory pressure exceeds the pressure limit, in which case the flow ceases. With the realization that ventilatory pressures may be one of the inciting factors of lung injury, other ventilatory modes have been explored.

PCV uses a decelerating flow pattern, with maximal flow at the beginning of inspiration until the set pressure is reached, after which flow rapidly decreases balancing the decreasing compliance of the expanding lung. This resembles the spontaneous mammalian breath which also follows a decelerating pattern, as negative intrathoracic pressure induced by contracting diaphragm and intercostal muscles cause a high initial airflow [15]. Tidal volumes can be highly variable during PCV and may fall precipitously with changes in lung compliance, such as with surgical manipulation. As the majority of the tidal volume is delivered in the early part of the inspiration, mean airway and alveolar pressure tend to be higher during PCV. The decelerating flow pattern results in a more homogeneous distribution of the tidal volume, improving static and dynamic lung compliance due to recruitment of poorly ventilated lung regions, and improving oxygenation and dead-space ventilation [69]. Whether PCV during OLV improves oxygenation is controversial. Tuğrul et al. studied 48 patients undergoing thoracotomy and lung resection. Patients received VCV or PCV during OLV, both delivering 10 mL/kg – ZEEP –100% O_2, in a cross-over fashion. PCV was associated with statistically significant decreases in peak and plateau airway pressures, as well as improved oxygenation and shunt fraction. Oxygenation improved more in patients with poor preoperative lung function, which may relate to the more homogeneous distribution of ventilation achieved with the pressure-control breath [70]. The same group investigated the benefit of adding PEEP 4 cmH_2O to OLV with PCV and showed that it provided an additional significant improvement in oxygenation and shunt fraction in their patients [71]. Other groups, however, have failed to reproduce the oxygenation benefit in PCV studies during OLV [72–74].

The effect of intraoperative ventilatory mode on postoperative oxygenation is equally controversial. Although a better postoperative oxygenation was shown in the PCV group compared with VCV in a trial of patients undergoing MIDCAB surgery [75], no significant difference was demonstrated in a study of patients after thoracic surgery [76]. Despite the lack of a clear oxygenation benefit, PCV is likely preferable over VCV due to the potential to decrease ventilatory pressures and the ability to recruit lung units.

High-frequency jet ventilation (HFJV) is another ventilatory mode that has been successfully used in thoracic surgery [77]. HFJV, when applied to the operative lung during prolonged OLV in aortic surgery, is more effective than continuous positive airway pressure (CPAP) in improving P_aO_2 [78]. This may be particularly relevant in the poor operative candidate after prior contra-lateral lung resection [79]. One recent study evaluated the value of two-lung HFJV via a standard endotracheal tube for thoracic surgery. Sixty patients were randomized to HFJV (1 atm pressure, rate 200/min, 100% O_2) or standard OLV (10 mL/kg, 100% O_2, ZEEP). HFJV was associated with lower ventilating pressures, improved oxygenation and shunt fraction and importantly no detriment in surgical exposure or intraoperative hemodynamic variables [80]. More recently, Buise et al. reported that HFJV was associated with a lower mean blood loss and less crystalloids administration during esophagectomy, compared with the OLV group. They speculated that higher ventilatory pressures in the OLV group resulted in higher intrathoracic pressure and central venous pressure, and thus splanchnic congestion, which increased blood loss relative to the HFJV group [81]. Difficulties in monitoring ventilatory pressures, tidal volumes and end-tidal CO_2 concentrations, in addition to the inherent risks of barotrauma associated with this technique, continue to limit its widespread adoption [77].

Another ventilatory mode, which has only been used as a CPAP equivalent at this point, is high-frequency percussive ventilation (HFPV). It is a ventilatory technique providing convective and diffusive ventilation that can reduce the physiologic right-to-left shunt and improve arterial oxygenation [82–84]. Lucangelo et al. recently assessed the effects of HFPV (F_iO_2 1.0, 500 cycles/min, mean pressure 5 cmH_2O, with pressures oscillating between 2 and 8 cmH_2O) applied to the nondependent lung compared to standard CPAP in patients undergoing elective lung resection. Before nondependent lung re-expansion, HFPV patients showed higher P_aO_2 than CPAP. HFPV was also associated with better clearance of secretions and shortened hospital stay [85].

Recruitment/Re-Expansion

Atelectasis has long been known to occur in dependent lung areas of anesthetized patients. The primary reasons for alveolar collapse during anesthesia are extrinsic compression and gas resorption. Recent studies have shown that atelectatic alveoli are not simply air-less, but may also be fluid or foam-filled. Beyond simple lung collapse, atelectasis is therefore now considered both a potential cause and a manifestation of ALI [55]. Interestingly, re-expansion of collapsed alveoli causes injury not only to the alveoli that are being recruited, but also to remote nonatelectatic alveoli [55]. This may be in part to the early realization by Mead that expansion of a gas-free alveolus with a trans-pulmonary pressure of 30 cmH_2O creates a shear force of 140 cmH_2O to adjacent alveoli [13]. PEEP has been shown to prevent lung injury associated with both high and low tidal volumes, by stabilizing alveoli, and preventing their collapse [55]. In animal models of ARDS it has been shown that atelectasis is associated with vascular leak, right ventricular failure and eventual death in 31% of rats, and is easily avoided with PEEP [86].

Atelectasis formation in the nonoperative lung is highly undesirable during OLV as it worsens the already high shunt fraction, increasing the potential for hypoxemia. Among the risk factors that predispose to lung de-recruitment during

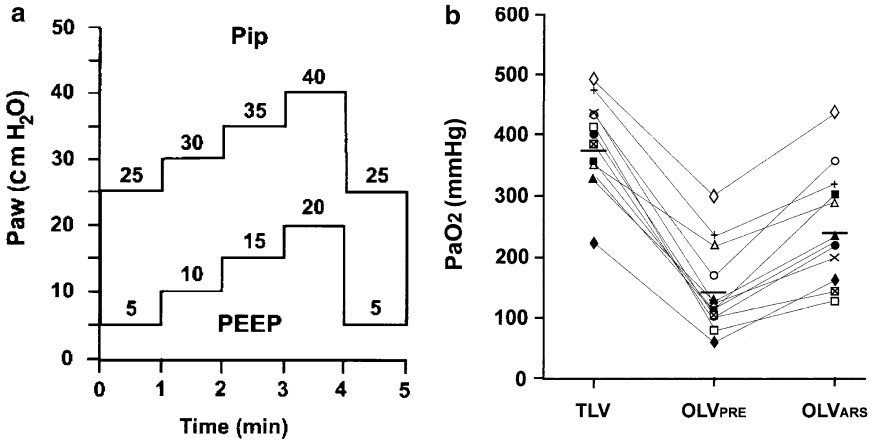

FIG. 6.8. Lung recruitment improves oxygenation during OLV. (**a**) Schematic representation of the ARM. In PCV, the pressure amplitude of 20 cmH_2O remains constant throughout the maneuver. Respiratory rate is 12 bpm and I:E ratio 1:1. Each pressure step is maintained for 1 min. After recruitment pressures of 40/20 cmH_2O, pressures decreased to 30/10 cmH_2O. Then, the initial settings are resumed (paw airway pressure; Pip peak inspiratory pressure). (**b**) P_aO_2 (mmHg) in all patients during two-lung ventilation (TLV) and during one-lung ventilation before (OLV_{PRE}) and after (OLV_{ARS}) the (ARM). Each symbol represents one patient in every point of the study. *Horizontal bars* represent mean values at each point (reprinted from Tusman et al. [43], with permission).

