Clinical Management of One-Lung Ventilation

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Travis Schisler and Jens Lohser

Key Points

- OLV needs to be individualized for the underlying lung pathology, BMI, and ventilatory mechanical characteristics.
- OLV is a modifiable risk factor for acute lung injury.
- Protective OLV is a combination of small tidal volumes, low peak and plateau pressures, routine PEEP (adequate PEEP to facilitate open lung ventilation), and permissive hypercapnia.
- Hypoxemia during one-lung ventilation is rare and often secondary to alveolar de-recruitment in the face of hypoventilation.
- Management of hypoxemia requires a structured treatment algorithm.

Introduction

The development of thoracic surgery as a subspecialty only occurred after lung isolation and OLV had been reported. Prior to the description of endotracheal intubation and the cuffed endotracheal tube, only short intrathoracic procedures had been feasible [1]. 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 learned 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 with routine use of fiber-optic bronchoscopy and the use of anesthetic agents with little or no detrimental effects on hypoxic pulmonary vasoconstriction (HPV). Acute lung injury (ALI) has replaced hypoxemia as the chief concern associated with OLV [2]. Data has emerged in the past 10 years from both critical care and the operating room that has better elucidated the causative biomechanical and ventilatory factors involved in ventilator-induced lung injury (VILI). Translation of this data has yielded significant progress in harm reduction strategies in the routine application of mechanical ventilation.

Acute Lung Injury

Lung injury after lung resection was first recognized in the form of post-pneumonectomy 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 non-pulmonary intrathoracic procedures, which employ 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 PaO_2/FiO_2 (P/F). Critical care consensus guidelines define ALI as a P/F ratio < 300 and ARDS as a P/F ratio < 200 [6]. The criteria have recently been made more stringent by requiring that a minimum of 5 cmH_2O of PEEP or CPAP be applied at the time of the P/F ratio determination [7]. 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 (prolonged intubation and hospitalization) and

T. Schisler · J. Lohser (✉)
Department of Anesthesiology, Pharmacology, and Therapeutics, University of British Columbia, Vancouver General Hospital, Vancouver, BC, Canada
e-mail: jens.lohser@vch.ca

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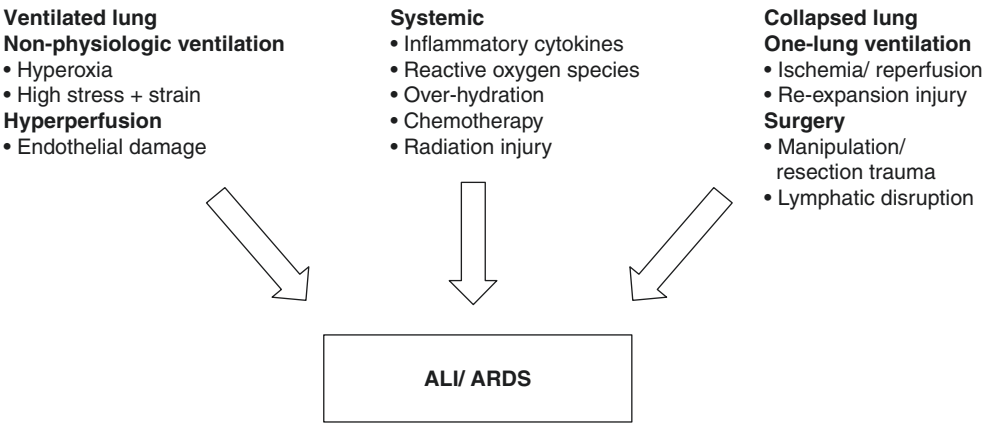

Fig. 6.1 Proposed mechanisms for ALI and ARDS after lung resection surgery

mortality [5]. Mortality, which was reported to be as high as 37–64% among patients with ALI [8–10], appears to be on the decline, as more recent reports indicated a mortality rate of 25–40% [11]. Similarly, Tang et al. reported a decrease in both the ARDS incidence of (3.2–1.6%) and mortality (72–45%) after pulmonary resection in a single institution cohort over a 10-year period. Their data 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 [12].

The etiology of lung injury is complex and likely multifactorial (Fig. 6.1). Historically, risk factors were felt to be right-sided surgery and large perioperative fluid loads. However, impaired lymphatic drainage, surgical technique, mechanical ventilation, transfusion, aspiration, infection, oxidative stress, and ischemia-reperfusion have all since been implicated (Table 6.1) [13]. 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 [14]. In ARDS patients, application of protective lung ventilation (PLV) with smaller tidal volumes and high positive end-expiratory pressure (PEEP) improved survival [15]. Additionally, protective ventilation was shown to inhibit progression of lung injury compared to high tidal volume ventilation [14] and to inhibit the development of lung injury in ICU patients [16–19]. It is now generally accepted that mechanical ventilation by itself may induce lung injury even in the patient with healthy lungs [20]. In patients undergoing either non-thoracic or thoracic surgery, mechanical ventilation with high tidal volumes and low PEEP is associated with lung injury, increased postoperative morbidity (including prolonged hospital and critical care length of stay), and most importantly increased mortality [21]. The first large-scale multicenter randomized controlled trial to investigate this principle occurred in 2013 in high-risk patients undergoing major abdominal surgery. Patients were randomized to a protective two-lung ventilation (TLV) strategy characterized by tidal volumes of 6–8 mL/kg, PEEP 6 to 8 cmH_2O, and frequent recruitment maneuvers or to a conventional strategy with tidal volumes of 10 mL/kg, no PEEP, and no recruitment maneuvers. Postoperative pulmonary complications occurred in 27% of the conventional ventilation group and in only 10% of the protective ventilation group [22]. Several studies have substantiated this report, and meta-analyses support the use of low tidal volumes (< 8 mL/kg during TLV) and some PEEP (greater than 3 cmH_2O) [23, 24]. It should be pointed out that low tidal volumes without adequate PEEP are harmful as evidenced by a greater incidence of hypoxemia, postoperative complications, and mortality [25]. Sufficient PEEP in addition to low tidal volumes is equally important in thoracic surgery and supported by an ever-increasing body of literature. In patients undergoing lobectomy, protective ventilation led to fewer postoperative pulmonary complications [26]. A retrospective analysis of over a thousand patients undergoing one-lung ventilation found that low tidal volume ventilation was protective but only when accompanied with adequate PEEP [27]. During

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

minimally invasive three-hole esophagectomy, a protective strategy reduced postoperative pulmonary complications [28]. Tidal volume reduction to 4–6 mL/kg for all patients undergoing one-lung ventilation with PEEP titrated to at least 5–10 cmH_2O should now be considered routine practice [29].

