Perioperative lung protective strategies

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Table 1
1. Introduction

Currently, the incidence of postoperative pulmonary complications (PPC) far outnumbers cardiovascular complications. (1) They vary from 10% to 70%, depending on their definition, retro- or prospective study design, the heterogeneity of patient populations and the type of procedure. (2) In thoracic surgery, the main causes of perioperative deaths have now shifted from cardiovascular to infectious and pulmonary complications. (3,4) Pulmonary morbidity has also been associated with increasing health care costs and poor outcome as reflected by prolonged hospital stay, (re-)admission in intensive care units and reduced long-term survival. (5,6)

Transient and self-limiting impairments in gas exchange should be considered part of the physiological response to surgery along with anesthesia emergence. Most patients undergoing cardiothoracic or abdominal operations present some degree of hypoxemia and diffuse micro-atelectasis that will barely impact on the postoperative clinical course. In contrast, pleural effusions, sustained bronchospasm, lobar atelectasis or hypoxemia unresponsive to supplemental oxygen may forecast serious adverse events such as bronchopleural fistula, bronchopneumonia, acute lung injury (ALI) or respiratory failure. (7)

Predictive factors for PPCs include patient-related factors (e.g., chronic obstructive pulmonary disease [COPD], advanced age, poor nutritional status, decreased exercise tolerance, heart failure) and intra-operative related factors (i.e., emergency surgery, upper abdominal and intra-thoracic procedures, duration of anesthesia, presence of a nasogastric tube, ventilatory settings, fluid balance). (2,8) These procedure-related factors are much more amenable to modification than preexisting chronic diseases.

In an effort to standardize the reporting of adverse perioperative events, Dindo and coll. have validated a 5-grade scoring system based on the therapeutic consequences and residual disabilities in relation to surgical operations. (9) Grade I complications entail any deviation from the normal postoperative course with no need for medical interventions (except a slight increase in inspiratory oxygen fraction [FIO$_2$] or lung recruitment maneuvers). Grades II and III complications require non-invasive ventilatory support, pharmacological treatment (e.g., bronchodilators, diuretics) or specific interventions (e.g., fiberoptic bronchoscopy, thoracic drainage). Grade IV includes life-threatening complications (single-or multiple organ failure) requiring ICU admission and/or mechanical ventilation.

2. Mechanisms of perioperative pulmonary injuries

2.1. Atelectasis

Collapsed lung areas or atelectasis developed in about 90% anesthetized patients, irrespective of ventilatory control (spontaneous or mechanically controlled) and anesthesia type (intravenous, balanced or combined general and regional anesthesia). (10) The predominant mechanisms of atelectasis formation are related to reduction of lung volumes (absorption atelectasis) and to deficient surfactant synthesis/effects. Compression of lung tissue by interstitial/alveolar edema may be implicated in obese patients and those with ongoing inflammatory lung process where the weight of the chest/abdominal wall and the “wet lung” may push air/gas out of the alveola (as in the ALI syndrome).

By changing from upright to supine position, the functional respiratory capacity (FRC) is decreased by 0.8-1.0 L and a further reduction of 0.4-0.5 L occurs after the induction of anesthesia owing to relaxation of the respiratory muscles and the decrease in thoracic
elastice recoil.\(^{11,12}\) Ventilation with enriched oxygen mixture (FIO\(_2\) > 80%) promotes the development (or reappearance after lung recruitment) of atelectasis as a result of complete absorption of O\(_2\) in poorly ventilated lung regions. Accordingly, 3% to 40% of the total lung volume collapses in the dependent zone resulting in impaired gas exchange intraoperatively.\(^{13}\) Moreover, atelectasis impairs the clearing of bronchial secretions, it may impede lymphatic flow and become a focus of infection in the postoperative period.

2.2. Ventilator-induced lung injuries (VILI)

During spontaneous ventilation (at rest), tidal volume (V\(_T\)) and transpulmonary pressure (Ptp) in healthy subjects vary within tight limits of 4 to 6 ml per kg of ideal body weight (IBW) and 4 to 8 mmHg, respectively. In contrast, anesthetists have been taught to apply “unphysiological” large tidal volume (10 to 15 ml/kg) with the aim to prevent the atelectasis.

Mechanical inflation of “physiological” low V\(_T\) (4-8 ml/kg) is associated with higher Ptp and when delivered over several hours this may produce subtle lung injuries even in healthy lungs: neutrophil infiltration, rupture of alveolar-branchial attachment and chondroitin-sulfate proteoglycan fragmentation in the extra-cellular matrix (ECM).\(^{14}\) When a larger V\(_T\) is delivered (with or without increased Ptp), there is further macro-molecular fragmentation, activation of matrix metallo-protease and upregulation of collagen synthesis in the ECM that all represent autoregulatory responses to maintain low pulmonary compliance while protecting the ECM against fluid overload.\(^{(15-17)}\) In addition, the cyclic stretch and hyperoxic exposure of lung epithelial and endothelial cells have been shown to trigger the formation of reactive oxygen/nitrogen intermediates (ROIs/RNs) and to induce various patterns of cell death (necrosis and apoptosis) resulting in alteration in the alveolar-capillary barrier. \(^{(18-20)}\) An upregulation of pro-inflammatory mediators (TNF-\(\alpha\) and interleukin-8) associated with diffuse alveolo-capillary lesions was also demonstrated when rabbits were ventilated with large V\(_T\) and moderate hyperoxia (compared with normoxia/large V\(_T\) and hyperoxia/normal V\(_T\)).\(^{(21,22)}\)