OLV are high F_iO_2, traditional lack of PEEP and extrinsic compression by abdominal contents, heart and mediastinum. The best evidence for the presence of atelectasis during OLV comes from a lung recruitment study, which investigated an aggressive alveolar recruitment maneuver (ARM) with increasing pressure breaths over a 4-min period up to a peak pressure of 40 cmH_2O and a PEEP level of 20 cmH_2O (Fig. 6.8a). Recruitment increased P_aO_2 on OLV from a mean of 144 mmHg to a mean of 244 mmHg (Fig. 6.8b) [43].

Cinnella et al. demonstrated that the alveolar recruitment achieved by such an ARM resulted in a significant decrease in static elastance of the dependent lung [87]. Hemodynamic instability is a well-recognized risk of such an aggressive ARM as the sustained intrathoracic pressure increases right ventricular afterload, resulting in impaired venous return and left heart preload [88, 89]. A recent study showed that stroke volume variation (an indicator of preload responsiveness) increases dramatically after an ARM, while both cardiac index and venous oxygen saturation decrease. These changes, however, were transient and completely recovered within 3 min [90].

Caution is required with the implementation of PLV, as low tidal volumes and plateau pressures may promote atelectasis formation and increase F_iO_2 and PEEP requirements [16]. Frequent de-recruitment and therefore need for repeated recruitment maneuvers, as may be the case with low tidal volume ventilation with insufficient PEEP, are potentially deleterious. In animal models of lung injury, repeated de-recruitment and recruitment maneuvers are associated with histological evidence of lung injury [91, 92]. Even a single recruitment maneuver of 40 cmH_2O for 40 s has been shown to elevate biomarkers of lung injury in the rat model without preexisting lung injury [93]. The same may potentially be true in humans, although this aspect has only been studied in critically ill patients. Halbertsma et al. demonstrated that a single ARM could increase translocation of pro-inflammatory cytokines from the alveolar space into the systemic circulation in ventilated critically ill children. Fifteen minutes after the ARM, an increase was observed in plasma TNFα, IL-6 and IL-1β [94]. Another critical care study found that 4 out of 28 patients with ALI/ARDS developed barotrauma necessitating intervention following an ARM [95]. This does create a curious dilemma as the increased use of PLV, with low tidal volumes, may promote atelectasis formation and therefore increase the need for recruitment maneuvers [16]. The best ventilatory strategy is therefore one that follows the "open lung" concept and maintains lung recruitment.

Atelectasis formation in the operative lung is routine and occurs gradually over a 10–20 min period as residual oxygen is being absorbed, which parallels the gradual decline in P_aO_2 on OLV. Ko et al. compared three different gas mixtures during TLV immediately prior to OLV (air/O_2, N_2O/O_2, O_2) and investigated which gas mixture would best collapse the operative lung while maintaining arterial oxygenation in patients undergoing lung resection surgery. F_iO_2 was 0.4 in the air/O_2 and N_2O/O_2 group, and 1.0 in the O_2 group during TLV. All groups received 100% oxygen on initiation of OLV. Not surprisingly, lung deflation was worse if nitrogen (i.e., air) was administered prior to lung collapse, due to the poor solubility of nitrogen in blood (Fig. 6.6). A nitrous oxide/O_2 mixture was superior to oxygen alone for lung collapse, but nitrous oxide is contraindicated in many thoracic patients. Administering 100% oxygen pre-OLV temporarily improved OLV oxygenation, but only until the nonventilated lung becomes atelectatic. Once the operative lung has collapsed at around 15 min of OLV, that oxygen reservoir and any benefit from it has disappeared (Fig. 6.7) [57].

Atelectasis is complete, unless CPAP is applied to the operative lung. CPAP, or its variant HFJV, if applied to the at least partially recruited operative lung, effectively improves *V*/*Q* matching and hypoxemia [78]. Gradual re-expansion of the operative lung at the conclusion of OLV is achieved with a continuous pressure hold of 20–30 cmH_2O, which is lower than standard recruitment regimens, in order to prevent disruption of staple lines. As discussed, re-expansion of lung tissue may be harmful. Re-expansion injury after prolonged lung collapse consists of alveolar-capillary membrane edema and increase in lymphocyte and neutrophil infiltration [96]. Re-expansion of isolated rabbit lungs after 55 min of lung collapse showed significant elevations in myeloperoxidase (MPO) levels, as well as IL-1β and TNF-α mRNA, when compared to an open lung control [20]. Intermittent lung re-expansion may mitigate these effects, as intermittent recruitment of the operative lung during OLV has been shown to decrease pro-inflammatory mediators during esophagectomy [97]. Lung recruitment with continuous high pressure hold may result in significant hypotension if applied to both lungs. However, even in the setting of hypovolemia, recruitment is well tolerated, if it is selectively applied to one lung at a time, with the other lung open to atmosphere [98]. Re-expansion pulmonary edema is fortunately rare if a gradual, gentle recruitment technique is applied, and is more likely after sudden recruitment of long-standing lung collapse [99]. Yet, even a single recruitment maneuvers has the potential to cause lung injury in animal models [93]. Low oxygen tensions should likely be used for re-expansion, as recruitment of the operative lung is associated with substantial oxidative stress, particularly after prolonged OLV [53, 54].

OLV Duration

Mechanical stress due to OLV can be minimized by optimization of ventilatory parameters. However, even minimal stress using "protective" parameters becomes significant if exposure is prolonged. Retrospective case series have shown that OLV lasting more than 100 min is associated with an increased risk for postoperative lung injury [7]. Part of the damage may be due to oxidative stress. A recent animal study exposed rats to increasing durations of OLV from 1 to 3 h. At the conclusion of the experiment animals were sacrificed and analyzed for biochemical indicators of oxidative stress and histologic changes in lung tissue. Increasing the duration of OLV from 1 to 3 h resulted in significant elevations of malondialdehyde (MDA) activity and increased the amount of tissue damage on histological analysis [100]. A prospective analysis of patients undergoing lobectomy for nonsmall cell cancer with either TLV or OLV lasting more than 60, 90 or 120 min compared MDA plasma levels at lung re-expansion. Again, MDA levels increased significantly with increasing OLV duration, indicating cumulative oxidative stress [53]. Anesthesiologists have limited control over the duration of OLV as it is mostly determined by the surgical procedure. However, initiation of OLV should occur as close to pleural opening as possible (except for thoracoscopic procedures), and TLV should resume as early as possible. With the increasing use of OLV outside the thoracic theater, it is essential to ensure that the nonthoracic surgeon appreciates the need to minimize the length of OLV.