OLV predisposes the patient to ALI. Radiologic density changes in patients with ALI after thoracic surgery are more pronounced in the nonoperative, ventilated lung [30]. An increased duration of OLV was found to be an independent predictor of ALI in a retrospective analysis [8]. 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 [31, 32]. Re-expansion of lung tissue after short-term OLV incites pro-inflammatory cytokine release in animals [33]. Similar cytokine elevations are found in patients undergoing thoracic surgery [34, 35]. 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 [36]. Analogous to ARDS, high tidal volumes were therefore hypothesized to 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 to 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 [37]. The possible benefit of inhalational anesthesia is not without merit, as volatile anesthetics have been shown to confer attenuating effects in a model of alveolar epithelial injury [38]. Inhalational anesthesia has been shown to minimize ischemia-reperfusion injury [39] and secondary glycocalyx breakdown [40, 41]. Significantly elevated levels of pro-inflammatory cytokine levels have been demonstrated in the alveolus of patients undergoing thoracic surgery under propofol anesthesia, when compared to patients done using inhalational anesthesia with sevoflurane or desflurane [42, 43], although no difference was demonstrated in circulating cytokine levels [43]. 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. This however illustrates the fact that the true answer to lung injury avoidance is more complex than simple tidal volume reduction.

Individual Ventilator Settings

Tidal Volume

Tidal volumes used during TLV (10–12 mL/kg) used to be maintained into the period of OLV [44, 45]. Large tidal volumes were recommended because they had been found to improve oxygenation and decrease shunt fraction, during both TLV [46] and OLV, irrespective of the level of PEEP applied [47]. Large tidal volumes were shown to provide end-inspiratory alveolar recruitment (Fig. 6.2), resulting in improved oxygenation in the setting of zero end-expiratory pressure (ZEEP). 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 [48]. However, computed tomography images demonstrate gross overexpansion of the dependent lung during OLV in pigs when using tidal volumes of 10 ml/kg as compared to 5 ml/kg (Fig. 6.2). Based on the recent literature on patients with both healthy and injured lungs, it is 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 1000 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 [8, 50]. 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 [51]. 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 liters of fluid intraoperatively [52]. 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 cmH_2O increase (95% confidence interval 1.46–3.67) [53].

One of the earliest trials of tidal volume reduction during OLV was an animal study published in 2003 [54]. Isolated rabbit lungs were subjected to OLV with either 8 mL/kg ZEEP or the "protective" 4 mL/kg – average PEEP 2.1 cmH_2O (based on the dynamic pressure-time curve). OLV was

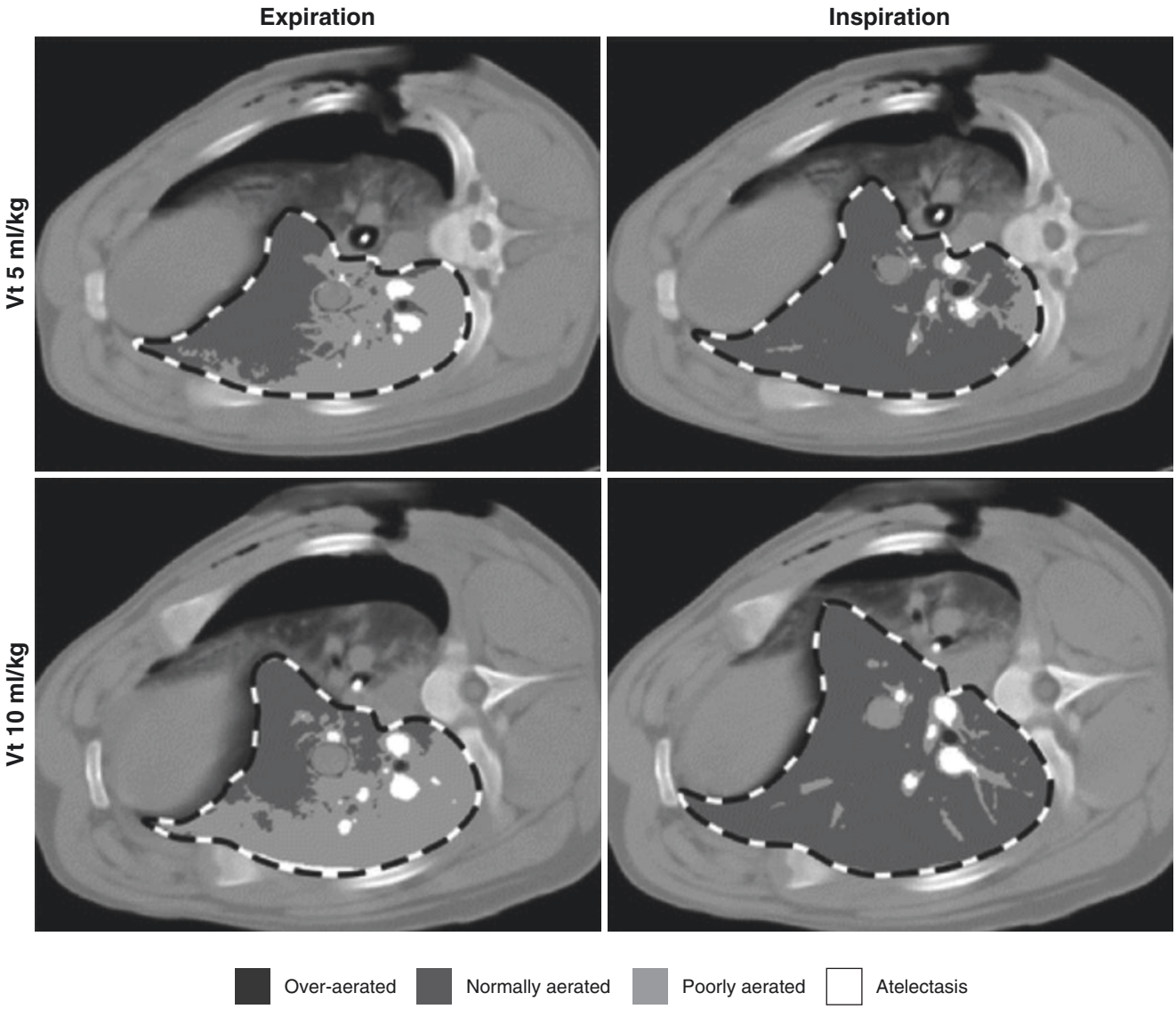

Fig. 6.2 Juxtadiaphragmatic lung computed tomographic scans of pigs during one-lung ventilation (OLV) with a tidal volume of 5 or 10 ml/kg. In each image, the region of interest includes the following (Hounsfield units in parentheses): over-aerated (from −1000 to −900), normally aerated (from −900 to −500), poorly aerated (from −500 to −100), and atelectatic (from −100 to 100) lung areas. The regions are coded by gray scale. The dependent lung border is outlined by the dashed line. Note the marked lung heterogeneity at end-expiration and the marked hyperinflation at end-inspiration with 10 ml/kg tidal volume. (Reprinted from Kozian et al. [49] with permission)

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 [54]. 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 (EVLW, a surrogate for lung injury), compared to 12 mL/kg ZEEP [55]. This finding has recently been refined in a trial demonstrating increases in EVLW when using tidal volumes of 6 or 8 ml/kg during OLV, while EVLW actually decreased when using tidal volumes of 4 ml/kg (Fig. 6.3) [56]. Tidal volume reduction by itself, however, is unlikely to be sufficient to improve outcomes. This point was best illustrated by an animal study comparing low versus 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 [57].