Ventilatory Strategy

The cumulative evidence is overwhelmingly in favor of adopting a protective lung ventilatory strategy for OLV, which has been shown to decrease surrogate markers of lung injury as well as the incidence of ALI itself. Protective ventilation is not synonymous with low tidal volume ventilation, but includes all of routine PEEP, lower FiO_2 and particularly lower ventilatory pressures through the use of PCV and permissive hypercapnea. This strategy follows the "open-lung" concept that has been widely adopted for management of ARDS patients in intensive care units. As part of the open-lung concept frequent recruitment of the lung has to be considered as another component of a PLV strategy. Recruitment should occur at the beginning of OLV, during OLV if indicated by worsening oxygenation and for lung re-expansion. Lung de-recruitment may potentially be more prevalent with low tidal volumes due to the loss of end-inspiratory stretch in the setting of high F_iO_2. External PEEP should help to minimize de-recruitment. However, PEEP titration is difficult in the intra-operative setting for two reasons. First, determination of inflection points and auto-PEEP would require inline spirometry, as routine expiratory holds are not feasible intra-operatively. Second, other than the ICU, where as long as cardiac output is maintained, PEEP can be increased to maintain "open lung"; in the OLV setting excessive PEEP will cause pulmonary blood flow diversion to the operative lung and worsens oxygenation. As such, low tidal volume ventilation has the potential to worsen oxygenation, either due to lung de-recruitment with inadequate PEEP or due to pulmonary blood flow diversion with excessive PEEP. Low tidal volume ventilation increases dead-space and CO_2 elimination is therefore consistently worse with this technique. This should not present a problem in the majority of patients, unless CO_2 elimination is already compromised by severe obstructive lung disease (e.g., cystic fibrosis). In cases of severe respiratory acidosis, marked pulmonary hypertension or right ventricular dysfunction, "protective" low-tidal volume – high rate ventilation may need to be aborted in favor of higher tidal volume ventilation at a lower respiratory rate (to maximize CO_2 elimination), as the imminent risk of hemodynamic dysfunction trumps the potential risk of ALI. Dynamic hyperinflation is common during OLV and is increased with the application of PEEP and the use of higher respiratory rates. The risk of hyperinflation may be increased with a PLV strategy, which has to be considered, particularly in patients with severe emphysema and during periods of hemodynamic instability. Providing adequate expiratory time and use of permissive hypoventilation should minimize the risk of significant hyperinflation in all but the patients with severe obstructive lung.

Table 6.2. Summary of ventilatory strategies.

Tidal volume: protective: 4–6 mL/kg; hypoxia or severe hypercapnea: consider 6–8 mL/kg
PEEP: protective/restrictive/normal: 5–10 cmH_2O; obstructive: 2–5 cmH_2O (minimize intrinsic PEEP)
RR: protective: 12–15 bpm; severe hypercapnea: 6–8 bpm
F_iO_2: transplant: 21%+, routine 50–80%, hypoxia 100%
I:E ratio: restrictive: 1:1 or inverse ratio; normal: 1:2; obstructive: 1:3–4
Pressures: plateau <20 cmH_2O, peak <35 cmH_2O
Minute volume: P_aCO_2 50–70 mmHg (rarely higher: severe obstruction, lung transplantation)
Ventilator mode: PCV (? HFJV)

While PLV should be the norm for all patients, it is particularly important in patients with risk factors for ALI and during procedures that trigger a higher inflammatory response, such as pneumonectomy, esophageal surgery or lung transplantation. Respiratory mechanics vary widely between restrictive and obstructive lung disease so that any ventilatory strategy needs to be individualized for the particular patient (Table 6.2).

Hypoxia

Prediction

Hypoxia used to be the major concern during OLV. Early reports indicated that 40–50% of patients suffered hypoxemia during OLV [101]. Predictors for possible desaturation have been identified (Table 6.3). Hurford et al. examined the intraoperative oxygenation of patients who had undergone preoperative *V/Q* scanning [101]. They found that the amount of preoperative perfusion (and ventilation) to the operative lung inversely correlated with P_aO_2 after 10 min of OLV. As HPV is only able to halve blood flow through the operative lung during OLV, the authors concluded that the extent of preoperative blood flow helped to predict the amount of intra-operative shunt. Slinger et al. showed that P_aO_2 during OLV relates to multiple factors. Poor oxygenation during TLV was predictive of continued oxygenation difficulties as were right-sided operations (due to the increased perfusion to that side). Good preoperative pulmonary function (FEV_1) was found to be predictive of poor OLV oxygenation, which is felt to be due to the lack of auto-PEEP and secondary de-recruitment in normal lungs [102]. Two recent studies correlated the risk of hypoxemia to the end-tidal CO_2 gradients. One study showed that the difference of end-tidal CO_2 between the lungs in the lateral position significantly correlates with the P/F ratio at 15 min of OLV [103]. The other study demonstrated that there was a significant negative correlation between the lowest P_aO_2 recorded during the first 45 min of OLV and the end-tidal CO_2 difference between TLV and the early phase of OLV [104]. Both studies postulated that elevated CO_2 gradients were indicative of *V/Q* mismatching and therefore explained the risk of hypoxemia.

Over the years the incidence of hypoxemia has been declining. Improvements in anesthetic technique including improved lung isolation, confirmation of lung isolation with FOB and use of anesthetic agents with less effects on HPV are being credited for the reduction of oxygenation difficulties. In 1993 the incidence of hypoxia <90% occurring during OLV was quoted at 9% [105]. By 2003 the published incidence of hypoxemia was down to 1% of OLV cases in some hands [106]. However, another more recent study again showed a 10% incidence of hypoxemia <90% in a single institution between 2003 and 2004. The discrepancy could be due to variations in clinical management. Alternatively, it may indicate the difference between manual and electronic charting, as the latter study consisted of automatic recording of saturation every 30 s [107]. Although rare, significant hypoxia may still occur, at times without warning [108].

Table 6.3. Predictors of hypoxemia during one-lung ventilation.

Preferential perfusion of the operative lung
Right-sided surgery
Prior contralateral resection
Supine position
Normal FEV_1
Poor oxygenation on TLV
High *A–a* gradient for CO_2

Table 6.4. Approach to hypoxemia during one-lung ventilation.

Mild hypoxemia (90–95%)
Confirm position of lung isolation device
Recruit ventilated lung
Ensure adequate cardiac output
Increase F_iO_2 towards 1.0
Optimize PEEP to nonoperative lung (up or down; towards lower inflection point)
CPAP/HFJV/O_2 insufflation to operative lung (IPAP, FOB)
Consider reduction in vapor anesthetic and/or total intravenous anesthesia
Ensure adequate oxygen carrying capacity (hemoglobin)
Severe (<<90%) or refractory hypoxemia
Resume TLV with 100% O_2
If not possible, consider
Pulmonary artery clamp on operative side during pneumonectomy, transplant
Inhaled NO and/or infusions of almitrine/phenylephrine
Extracorporeal support during lung transplantation (Nova-lung, CPB)

Treatment

For a rational approach to hypoxia during OLV it has to be appreciated that CPAP and TLV are uniformly effective (Table 6.4). CPAP always decreases shunt flow and TLV essentially eliminates shunt flow. Aside from procedures such as pneumonectomy and lung transplantation where these techniques are not available, patients should therefore not have to suffer prolonged hypoxemia. Assuming that the lung isolation device is properly positioned, these two maneuvers are the most effective treatments for hypoxemia. They are not chosen as first-line interventions, however, because they will impair surgical access to the lung, particularly during thoracoscopic procedures.

CPAP is easily applied via one of the commercially available units that connect to the open lumen of the DLT, or the suction port of the bronchial blocker via the CPAP adaptor (Fig. 6.9). Alternatively, a standard AMBU bag with a PEEP valve can be used if no CPAP unit is available. CPAP does require some degree of lung recruitment, which is not always feasible (lung lavage, bronchopleural fistula) and will impact surgical exposure. Recently, Russell et al. described an intermittent positive airway pressure (IPAP) technique, which does not elicit lung inflation and therefore should not impact surgical exposure (Fig. 6.10). While the technique does not call for lung recruitment, it is unlikely to be of benefit in the setting of complete lung collapse. It is based on intermittent delivery of short bursts of low-flow oxygen (2 L/min) to the nonventilated lung to treat hypoxemia, circumventing significant lung movement in the surgical field. Placing a standard bacteriostatic filter on the open lumen of the DLT, with oxygen connected to the CO_2 sampling port, manual occlusion of open filter end allows for "jet-insufflation" of oxygen into the collapsed lung. A 2-s burst of flow will deliver 66 mL of oxygen to the nonventilated lung. In this study, all of the ten patients with relative hypoxemia ($SpO_2 < 95\%$) were successfully treated by repeated 2-s bursts of oxygen, followed by 10-s exhalations and no surgical interference was noted [109].