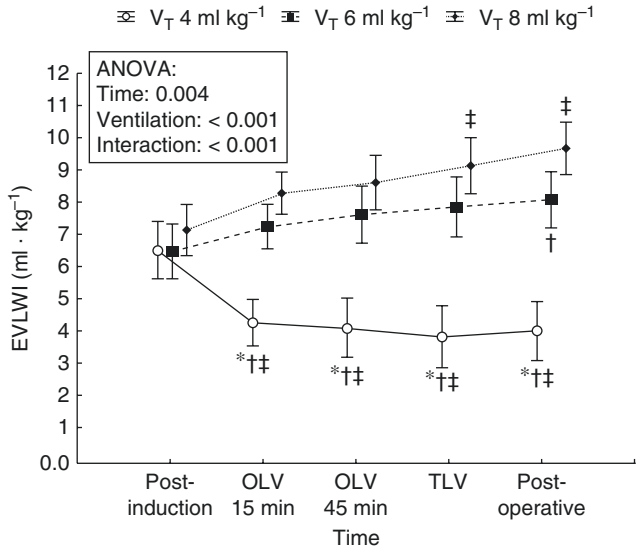

Fig. 6.3 Perioperative changes in the extravascular lung water index. Data are presented as mean (95% CI). ANOVA analysis of variance, EVLWI extravascular lung water index, OLV one-lung ventilation, TLV two-lung ventilation, VT tidal volume. $P < 0.05$ compared with *6 ml/kg, ţ8ml/kg and ŧpostinduction values. (Reproduced from Qutub [56] with permission)

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 [58] and baseline plasma levels of IL-6, IL-8, and IL-10 are associated with an increased risk of death in patients with ARDS [59]. 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 [60]. 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 [35]. 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 liters of fluid, only the low tidal volume group received PEEP during OLV, and no patient received PEEP during the remainder of the operation [35]. 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 [61]. 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 [34].

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) [4]. 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 toward fast-tracking of patients are established. However, the definition of ALI was consistent during the study period, and the authors were able to show a significant reduction in ALI from 3.8% to 0.9% [62].

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 [35, 55]. However, with inadequate or no PEEP, low tidal volume ventilation may be associated with worse shunt and oxygenation [34]. 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 (see expiratory images in Fig. 6.2). Despite the presence of atelectatic lung prior to the recruitment maneuver, however, oxygenation was adequate in all patients [63]. 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 [62].

Additional tools are emerging to support the clinician in the appropriate selection of tidal volume during one-lung

ventilation. Hoftman and colleagues demonstrated that forced vital capacity (FVC) may be a better predictor of ideal tidal volume during thoracic surgery than predicted body weight. FVC below 3.5 liters was found to be a good predictor of reduced lung compliance, and adjustment for preoperative FVC (VT = FRC/8) allowed for more appropriate one-lung tidal volume selection [64].

PEEP

Positive-end expiratory pressure minimizes alveolar collapse and atelectasis formation by providing resistance to airway collapse during exhalation. Applied PEEP should therefore be routine for all ventilated patients during TLV [65]. Klingstedt et al. demonstrated that the mediastinal weight results in significant compression of the dependent lung in the lateral position during TLV, which can be resolved with the application of selective PEEP to the dependent lung [66]. Due to the relative position of the heart in the left hemithorax, mediastinal shift and dependent lung compression are more marked in the left lateral position than the right lateral position (Fig. 6.4) [67].

PEEP does attenuate lung injury, both in the setting of high and low tidal volumes [13]. Intrinsic or auto-PEEP occurs if expiratory time is too short to allow lung units to empty toward 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 derecruitment [68]. The total PEEP after application of external PEEP is also unpredictable, due to the heterogeneous nature of auto-PEEP [69].

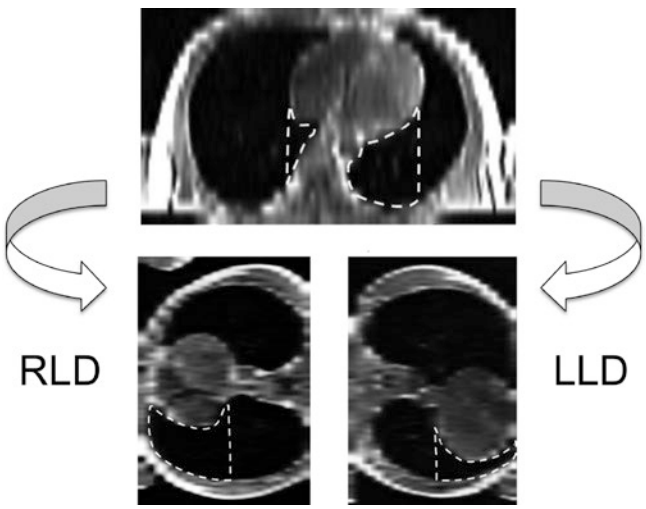

Fig. 6.4 Mediastinal shift as imaged with magnetic resonance images. Hashed areas indicate compressed areas of the lung. Note that while right lateral decubitus does expose more lung area to compression, the compression is more severe in left lateral decubitus. (Modified from an open access article by Mase et al. [67])

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 [68]. These values are unlikely to be reflective of the amount of auto-PEEP that develops with one-lung tidal volumes of 4–5 ml/kg. 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 [70]. 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 [69]. Excessive total PEEP and dynamic hyperinflation are clearly undesirable as they may cause cardiovascular depression and may require fluid loading and/or inotropic support [71].

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 toward 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 overdistension, and increases in PVR resulting in an increased shunt fraction (Fig. 6.5) [72]. 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 [73].

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 been shown to decrease surrogate markers of lung injury [35, 54, 55]. 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 [62].