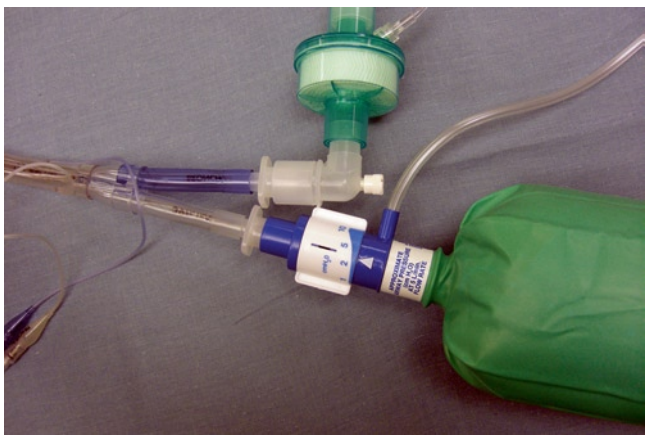

FIG. 6.9. Commercially available CPAP unit connected to the open lumen of a double-lumen tube. Flow rate is constant at 5 L/m of oxygen via wall outlet. CPAP pressure can be dialed in between 1 and 10 cmH_2O.

Hypoxemia during OLV for VATS presents a particular problem, as TLV and CPAP techniques are generally considered to be contraindicated. Ku et al. presented a novel method, which may be of benefit in select cases. They described the treatment of refractory hypoxemia during left-sided VATS for lung volume reduction surgery. A 4-mm FOB was inserted into the basilar segment of the left lower lobe bronchus and 5 L/min of oxygen was insufflated for approximately 20 s via the suction port (Fig. 6.11). Oxygenation successfully recovered within 2 min without impairing the surgical field and remained adequate for 20 min. There are two important considerations to this technique. First, it can only be applied if the insufflation occurs in a lung territory that is remote to the surgical site, and is therefore unlikely to be successful in case of a central lesion. In this case report, oxygen was insufflated into basilar segments while lung resection occurred at the apex. Second, insufflation of relatively high-flow oxygen has the potential to cause lung over-distention or barotrauma if the bronchoscope tip is allowed to wedge in the airway. The authors guarded against this by having the surgeon visualize the basilar lung

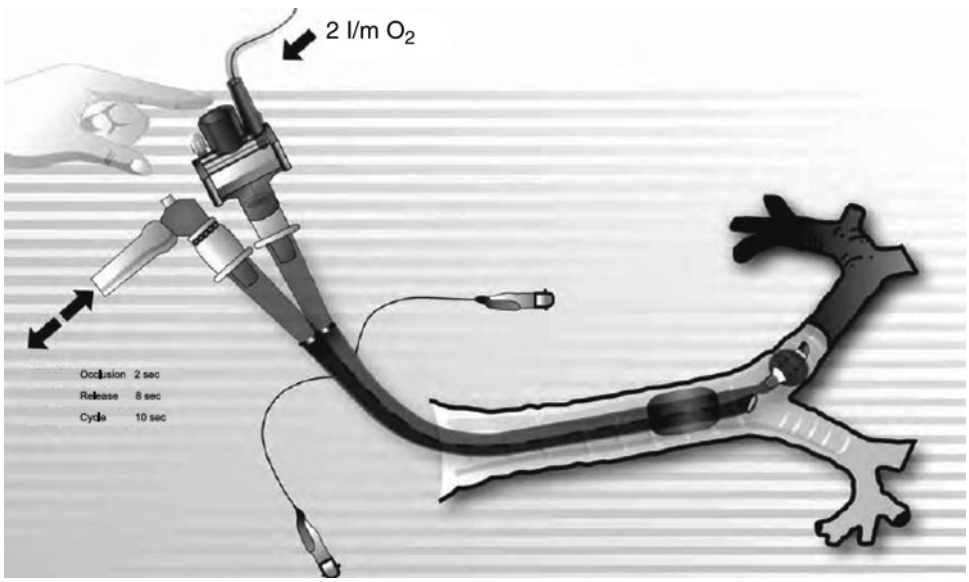

FIG. 6.10. Schematic illustration of intermittent positive airway pressure device. See text for details (reprinted from Russell [109], with permission).

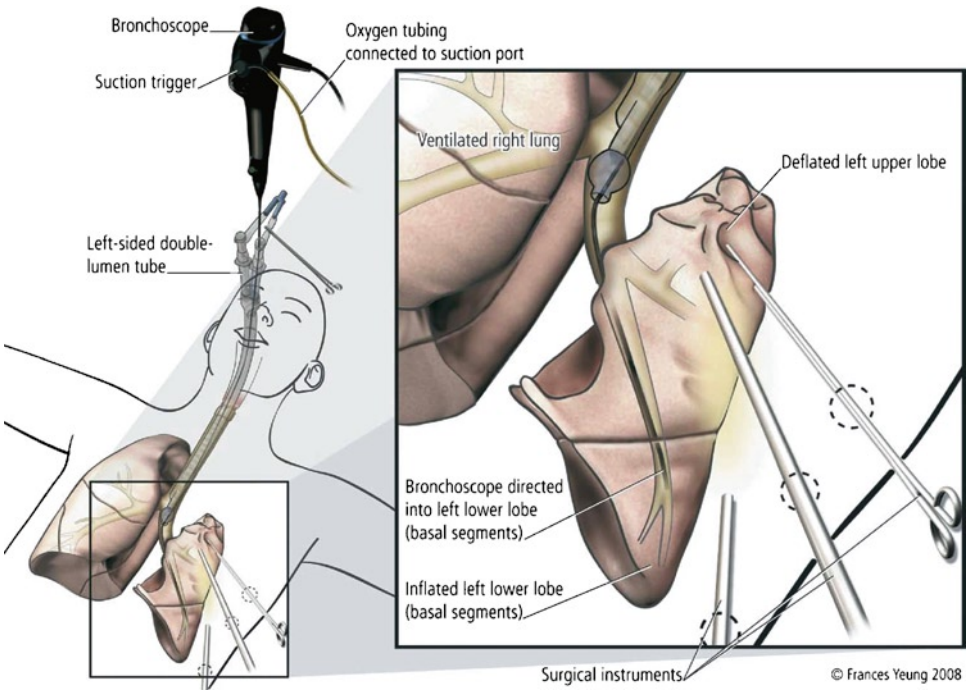

FIG. 6.11. Schematic illustration of oxygen supplementation during thoracoscopic surgery via bronchoscopy suction channel. See text for details (reprinted from Ku et al. [110], with permission).

segments throughout the period of insufflation [110]. Distal oxygen insufflation, particularly at relatively high flow rates as described in this report, should never be applied blindly. As another option, we have successfully used HFJV during VATS procedures. In order for this technique to succeed, the lung has to be allowed to collapse away from the chest wall prior to the institution of HFJV and driving pressures have to be low enough to only cause partial lung inflation. As previously stated, however, with proper attention to adequate lung isolation, "open lung" ventilation and maintenance of a normal cardiac output, these interventions should rarely be necessary.

Lung de-recruitment in the ventilated lung is common, easily reversed with recruitment maneuvers and preventable with appropriate PEEP levels. Low mixed venous oxygen saturation secondary to low cardiac output is another frequent and easily treatable cause of desaturation. Pharmacological modulation with vasoconstrictors (almitrine, phenylephrine) to strengthen HPV in the operative lung and vasodilators (inhaled NO) to improve pulmonary vascular capacitance in the ventilated lung may be helpful in extreme cases.

Systemic Effects

Even though hypoxia has become less of an anesthetic issue during OLV, relative hypoxemia may have a significant impact on vital nonpulmonary organ function due to the ever-increasing rate of co-morbid conditions in thoracic patients. In addition to hypoxemia, release of inflammatory cytokines and reactive oxygen metabolites may have yet unknown effects on organ function. A few recent studies have attempted to define the effects of OLV on organ function. More research is needed to delineate the end-organ effects of OLV.

A recent study by Mierdl et al. analyzed the impact of hypoxia during OLV on myocardial metabolism in patients with severe multi-vessel coronary artery disease. Patients underwent minimally invasive coronary artery bypass grafting via small lateral thoracotomy. In their study measurements of arterial and coronary sinus PO_2, pH and lactate did not show any evidence of anaerobic metabolism, despite arterial P_aO_2 values between 50 and 70 mmHg during OLV. Additionally, no patient exhibited myocardial ischemia, which led the authors to conclude that OLV may be used in patients with multi-vessel coronary artery disease with an acceptable low risk of inducing anaerobic myocardial metabolism [111].

Neurocognitive dysfunction is a well-known complication of cardiac surgery, and has been shown to be associated with intraoperative episodes of cerebral oxygen desaturation. Standard pulse oximetry is insufficient to detect these events. Monitoring for, and treating cerebral desaturation events, may decrease the incidence of postoperative neurocognitive dysfunction [112, 113]. Tobias et al. investigated the incidence and risk factors for cerebral desaturation by monitoring cerebral oxygenation (rSO_2) using near infrared spectroscopy in patients who required OLV for thoracic surgery [114]. In 8 of 40 patients, prolonged decreases in rSO_2 to less than 75% of the baseline value were recorded for 25% or more of the

duration of OLV. These eight patients were older, weighed more and were more likely to be ASA III than the remainder of the patients. Since there was no significant difference in patient background or other monitoring values, the authors concluded that rSO_2 monitoring might be useful to detect cerebral desaturation and allow for early intervention in patients during OLV. Jugular bulb venous oxygen saturations during OLV were assessed in a study comparing sevoflurane- and propofol-based anesthesia in patients undergoing lung surgery [115]. The SjO_2 values were significantly higher in the sevoflurane group than in the propofol group, despite identical SaO_2 values. The lower SjO_2 values observed with propofol anesthesia may be explained by the fact that propofol reduces cerebral blood flow more than cerebral metabolic rate [116, 117].

Interestingly, cerebral oxygen desaturation also appears to be predictive of noncerebral postoperative complications. In a recent trial of 50 patients undergoing major thoracotomy with OLV, a minimal absolute regional cerebral oxygen saturation of less than 65% was found to be predictive of postoperative organ dysfunction based on the Sequential Organ Failure Assessment (SOFA) scoring system with an OR of 2.37 (95% CI 1.18–4.39, $P=0.043$) [118]. Cerebral tissue oxygenation depends on arterial oxygen content, oxygen delivery (cardiac output) and metabolic consumption and may therefore be a superior monitor to simple pulse oximetry.

Reactive oxygen metabolites are known to occur after re-expansion of the nonventilated lung. These metabolites may have deleterious effects on cellular function. Yuluğet al. investigated the effects of OLV and re-expansion on the tissue damage of the liver and ileum in rats [119]. Plasma aspartate aminotransferase (AST), alanine aminotransferase (ALT), tissue MDA, and MPO activities in both tissues were significantly increased associated with OLV and re-expansion. Tissue damage and apoptotic index increased in rats with longer OLV duration, suggesting that OLV may cause tissue damage in the liver and ileum. These are some of the early indicators that OLV may indeed have effects beyond lung tissue; future research will help to delineate the significance of these findings.

Conclusion

The last decade has seen a shift in OLV research from studies investigating hypoxemia to various aspects of lung injury pathophysiology and prevention. Much has been learned about ventilation strategies that minimize lung injury. Evidence to date supports PLV based on reduction of surrogate markers, but more importantly now also indicates reduction of adverse outcomes. Ventilatory parameters have to be individualized for each patient's unique pulmonary mechanics, but should focus on an "open-lung" strategy. Hypoxemia is infrequent and should lead to a re-evaluation of ventilatory parameters. Routine algorithms for treatment of hypoxemia, as well as advanced management techniques are available, such that prolonged hypoxia should be exceedingly rare. There are early indicators that OLV may impact systemic organ function, but future research is needed to address end-organ effects.

References

1. Brodsky JB. The evolution of thoracic anesthesia. Thorac Surg Clin. 2005;15(1):1–10.
2. Lohser J. Evidence-based management of one-lung ventilation. Anesthesiol Clin. 2008;26(2):241–72.
3. Zeldin RA, Normandin D, Landtwing D, Peters RM. Postpneumonectomy pulmonary edema. J Thorac Cardiovasc Surg. 1984;87(3):359–65.
4. Licker M, Fauconnet P, Villiger Y, Tschopp JM. Acute lung injury and outcomes after thoracic surgery. Curr Opin Anesthesiol. 2009;22(1):61–7.
5. Dulu A, Pastores SM, Park B, Riedel E, Rusch V, Halpern NA. Prevalence and mortality of acute lung injury and ARDS after lung resection. Chest. 2006;130(1):73–8.
6. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med. 1994;149(3 Pt 1):818–24.
7. Licker M, de Perrot M, Spiliopoulos A, et al. Risk factors for acute lung injury after thoracic surgery for lung cancer. Anesth Analg. 2003;97(6):1558–65.
8. Ruffini E, Parola A, Papalia E, et al. Frequency and mortality of acute lung injury and acute respiratory distress syndrome after pulmonary resection for bronchogenic carcinoma. Eur J Cardiothorac Surg. 2001;20(1):30–7.
9. Kutlu CA, Williams EA, Evans TW, Pastorino U, Goldstraw P. Acute lung injury and acute respiratory distress syndrome after pulmonary resection. Ann Thorac Surg. 2000;69(2):376–80.
10. Alam N, Park BJ, Wilton A, et al. Incidence and risk factors for lung injury after lung cancer resection. Ann Thorac Surg. 2007;84(4):1085–91.
11. Tang SS, Redmond K, Griffiths M, Ladas G, Goldstraw P, Dusmet M. The mortality from acute respiratory distress syndrome after pulmonary resection is reducing: a 10-year single institutional experience. Eur J Cardiothorac Surg. 2008;34(4):898–902.
12. Jordan S, Mitchell JA, Quinlan GJ, Goldstraw P, Evans TW. The pathogenesis of lung injury following pulmonary resection. Eur Respir J. 2000;15(4):790–9.
13. Tremblay LN, Slutsky AS. Ventilator-induced lung injury: from the bench to the bedside. Intensive Care Med. 2006;32(1):24–33.
14. Amato MB, Barbas CS, Medeiros DM, et al. Effect of a protective ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med. 1998;338(6):347–54.
15. Schultz MJ, Haitsma JJ, Slutsky AS, Gajic O. What tidal volumes should be used in patients without acute lung injury? Anesthesiology. 2007;106(6):1226–31.
16. Putensen C, Wrigge H. Tidal volumes in patients with normal lungs: one for all or the less, the better? Anesthesiology. 2007;106(6):1085–7.
17. Padley SPG, Jordan SJ, Goldstraw P, Wells AU, Hansell DM. Asymmetric ARDS following pulmonary resection: CT findings initial observations. Radiology. 2002;223(2):468–73.