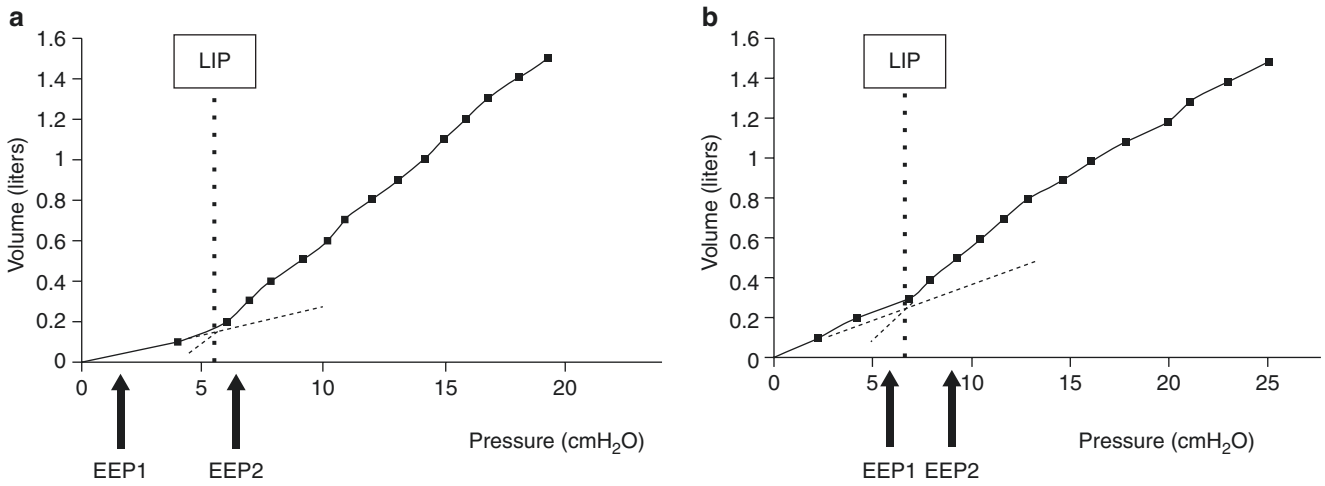

Fig. 6.5 Effect of applied PEEP on total PEEP and oxygenation during OLV. Static compliance curves of patients undergoing OLV. End-expiratory pressure before (EEP1) and after application of 5 cmH2O PEEP (EEP2) as well as lower inflection points (LIP) are indicated. Patients with normal pulmonary function and low EEP1 (**a**), in whom EEP2 moved closer to LIP, were more likely to show oxygenation benefits after PEEP application than patients with poor lung function and intrinsic PEEP (**b**). See text for details. (Modified from Slinger et al. with permission [72])

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. Additionally, due to the compression by abdominal contents and the mediastinal structures, marked de-recruitment and lung heterogeneity is present in the dependent lung at end-expiration (Fig. 6.2). Lack of PEEP in the setting of low tidal volume OLV has been shown to worsen oxygenation [34]. 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 bronchopleural 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 or more. 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 [62]. Early, routine application of PEEP helps to prevent atelectasis and shunt formation and thereby improves oxygenation during OLV [74].

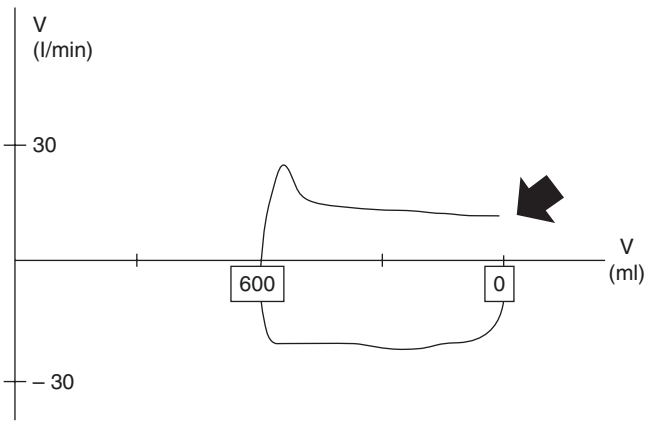

Fig. 6.6 Auto-PEEP detection by in-line spirometry. Flow-volume curve with expiration above and inspiration below the line. Expiratory flow normally returns to zero prior to inspiration. Interrupted airflow at end-expiration (arrow) indicates the presence of auto-PEEP. (Modified from Bardoczky et al. [75] with permission)

Clearly it would be best to measure total PEEP for each patient in order to rationally apply external PEEP [69]. 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. 6.6) [75]. 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.

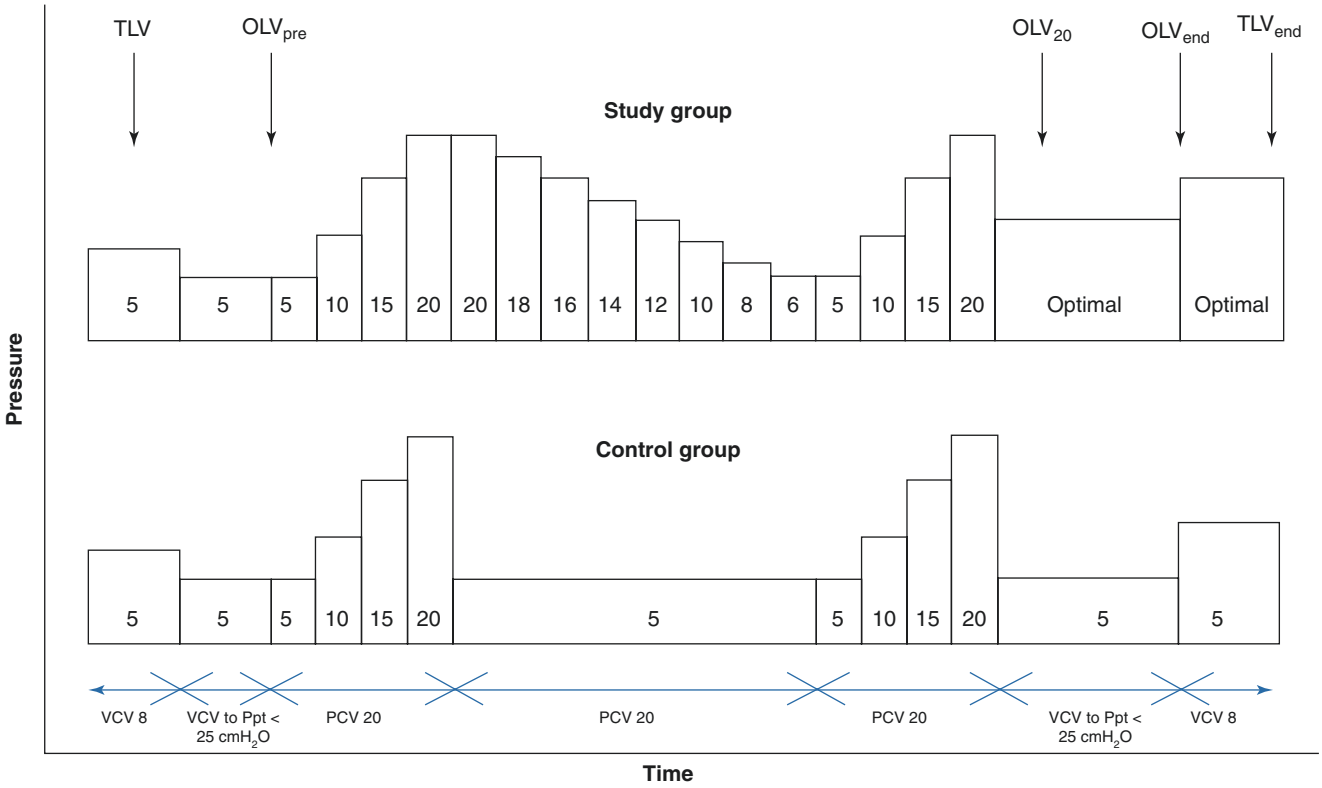

Fig. 6.7 PEEP titration during OLV after formal lung recruitment. In the study arm, optimal PEEP was determined by a stepwise decrement trial toward the point of optimal lung compliance. The control arm patients received a standard PEEP of 5 cmH2O. Individualized PEEP was higher than routinely used (10 ± 2 cmH2O) and resulted in better oxygenation both during and after OLV. (Reproduced from Ferrando et al. with permission [78])

It is possible to find the optimal level of PEEP for each individual patient during both one- and two-lung ventilation [76]. Static or dynamic lung compliance as calculated from the ventilator is influenced by FRC and the recruitable lung volume [76]. As the lung is recruited and FRC improves, so do PaO_2, dead space, and lung compliance. Lung compliance is therefore a reliable surrogate of FRC during general anesthesia. A PEEP titration study utilizing a PEEP decrement trial whereby PEEP is titrated to the best compliance following a recruitment maneuver is a reliable method to determine adequate PEEP [77] and tends to result in higher levels of PEEP than traditionally selected (Fig. 6.7) [78].