18. Yin K, Gribbin E, Emanuel S, et al. Histochemical alterations in one-lung ventilation. J Surg Res. 2007;137(1):16–20.
19. Kozian A, Schilling T, Fredén F, et al. One-lung ventilation induces hyperperfusion and alveolar damage in the ventilated lung: an experimental study. Br J Anaesth. 2008;100(4):549–59.
20. Funakoshi T, Ishibe Y, Okazaki N, et al. Effect of re-expansion after short-period lung collapse on pulmonary capillary permeability and proinflammatory cytokine gene expression in isolated rabbit lungs. Br J Anaesth. 2004;92(4):558–63.
21. Schilling T, Kozian A, Huth C, et al. The pulmonary immune effects of mechanical ventilation in patients undergoing thoracic surgery. Anesth Analg. 2005;101(4):957–65.
22. Michelet P, D'Journo XB, Roch A, et al. Protective ventilation influences systemic inflammation after esophagectomy: a randomized controlled study. Anesthesiology. 2006;105(5):911–9.
23. Sentürk M. New concepts of the management of one-lung ventilation. Curr Opin Anaesthesiol. 2006;19(1):1–4.
24. De Conno E, Steurer MP, Wittlinger M, et al. Anesthetic-induced improvement of the inflammatory response to one-lung ventilation. Anesthesiology. 2009;110(6):1316–26.
25. Giraud O, Molliex S, Rolland C, et al. Halogenated anesthetics reduce interleukin-1β-induced cytokine secretion by rat alveolar type II cells in primary culture. Anesthesiology. 2003;98(1):74–81.
26. Schilling T, Kozian A, Kretzschmar M, et al. Effects of propofol and desflurane anaesthesia on the alveolar inflammatory response to one-lung ventilation. Br J Anaesth. 2007;99(3):368–75.
27. Cohen E. Management of one-lung ventilation. Anesthesiol Clin North America. 2001;19(3):475–95.
28. Brodsky JB, Fitzmaurice B. Modern anesthetic techniques for thoracic operations. World J Surg. 2001;25(2):162–6.
29. Bendixen HH, Hedley-Whyte J, Laver MB. Impaired oxygenation in surgical patients during general anesthesia with controlled ventilation. A concept of atelectasis. N Engl J Med. 1963;269:991–6.
30. Katz JA, Laverne RG, Fairley HB, Thomas AN. Pulmonary oxygen exchange during endobronchial anesthesia: effect of tidal volume and PEEP. Anesthesiology. 1982;56(3):164–71.
31. Flacke JW, Thompson DS, Read RC. Influence of tidal volume and pulmonary artery occlusion on arterial oxygenation during endobronchial anesthesia. South Med J. 1976;69(5):619–26.
32. van der Werff YD, van der Houwen HK, Heijmans PJ, et al. Postpneumonectomy pulmonary edema. A retrospective analysis of incidence and possible risk factors. Chest. 1997;111(5): 1278–84.
33. Fernández-Pérez 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):14–8.
34. Neustein S. Association of high tidal volume with postpneumonectomy failure. Anesthesiology. 2007;106(4):875–6.
35. Jeon K, Yoon JW, Suh GY, et al. Risk factors for postpneumonectomy acute lung injury/acute respiratory distress syndrome in primary lung cancer patients. Anaesth Intensive Care. 2009;37(1):14–9.
36. Gama de Abreu M, Heintz M, Heller A, Szechenyi R, Albrecht DM, Koch T. 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(1):220–8.
37. Kuzkov VV, Suborov EV, Kirov MY, et al. Extravascular lung water after pneumonectomy and one-lung ventilation in sheep. Crit Care Med. 2007;35(6):1550–9.
38. Chiumello D, Pristine G, Slutsky A. Mechanical ventilation affects local and systemic cytokines in an animal model of acute respiratory distress syndrome. Am J Respir Crit Care Med. 1999;160(1):109–16.
39. Cepkova M, Brady S, Sapru A, Matthay MA, Church G. Biological markers of lung injury before and after the institution of positive pressure ventilation in patients with acute lung injury. Crit Care. 2006;10(5):R126.
40. Parsons PE, Eisner MD, Thompson BT, et al. Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. Crit Care Med. 2005;33(1):1–6.
41. Wrigge H, Uhlig U, Zinserling J, et al. The effects of different ventilatory settings on pulmonary and systemic inflammatory responses during major surgery. Anesth Analg. 2004;98(3):775–81.
42. Boyle NH, Pearce A, Hunter D, Owen WJ, Mason RC. Intraoperative scanning laser Doppler flowmetry in the assessment of gastric tube perfusion during esophageal resection. J Am Coll Surg. 1999;188(5):498–502.
43. Tusman G, Böhm SH, Suárez Sipmann F, Maisch S. Lung recruitment improves the efficiency of ventilation and gas exchange during one-lung ventilation anesthesia. Anesth Analg. 2004;98(6):1604–9.
44. Licker M, Diaper J, Villiger Y, et al. Impact of intraoperative lung-protective interventions in patients undergoing lung cancer surgery. Crit Care. 2009;13(2):R41.
45. Klingstedt C, Hedenstierna G, Baehrendtz S, Lundqvist H, Strandberg A, Tokics L, et al. Ventilation-perfusion relationships and atelectasis formation in the supine and lateral positions during conventional mechanical and differential ventilation. Acta Anaesthesiol Scand. 1990;34(6):421–9.
46. Ducros L, Moutafis M, Castelain MH, Liu N, Fischler M. Pulmonary air trapping during two-lung and one-lung ventilation. J Cardiothorac Vasc Anesth. 1999;13(1):35–9.
47. Slinger PD, Hickey DR. The interaction between applied PEEP and auto-PEEP during one-lung ventilation. J Cardiothorac Vasc Anesth. 1998;12(2):133–6.
48. Caramez MP, Borges JB, Tucci MR, et al. Paradoxical responses to positive end-expiratory pressure in patients with airway obstruction during controlled ventilation. Crit Care Med. 2005;33(7):1519–28.
49. Slinger PD, Kruger M, McRae K, Winton T. Relation of the static compliance curve and positive end-expiratory pressure to oxygenation during one-lung ventilation. Anesthesiology. 2001;95(5):1096–102.
50. Valenza F, Ronzoni G, Perrone L, et al. Positive end-expiratory pressure applied to the dependent lung during one-lung ventilation improves oxygenation and respiratory mechanics in patients with high FEV1. Eur J Anaesthesiol. 2004;21(12):938–43.
51. Ren Y, Peng ZL, Xue QS, Yu BW. The effect of timing of application of positive end-expiratory pressure on oxygenation during one-lung ventilation. Anaesth Intensive Care. 2008;36(4):544–8.
52. Bardoczky GI, d'Hollander AA, Cappello M, Yernault JC, et al. Interrupted expiratory flow on automatically constructed flow volume curves may determine the presence of intrinsic positive end-expiratory pressure during one-lung ventilation. Anesth Analg. 1998;86(4):880–4.
53. Misthos P, Katsaragakis S, Theodorou D, Milingos N, Skottis I. The degree of oxidative stress is associated with major adverse effects after lung resection: a prospective study. Eur J Cardiothorac Surg. 2006;29(4):591–5.