FiO_2

One hundred percent oxygen used to be a routine component of OLV, as hypoxemia was its most feared complication. However, with the decline in the incidence of hypoxemia and the realization that high FiO_2 may be detrimental, even this practice has been questioned. Oxygen toxicity is a well-recognized consequence of prolonged exposure to high FiO_2, characterized by histopathologic changes similar to ALI. Oxygen toxicity occurs during OLV and involves ischemia-reperfusion injury and oxidative stress [13]. 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 [79]. Lung re-expansion should likely occur at a lower FiO_2, as hypoxemic reperfusion has been shown to attenuate the reperfusion syndrome [80]. This is of particular relevance after lung transplantation. Even short-term exposure to high FiO_2 during the induction of anesthesia has been shown to cause significant absorption atelectasis [81]. Studies have shown that an FiO_2 as low as 0.4 may provide adequate oxygenation for OLV in the lateral decubitus position [82]. Due to the potential for lung injury, particularly in the high-risk patient, after adjuvant therapy or undergoing lung transplantation, FiO_2 should be titrated to effect. At the initiation of OLV, a FiO_2 of 0.8 may be appropriate, but 15–20 min later, when the nadir of oxygenation has occurred, the FiO_2 should be gradually decreased to the minimum that is required to maintain a stable saturation level above 90–92%. During lung resection surgery, further reductions in FiO_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.

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 (VATS). 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 [83]. FiO_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. A nitrous oxide/O_2 mixture was superior to oxygen alone for lung collapse, but nitrous oxide is rarely used nowadays. 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 have disappeared [83].

While 100% oxygen facilitates collapse of the operative lung, it also facilitates the development of de-recruitment and atelectasis in the nonoperative lung, producing shunt and facilitating hypoxemia. The greater the FiO_2 following endotracheal intubation, the larger the degree of atelectasis is seen on computed tomography [84]. While no prospective studies have evaluated the impact of lower than 100% oxygen prior to lung collapse, the individual practitioner should weigh the risks and benefits of lower FiO_2 and consider using the lowest inspired oxygen necessary to maintain acceptable arterial oxygenation.

Minute Ventilation/Permissive Hypercapnia

Permissive hypercapnia 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 [85], as hypercapnia appears to attenuate the cytokine response [86].

Permissive hypercapnia 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) [54]. 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. $PaCO_2$ values rose from 42 to 64 mmHg, which was associated with a 42% increase in PVR, but no change in oxygenation. Hypercapnia was well tolerated; however, higher-risk patients with pulmonary hypertension or major cardiac rhythm disturbances were excluded [87]. In a case series of 24 patients undergoing volume reduction surgery for advanced emphysema, permissive hypercapnia was used electively as part of a barotrauma avoidance strategy. The mean $PaCO_2$ 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 hypercapnia was well tolerated; however, inotropic support was required in over 50% of patients [88]. Even higher $PaCO_2$ levels have been described in a small series of ten patients with severe emphysema that were again managed with elective hypoventilation for barotrauma avoidance. $PaCO_2$ values rose to peak levels of 70–135 mmHg, resulting in pH values as low as 7.03 (despite bicarbonate administration). Hypercapnia 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 [89]. Significant hypercapnia 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 [71, 89]. Moderate hypercapnia potentiates the HPV response and is therefore unlikely to adversely affect oxygenation [90]; however, the same may not hold true for extreme CO_2 elevations [89]. A protective ventilation strategy including permissive hypercapnia has been shown to reduce the incidence of ALI in a cohort analysis by Licker et al. [62]. While not explicitly discussed in the manuscript, permissive hypercapnia 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 [62]. Permissive hypercapnia should be considered a routine component of a PLV strategy for OLV. Assuming a reasonable cardiovascular reserve, and in particular right ventricular function, $PaCO_2$ levels

<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 toward FRC, due to poor elastic recoil and conducting airway collapse. Decreasing the I:E ratio toward 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 [91]. 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 [92]. For illustration, a patient ventilated at 20 bpm of 400 ml receives the same minute ventilation as a patient ventilated at 10 bpm of 800 ml. However, dead space ventilation, which occupies about 150 mL of each breath, has doubled from 1500 mL at 10 bpm to 3000 mL at 20 bpm. Alveolar ventilation has therefore been reduced from 6500 mL (8000–1500) to 5000 mL (8000–3000). 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 airway resistance. It 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 [93]. 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 [92]. 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 [50]. Recently, Fernández-Pérez et al. reviewed 4420 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 FiO_2 were associated with ALI after adjusting for nonventilatory parameters [94]. 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 less than 35 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 [62].

Driving Pressure

One of the primary mechanisms driving ventilator-induced lung injury (VILI) is excessive stress and strain on lung parenchyma during inspiration. Transpulmonary pressure is calculated as plateau pressure minus pleural pressure and is a surrogate of both lung stress and strain [95]. Calculating transpulmonary pressure requires a plateau

pressure measurement. Plateau pressure can be measured on most present-day anesthetic machines by simply setting an inspiratory hold of at least 40% of the delivery time during a square wave flow delivery (volume control ventilation) [96]. Driving pressure is calculated as the plateau pressure minus the PEEP and frequently and closely approximates transpulmonary pressure when PEEP equals pleural pressure [95]. Driving pressure is a surrogate of lung stress and strain and should be kept as low as possible and ideally below 13 cmH_2O [97] as higher levels are associated with excessive lung stress [95]. Driving pressure is now considered an important independent predictor of mortality in ARDS and more influential than tidal volume or plateau pressure. In fact, any ventilator maneuver (PEEP titration, tidal volume titration) that reduces driving pressure also reduces mortality in patients with ARDS [97]. Driving pressure is also an important marker of postoperative pulmonary complications in patients with healthy lungs in the operating room. An analysis of individual patient data from several randomized controlled trials demonstrated that an increase in driving pressure resulted in a greater incidence of postoperative pulmonary complications [98]. Importantly, any change in PEEP (increase or decrease) that resulted in a lower driving pressure translated to a lower incidence of postoperative pulmonary complications. To date, a similar analysis has not been reported in patients undergoing one-lung ventilation; however Blank and colleagues found an association between driving pressure and postoperative pulmonary complications in their retrospective analysis [27].

Ventilatory Mode

Volume-control ventilation (VCV) has been the predominant 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 toward 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.

Pressure-control ventilation (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 [65]. Tidal volumes can be highly variable during PCV and may fall precipitously with changes in lung compliance, particularly 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 [99]. 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 crossover 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 [100]. 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 [101]. Other groups, however, have failed to reproduce the oxygenation benefit in PCV studies during OLV [102–104].

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 [105], no significant difference was demonstrated in a study of patients after thoracic surgery [106]. 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 [107]. HFJV, when applied to the operative lung during prolonged OLV in aortic surgery, is more effective than continuous positive airway pressure (CPAP) in improving PaO_2 [108]. This may be particularly relevant in the poor operative candidate after prior contralateral lung resection [109, 110]. Misiolek et al. 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 [111]. 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 [112]. 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 [107].

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 [113–115]. Lucangelo et al. assessed the effects of HFPV (FiO_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. HFPV patients showed higher PaO_2 during OLV than CPAP and exhibited better clearance of secretions and shortened hospital stays [116].

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. Studies have shown that atelectatic alveoli are not simply airless, 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 [81]. Interestingly, re-expansion of collapsed alveoli causes injury not only to the alveoli that are being recruited but also to remote nonatelectatic alveoli [81]. This may be in part due to the early realization by Mead that expansion of a gas-free alveolus with a transpulmonary pressure of 30 cmH_2O creates a shear force of 140 cmH_2O to adjacent alveoli [14, 117]. PEEP has been shown to prevent lung injury associated with both high and low tidal volumes, by stabilizing alveoli and preventing their collapse [81]. 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 [118].

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 OLV are high FiO_2, traditional lack of PEEP, and extrinsic compression by abdominal contents, the 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. 6.7). Recruitment increased PaO_2 on OLV from a mean of 144 mmHg to a mean of 244 mmHg (Fig. 6.8) [63].

However, it is not only for oxygenation purposes that lung recruitment is important. Establishment (and retention) of open lung optimizes lung compliance and optimizes ventilation by reducing dead space ventilation to its lowest level (Fig. 6.9). It is an often overlooked benefit of lung recruitment that it optimizes the amount of CO_2 clearance and therefore may in fact allow for a reduction in minute ventilation with secondary further decreases in lung stress and strain.

Cinnella et al. demonstrated that the alveolar recruitment achieved by a formal ARM resulted in a significant decrease in static elastance of the dependent lung [120]. 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 [35, 121]. A recent study showed that stroke volume variation (an indicator of preload responsiveness) increases dramatically after an ARM, while both

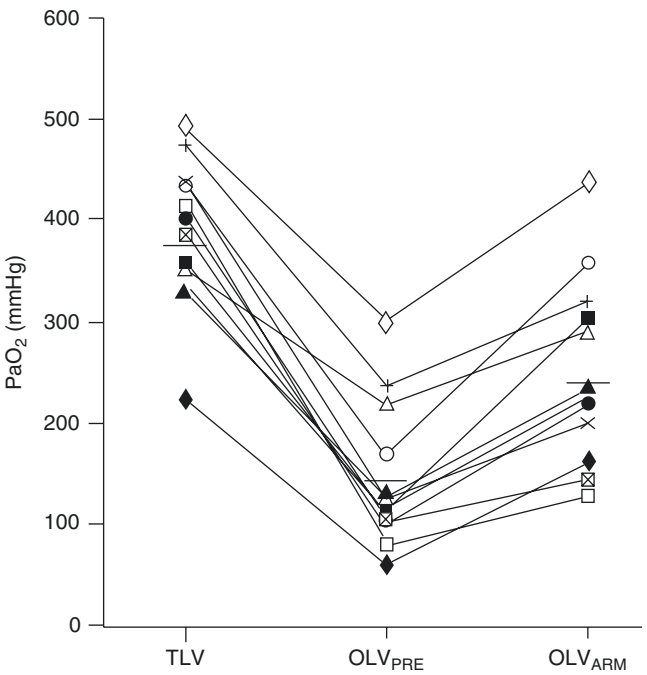

Fig. 6.8 Lung recruitment improves oxygenation during OLV. PaO2 (mmHg) in all patients during two-lung ventilation (TLV) and during one-lung ventilation before (OLVPRE) and after (OLVARM) the alveolar recruitment maneuver consisting of stepwise increases in PEEP from 5 to 20 cmH2O with a stable pressure-control driving pressure. Each symbol represents one patient in every point of the study. Horizontal bars represent mean values at each point. (Reprinted from Tusman et al. [63] with permission)