54. Douzinas EE, Kollias S, Tiniakos D, et al. Hypoxemic reperfusion after 120 mins of intestinal ischemia attenuates the histopathologic and inflammatory response. Crit Care Med. 2004;32(11):2279–83.
55. Duggan M, Kavanagh BP. Atelectasis in the perioperative patient. Curr Opin Anaesthesiol. 2007;20(1):37–42.
56. Bardoczky GI, Szegedi LL, d'Hollander AA, Moures JM, De Francquen P, Yernault JC. Two-lung and one-lung ventilation in patients with chronic obstructive pulmonary disease: the effects of position and F(IO)2. Anesth Analg. 2000;90(1):35–41.
57. Ko R, McRae K, Darling G, et al. The use of air in the inspired gas mixture during two-lung ventilation delays lung collapse during one-lung ventilation. Anesth Analg. 2009;108(4):1092–6.
58. Kregenow DA, Rubenfeld GD, Hudson LD, Swenson ER. Hypercapnic acidosis and mortality in acute lung injury. Crit Care Med. 2006;34(1):1–7.
59. Lang CJ, Barnett EK, Doyle IR. Stretch and CO2 modulate the inflammatory response of alveolar macrophages through independent changes in metabolic activity. Cytokine. 2006;33(6):346–51.
60. Sticher J, Muller M, Scholz S, Schindler E, Hempelmann G. Controlled hypercapnia during one-lung ventilation in patients undergoing pulmonary resection. Acta Anaesthesiol Scand. 2001;45(7):842–7.
61. Zollinger A, Zaugg M, Weder W, et al. Video-assisted thoracoscopic volume reduction surgery in patients with diffuse pulmonary emphysema: gas exchange and anesthesiological management. Anesth Analg. 1997;84(4):845–51.
62. Morisaki H, Serita R, Innami Y, Kotake Y, Takeda J. Permissive hypercapnia during thoracic anaesthesia. Acta Anaesthesiol Scand. 1999;43(8):845–9.
63. Balanos GM, Talbot NP, Dorrington KL, Robbins PA. Human pulmonary vascular response to 4 h of hypercapnia and hypocapnia measured using Doppler echocardiography. J Appl Physiol. 2003;94(4):1543–51.
64. Robinson RJ, Shennib H, Noirclerc M. Slow-rate, high-pressure ventilation: a method of management of difficult transplant recipients during sequential double lung transplantation for cystic fibrosis. J Heart Lung Transplant. 1994;13(5):779–84.
65. Szegedi LL, Barvais L, Sokolow Y, Yernault JC, D'Hollander AA. Intrinsic positive end-expiratory pressure during one-lung ventilation of patients with pulmonary hyperinflation. Influence of low respiratory rate with unchanged minute volume. Br J Anaesth. 2002;88(1):56–60.
66. Slinger PD, Lesiuk L. Flow resistances of disposible double-lumen, single-lumen, and univent tubes. J Cardiothorac Vasc Anesth. 1998;12(2):142–4.
67. Szegedi LL, Bardoczky GI, Engelman EE, D'Hollander AA. Airway pressure changes during one-lung ventilation. Anesth Analg. 1997;84(5):1034–7.
68. Fernández-Pérez ER, Sprung J, Afessa B, et al. Intraoperative ventilator settings and acute lung injury after elective surgery: a nested case control study. Thorax. 2009;64(2):121–7.
69. Nichols D, Haranath S. Pressure control ventilation. Crit Care Clin. 2007;23(2):183–99.
70. Tuğul M, Camci E, Karadeniz H, Sentürk M, Pembeci K, Akpir K. Comparison of volume-controlled with pressure-controlled ventilation during one-lung anaesthesia. Br J Anaesth. 1997;79(3):306–10.
71. Sentürk NM, Dilek A, Camci E, et al. Effects of positive end-expiratory pressure on ventilatory and oxygenation parameters during pressure-controlled one-lung ventilation. J Cardiothorac Vasc Anesth. 2005;19(1):71–5.
72. Unzueta MC, Casas JI, Moral MV. Pressure-controlled versus volume-controlled ventilation during one-lung ventilation for thoracic surgery. Anesth Analg. 2007;104(5):1029–33.
73. Leong LM, Chatterjee S, Gao F. The effect of positive end-expiratory pressure on the respiratory profile during one-lung ventilation for thoracotomy. Anaesthesia. 2007;62(1):23–6.
74. Choi YS, Shim JK, Na S, Hong SB, Hong YW, Oh YJ. Pressure-controlled versus volume-controlled ventilation during one-lung ventilation in the prone position for robot-assisted esophagectomy. Surg Endosc. 2009;23(10):2286–91.
75. Heimberg C, Winterhalter M, Strüber M, Piepenbrock S, Bund M. Pressure-controlled versus volume-controlled one-lung ventilation for MIDCAB. Thorac Cardiovasc Surg. 2006;54(8):516–20.
76. Cruz Pardos P, Garutti I, Piñeiro P, Olmedilla L, de la Gala F. Effects of ventilatory mode during one-lung ventilation on intraoperative and postoperative arterial oxygenation in thoracic surgery. J Cardiothorac Vasc Anesth. 2009;23(6):770–4.
77. Ihra G, Gockner G, Kashanipour A, Aloy A. High-frequency jet ventilation in European and North American institutions: developments and clinical practice. Eur J Anaesthesiol. 2000;17(7):418–30.
78. Abe K, Oka J, Takahashi H, Funatsu T, Fukuda H, Miyamoto Y. Effect of high-frequency jet ventilation on oxygenation during one-lung ventilation in patients undergoing thoracic aneurysm surgery. J Anesth. 2006;20(1):1–5.
79. Knuttgen D, Zeidler D, Vorweg M, Doehn M. Unilateral high-frequency jet ventilation supporting one-lung ventilation during thoracic surgical procedures. Anaesthesist. 2001;50(8):585–9.
80. Misiolek H, Knapik P, Swanevelder J, Wyatt R, Misiolek M. Comparison of double-lung jet ventilation and one-lung ventilation for thoracotomy. Eur J Anaesthesiol. 2008;25(1):15–21.
81. Buise M, van Bommel J, van Genderen M, Tilanus H, van Zundert A, Gommers D. Two-lung high-frequency jet ventilation as an alternative ventilation technique during transthoracic esophagectomy. J Cardiothorac Vasc Anesth. 2009;23(4):509–12.
82. Lentz CW, Peterson HD. Smoke inhalation is a multilevel insult to the pulmonary system. Curr Opin Pulm Med. 1997;3(3):221–6.
83. Reper P, Dankaert R, van Hille F, van Laeke P, Duinslaeger L, Vanderkelen A. The usefulness of combined high-frequency percussive ventilation during acute respiratory failure after smoke inhalation. Burns. 1998;24(1):34–8.
84. Velmahos GC, Chan LS, Tatevossian R, et al. High-frequency percussive ventilation improves oxygenation in patients with ARDS. Chest. 1999;116(2):440–6.
85. Lucangelo U, Antonaglia V, Zin WA, et al. High-frequency percussive ventilation improves perioperatively clinical evolution in pulmonary resection. Crit Care Med. 2009;37(5):1663–9.
86. Duggan M, McCaul CL, McNamara PJ, Engelberts D, Ackerley C, Kavanagh BP. Atelectasis causes vascular leak and lethal right ventricular failure in uninjured rat lungs. Am J Respir Crit Care Med. 2003;167(12):1633–40.
87. Cinnella G, Grasso S, Natale C, et al. Physiological effects of a lung-recruiting strategy applied during one-lung ventilation. Acta Anaesthesiol Scand. 2008;52(6):766–75.
88. Michelet P, Roch A, Brousse D, et al. Effects of PEEP on oxygenation and respiratory mechanics during one-lung ventilation. Br J Anaesth. 2005;95(2):267–73.