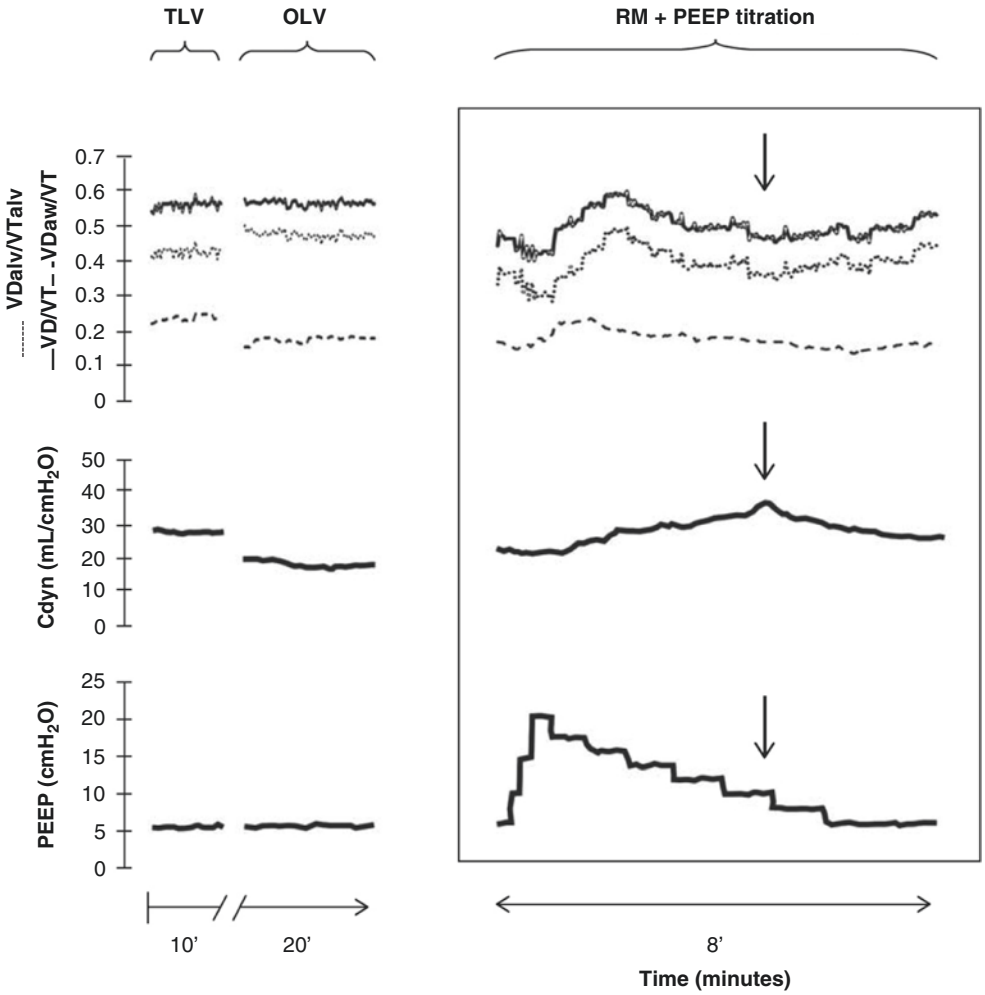

Fig. 6.9 Dynamic changes in dead space during thoracic surgery in one representative patient. All the measurements were performed in the right lateral position. The PEEP at the bottom is used as a marker of the RM and PEEP titration. The sequences of different representative periods of ventilation with two-lung (TLV, VT 8 ml/kg) or one-lung (OLV, VT 6 ml/kg) before and after RM are depicted. Rectangle: the time scale of the RM and PEEP titrations was magnified to highlight the interventions and their effects. The arrows indicate the closing pressure, thus the level of PEEP needed to maintain the lungs open after the RM, as identified by the highest dynamic compliance (Cdyn), which coincides with the lowest physiological (VD/VT) and alveolar (VDalv/VTalv) dead space values. PEEP, positive end-expiratory pressure; RM, recruitment maneuver. (Modified from Tusman et al. with permission [119])

cardiac index and venous oxygen saturation decrease. These changes, however, were transient and completely recovered within 3 min [122].

Caution is required with the implementation of PLV, as low tidal volumes and plateau pressures may promote atelectasis formation and increase FiO_2 and PEEP requirements [71]. 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 [123, 124]. 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 [125]. 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 [93]. Another critical care study found that 4 out of 28 patients with ALI/ARDS developed barotrauma necessitating intervention following an ARM [126]. 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 [71]. The best ventilatory strategy is therefore one that follows the "open lung" concept and maintains lung recruitment with appropriate levels of PEEP.

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 PaO_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. FiO_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. 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 have disappeared [83].

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 [108]. 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 [127]. 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 [33]. 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 [128]. 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 the atmosphere [129]. 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 [130]. 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 [79, 80].

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 [8]. 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 [131]. A prospective analysis of patients undergoing lobectomy for non-small 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 [79]. 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.

Combined Ventilator 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 also must include all of routine PEEP (set above the closing pressure and lower inflection point), lower FiO_2 (sufficient to maintain adequate arterial oxygenation), and particularly lower ventilatory pressures (driving pressure primarily) through the use of PCV and permissive hypercapnia. This strategy follows the "open lung" concept that has been widely adopted for the critical care management of ARDS patients but has since been expanded to include patients in the ICU without ARDS and to high-risk patients in the operating room or those undergoing major surgery. 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 a minimum following endotracheal intubation, at the beginning of OLV and on resumption of TLV. In addition, lung recruitment should be considered whenever oxygenation and lung compliance deteriorate. 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 FiO_2. Appropriate levels of external PEEP minimize de-recruitment in the setting of low tidal volume ventilation. PEEP titration is possible in the operating room with the use of spirometry and real-time measurement of pulmonary compliance. When PEEP is titrated to the best pulmonary compliance following maximal recruitment, FRC is maximized, atelectasis and dead space are reduced, oxygenation is improved, and atelectrauma is lessened [70]. Titrating PEEP to compliance individualizes the ventilator strategy to each patient's unique respiratory pathophysiology. As driving pressure is equal to tidal volume divided by pulmonary compliance, a reduction in driving pressure is achieved through an improvement in compliance. Titrating

PEEP allows one to also avoid overdistension which may produce pulmonary blood flow diversion to the operative lung and worsen hypoxemia and, as mentioned above, increases pulmonary complications [98]. There is no one-size-fits-all solution to PEEP selection as has become evident in recent RCTs [23]. Meta-analyses in both the ICU and the operating room have clearly demonstrated that PEEP titration toward lower driving pressure (due to improved compliance) improves patient outcomes [97, 98]. Once PEEP has been titrated to an optimal setting, the provider should then turn their attention to tidal volume. Excessive tidal volumes are often unintentionally provided in females, in the morbidly obese, and in patients of shorter stature, a fact that is avoidable by calculating ideal or predicted body weight [132]. Using driving pressure to optimize tidal volume is an important area that requires further investigation keeping in mind that driving pressure greater than 13 cmH_2O is an independent risk factor for postoperative pulmonary complications. One should consider decreasing tidal volume if this driving pressure threshold has been reached until more definitive data emerges.

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 the most severe form of obstructive lung disease.

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).

Table 6.2 Summary of ventilatory strategies

Tidal volume: protective, 3–5 mL/kg; hypoxemia or severe hypercapnia (consider 6–8 mL/kg (with decreased RR))
PEEP (approximate): normal lungs, 10 cmH_2O; obstructive, 2–5 cmH_2O (minimize intrinsic PEEP); restrictive, 10+ cmH_2O
RR: protective, 12–15 bpm; severe hypercapnia, 6–8 bpm (with increased VT)
FiO_2: transplant: 21%+, routine 50–80%, hypoxemia 100%
I:E ratio: restrictive, 1:1 or inverse ratio; normal, 1:1–1:2; obstructive, 1:3–4 (reduced RR)
Pressures: driving <15 cmH_2O, plateau <20 cmH_2O, peak <35 cmH_2O
Minute volume: $PaCO_2$ 40–60 mmHg (rarely higher: severe obstruction, lung transplantation)
Ventilator mode: PCV

Hypoxemia

Prediction

Hypoxemia used to be the major concern during OLV. Early reports indicated that 40–50% of patients suffered hypoxemia during OLV [133]. 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 [133]. They found that the amount of preoperative perfusion (and ventilation) to the operative lung inversely correlated with PaO_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 intraoperative shunt. Slinger et al. showed that PaO_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 [134]. 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 [135]. The other study demonstrated that there was a significant negative correlation between the lowest PaO_2 recorded during the first 45 min of OLV and the end-tidal CO_2 difference between TLV and the early phase of OLV [136]. Both studies postulated that elevated CO_2 gradients

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

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 fiber-optic bronchoscopy, and use of anesthetic agents with less effects on HPV are being credited for the reduction of oxygenation difficulties. In 1993 the incidence of hypoxemia (SpO_2 < 90%) occurring during OLV was quoted at 9% [133]. By 2003 the published incidence of hypoxemia was down to 1% of OLV cases in some hands [137]. 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 [138]. Although rare, significant hypoxemia may still occur, at times without warning [139].

Treatment

For a rational approach to hypoxemia 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. 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)

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 FiO_2 toward 1.0
Optimize PEEP to nonoperative lung (up or down, toward 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 (ECMO, CPB)

technique, which does not elicit lung inflation and therefore should not impact surgical exposure. 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 LPM) 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-second burst of flow will deliver 66 mL of oxygen to the nonventilated lung. In their study, all patients with relative hypoxemia (SpO_2 < 95%) were successfully treated with repeated 2-second bursts of oxygen, followed by 10-second exhalations, while no impairment in surgical exposure was noted [140]. Apneic oxygen insufflation via an endotracheal suction catheter at 3 LPM is another successful method that has been shown to reduce the incidence of hypoxemia while on OLV. This technique should result in fewer interruptions to surgery during a VATS procedure [141].

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 fiber-optic bronchoscope 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.6.10). 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

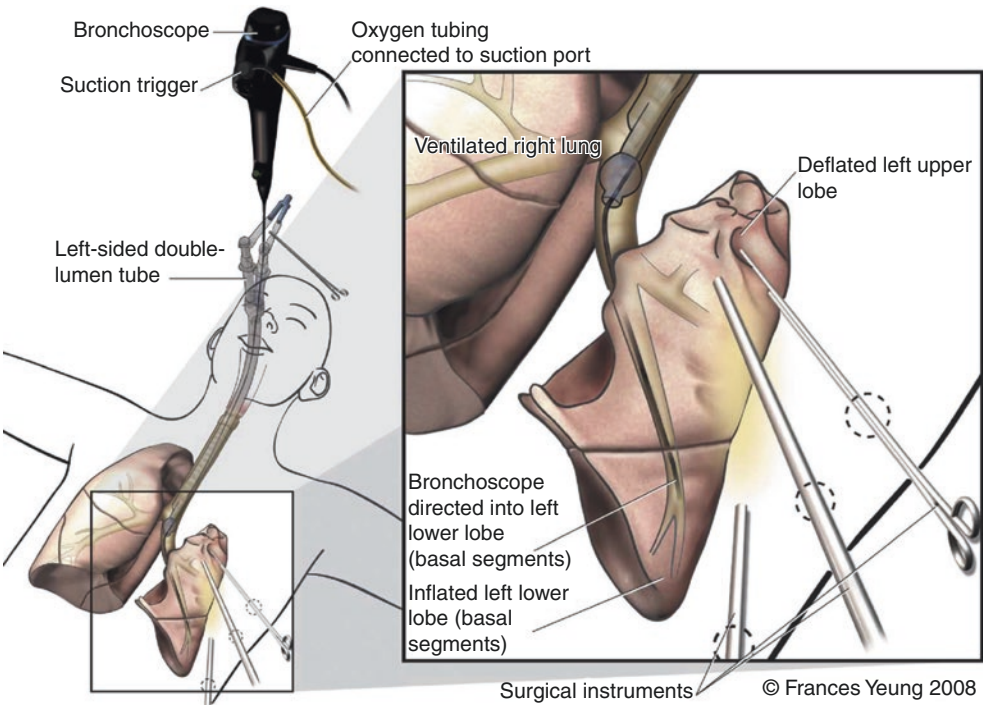

Fig. 6.10 Schematic illustration of oxygen supplementation during thoracoscopic surgery via bronchoscopy suction channel. See text for details. (Reprinted from Ku et al. [142] with permission)

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 overdistension 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 segments throughout the period of insufflation [142]. Distal oxygen insufflation, particularly at relatively high flow rates as described in this report, should never be applied blindly. As another option, HFJV has been successfully employed during VATS procedures [143]. 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 hypoxemia has become less of an anesthetic issue during OLV, relative hypoxemia may have a significant impact on vital nonpulmonary organ function given the ever-increasing rate of comorbid 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 recent study by Mierdl et al. analyzed the impact of hypoxemia during OLV on myocardial metabolism in patients with severe multivessel 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 PaO_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 multivessel coronary artery disease with an acceptable low risk of inducing anaerobic myocardial metabolism [144].

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 [145, 146]. 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 [147]. In 8 of 40 patients, prolonged decreases in rSO_2 to less than 75% of the baseline value were recorded during 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 [148]. 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 [149, 150].

Interestingly, cerebral oxygen desaturation also appears to be predictive of noncerebral postoperative complications. In a 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, $P = 0.043$) [151]. 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. Yuluğ et al. investigated the effects of OLV and re-expansion on the tissue damage of the liver and ileum in rats [152]. 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.

Alternatives to One-Lung Ventilation

With the uncommon yet legitimate concern about acute lung injury following one-lung ventilation, clinicians have sought alternatives to general anesthesia and positive pressure ventilation for patients undergoing thoracic surgery. One approach which has reemerged is the avoidance of endotracheal intubation and mechanical ventilation for thoracic surgery [153]. This has also been termed NIVATS, which stands for non-intubated video-assisted thoracic surgery. The goal of NIVATS is to avoid the risks associated with endotracheal intubation, general anesthesia, and positive pressure ventilation including mechanical airway injury, ventilator-induced lung injury, hypoxemia, cardiac arrhythmias, cognitive dysfunction, and other organ injury [154]. NIVATS has been used for a range of thoracic procedures from simple pneumothorax, effusions and empyema, wedge resection, mediastinal biopsy, bullectomy to more invasive procedures including lobectomy, pneumonectomy, thymectomy, and even carinal and tracheal resection. NIVATS is often facilitated with varying degrees of conscious sedation combined with regional anesthesia via an epidural, paravertebral, intercostal, or serratus anterior block with the maintenance of spontaneous ventilation in the lateral position, which favors ventilation perfusion matching. Complications associated with NIVATS include hypercapnia, coughing, disruption of the surgical field from mediastinal and diaphragm motion, and patient intolerance, which may require conversion to general anesthesia [155]. In a recent survey to members of the European Society of Thoracic Surgeons, 62 out of 105 respondents claimed an experience with NIVATS. The most common approach included intercostal blocks with minimal sedation followed by laryngeal mask with sedation and thoracic epidural blockade with sedation. The most common procedures in which NIVATS was utilized included the management of pleural effusion and lung or mediastinal biopsy [157]. So far data on outcomes using NIVATS compared to general anesthesia (GAVATS) is sparse but points to shorter hospital length of stay and less postoperative morbidity in high-risk individuals [154]. NIVATS offers a promising alternative to general anesthesia and endotracheal intubation in high-risk individuals for primarily simple thoracic procedures when the thoracic surgeon and anesthesiologist are comfortable using this modality and are prepared to convert to general anesthesia if the need arises. There is insufficient evidence to recommend this approach in more involved lung resections.

Conclusion

The last two decades have 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.

Performing a PEEP titration study and routinely monitoring and limiting driving pressure are two recent developments in the literature that deserve special attention and further investigation. 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 hypoxemia 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.

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