89. Vieillard-Baron A, Charron C, Jardin F. Lung "recruitment" or lung overinflation maneuvers? Intensive Care Med. 2006; 32(1):177–8.
90. Garutti I, Martinez G, Cruz P, Piñeiro P, Olmedilla L, de la Gala F. The impact of lung recruitment on hemodynamics during one-lung ventilation. J Cardiothorac Vasc Anesth. 2009;23(4): 506–8.
91. Koh WJ, Suh GY, Han J, et al. Recruitment maneuvers attenuate repeated derecruitment-associated lung injury. Crit Care Med. 2005;33(5):1070–6.
92. Suh GY, Koh Y, Chung MP, et al. Repeated derecruitments accentuate lung injury during mechanical ventilation. Crit Care Med. 2002;30(8):1848–53.
93. Farias LL, Faffe DS, Xisto DG, et al. Positive end-expiratory pressure prevents lung mechanical stress caused by recruitment/ derecruitment. J Appl Physiol. 2005;98(1):53–61.
94. Halbertsma FJ, Vanekern M, Pickkers P, Neeleman C, Scheffer GJ, van der Hoeven JG. A single recruitment maneuver in ventilated critically ill children can translocate pulmonary cytokines into the circulation. J Crit Care. 2010;25(1):10–5.
95. Meade MO, Cook DJ, Griffith LE, et al. A study of the physiologic responses to a lung recruitment maneuver in acute lung injury and acute respiratory distress syndrome. Respir Care. 2008;53(11):1441–9.
96. Sivrikoz MC, Tuncozgur B, Cekmen M, et al. The role of tissue reperfusion in the re-expansion injury of the lungs. Eur J Cardiothorac Surg. 2002;22(5):721–7.
97. Ojima H, Kuwano H, Kato H, et al. Relationship between cytokine response and temporary ventilation during one-lung ventilation in esophagectomy. Hepatogastroenterology. 2007;54(73):111–5.
98. Hansen LK, Koefoed-Nielsen J, Nielsen J, Larsson A. Are selective lung recruitment maneuvers hemodynamically safe in severe hypovolemia? An experimental study in hypovolemic pigs with lobar collapse. Anesth Analg. 2007;105(3): 729–34.
99. Mahfood S, Hix WR, Aaron BL, Blaes P, Watson DC. Re-expansion pulmonary edema. Ann Thorac Surg. 1988;45(3): 340–5.
100. Tekinbas C, Ulusoy H, Yulug E, et al. One-lung ventilation: for how long? J Thorac Cardiovasc Surg. 2007;134(2):405–10.
101. Hurford WE, Kolker AC, Strauss HW. The use of ventilation/ perfusion lung scans to predict oxygenation during one-lung anesthesia. Anesthesiology. 1987;67(5):841–4.
102. Slinger P, Suissa S, Adam J, Triolet W. Predicting arterial oxygenation during one-lung ventilation with continuous positive airway pressure to the nonventilated lung. J Cardiothorac Anesth. 1990;4(4):436–40.
103. Yamamoto Y, Watanabe S, Kano T. Gradient of bronchial end-tidal CO2 during two-lung ventilation in lateral decubitus position is predictive of oxygenation disorder during subsequent one-lung ventilation. J Anesth. 2009;23(2):192–7.
104. Fukuoka N, Iida H, Akamatsu S, Nagase K, Iwata H, Dohi S. The association between the initial end-tidal carbon dioxide difference and the lowest arterial oxygen tension value obtained during one-lung anesthesia with propofol or sevoflurane. J Cardiothorac Vasc Anesth. 2009;23(6):775–9.
105. Hurford WE, Alfille PH. A quality improvement study of the placement and complications of double-lumen endobronchial tubes. J Cardiothorac Vasc Anesth. 1993;7(5):517–20.
106. Brodsky JB, Lemmens HJ. Left double-lumen tubes: clinical experience with 1170 patients. J Cardiothorac Vasc Anesth. 2003;17(3):289–98.
107. Ehrenfeld JM, Walsh JL, Sandberg WS. Right- and left-sided Mallinckrodt double-lumen tubes have identical clinical performance. Anesth Analg. 2008;106(6):1847–52.
108. Baraka AS, Taha SK, Yaacoub CI. Alarming hypoxemia during one-lung ventilation in a patient with respiratory bronchiolitis-associated interstitial lung disease. Can J Anaesth. 2003;50(4):411–4.
109. Russell WJ. Intermittent positive airway pressure to manage hypoxia during one-lung anaesthesia. Anaesth Intensive Care. 2009;37(3):432–4.
110. Ku CM, Slinger P, Waddell TK. A novel method of treating hypoxemia during one-lung ventilation for thoracoscopic surgery. J Cardiothorac Vasc Anesth. 2009;23(6):850–2.
111. Mierdl S, Meininger D, Dogan S, et al. Does poor oxygenation during one-lung ventilation impair aerobic myocardial metabolism in patients with symptomatic coronary artery disease? Interact Cardiovasc Thorac Surg. 2007;6(2):209–13.
112. Casati A, Fanelli G, Pietropaoli P, et al. Continuous monitoring of cerebral oxygen saturation in elderly patients undergoing major abdominal surgery minimizes brain exposure to potential hypoxia. Anesth Analg. 2005;101(3):740–7.
113. Murkin JM, Adams SJ, Novick RJ, et al. Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. Anesth Analg. 2007;104(1):51–8.
114. Tobias JD, Johnson GA, Rehman S, Fisher R, Caron N. Cerebral oxygenation monitoring using near infrared spectroscopy during one-lung ventilation in adults. J Minim Access Surg. 2008;4(4):104–7.
115. Iwata M, Inoue S, Kawaguchi M, et al. Jugular bulb venous oxygen saturation during one-lung ventilation under sevoflurane- or propofol-based anesthesia for lung surgery. J Cardiothorac Vasc Anesth. 2008;22(1):71–6.
116. Van Hemelrijck J, Fitch W, Mattheussen M, Van Aken H, Plets C, Lauwers T. Effect of propofol on cerebral circulation and autoregulation in the baboon. Anesth Analg. 1990;71(1): 49–54.
117. Vandesteene A, Trempont V, Engelman E, et al. Effect of propofol on cerebral blood flow and metabolism in man. Anaesthesia. 1988;43(Suppl):42–3.
118. Kazan R, Bracco D, Hemmerling TM. Reduced cerebral oxygen saturation measured by absolute cerebral oximetry during thoracic surgery correlates with postoperative complications. Br J Anaesth. 2009;103(6):811–6.
119. YuluğE, Tekinbas C, Ulusoy H, et al. The effects of oxidative stress on the liver and ileum in rats caused by one-lung ventilation. J Surg Res. 2007;139(2):253–60.
120. Kozian A et al. Lung computed tomography density distribution in a porcine model of one-lung ventilation. Br J Anaesth. 2009;102(4):551–60.
121. Dueck R et al. A pilot study of expiratory flow limitation and lung volume reduction surgery. Chest. 1999;116:1762–71.