With the pioneering experimental work of Dreyfuss et al. in 1985, ICU physicians first became aware of the potential deleterious effects of positive pressure ventilation.\(^{(23)}\) Several reports suggested that the application of high V\(_T\) (\(>8\) ml/kg), high plateau inspiratory pressure and/or high inspiratory FIO\(_2\) (100%) in critically-ill patients (without ALI) may produce pulmonary changes mimicking ALI as expressed by diffuse alveolar damage, recruitment of inflammatory cells and production of pro-inflammatory mediators.\(^{(24)}\)

Over the last two decades, - in thoracic surgery requiring one-lung ventilation (OLV) -, the routine settings for V\(_T\) have been shifted downwards (from 10 to 12 ml/kg to 6-9 ml/kg) given the growing body of scientific knowledge supporting the injurious effects of large V\(_T\).\(^{(25)}\)

Some individuals are more prone to develop ALI if their lung defence and repair mechanisms (e.g., antioxidant, heat shock protein, p75 receptor for tumour necrosis factor alpha [TNF-\(\alpha\)]) fail to counteract the inflammatory and oxidative responses.\(^{(26)}\) Genetic disruption of the transcription factor Nrf2 (NF-E2 related factor 2) has been associated with overexpression of proinflammatory cytokines and increased risk of ALI due to hyperoxia and high V\(_T\). Relevant gene variants or single nucleotide polymorphisms (SNPs) in ALI candidate genes have been tested for differences in allelic frequency in cohort studies.\(^{(26)}\) The Nrf2-617 SNP (A/ or C/A allele) has been associated with a greater risk of post-trauma ALI relative to subjects bearing the wild type.\(^{(27)}\) Likewise, in patients undergoing oesophagectomy, SNP of the angiotensin-
converting enzyme (D/D genotype) was found to be highly predictive of major pulmonary complications.(28)

3. Perioperative lung protective strategies

3.1. Volatile anesthetics

Compared with intravenous hypnotics, volatile anesthetics induce bronchodilatation and may inhibit the hypoxic pulmonary vasoconstriction (HPV) although no significant difference has been reported regarding blood oxygenation when anesthetic administration is titrated to achieve a similar depth of anesthesia.(29)

Based on experimental models of lung ischemia-reperfusion (I-R) and lipopolysaccharide (LPS) or zymosan injuries, volatile anesthetics such as isoflurane and sevoflurane have demonstrated potent immunomodulatory properties.(30,31) In isolated rat lungs subjected to LPS challenge or I-R, pre-treatment with volatile anesthetics has been shown to attenuate lung edema and microvascular protein leakage as a result of a reduction in polymorphonuclear recruitment, decreased cytokine release from alveolar macrophages/monocytes as well as attenuation of the overproduction of pro-inflammatory mediators and nitric oxide. Besides multiorgan preconditioning effects, both isoflurane and sevoflurane also exert postconditioning effects as far as they are administered within 1-2 hours of the onset of LPS-induced ALI. Noteworthy, the concomitant administration of beta-blockers counteract the anti-inflammatory effects of volatile anesthetics.(32)

So far, these experimental data have not been confirmed in the clinical settings. However, preliminary data obtained in patients undergoing thoracic surgery lend support to the anti-inflammatory effects of volatile anesthetics, compared with propofol. Indeed, Schilling and coll reported an attenuate release of IL-8, IL-10, elastase TNF-α and soluble intercellular adhesion molecule type 1 in the bronchoalveolar lavage (BAL) of patients anesthetized with desflurane (vs propofol, n=30).(33) In another RCT (n=40), a reduction of inflammatory markers with a trend for fewer respiratory complications was found in patients anesthetized with sevoflurane anesthesia (vs propofol).(34)

3.2. Pressure or Volume controlled ventilation

Currently, volume controlled ventilation (VCV) is still considered the conventional mode of mechanical ventilation in surgical patients. In thoracic surgery, recent interest has been focused on the use of pressure controlled ventilation (PCV) given some potential benefits related to the attenuation of lung inflating pressures and the reduction of intrapulmonary shunt.

Unlike VCV which is characterized by a constant “square” wave inspiratory flow, the PCV mode produces a decelerating inspiratory flow in order to rapidly achieve and maintain the preset inspiratory pressure. Such flow characteristics are thought to allow more homogeneous distribution of gas mixture and improved ventilation-perfusion matching.

Basically, during VCV, airway pressure increases in response to reduced compliance, increased resistance, or active exhalation and may increase the risk of ventilator-induced lung injury (if light levels of anesthesia). In contrast, PCV by design, limits the maximum airway pressure delivered to the lung, but may result in variable tidal and minute volume.(36) The characteristics of both VCV and PCV may be combined in so-called dual-control modes, which are volume-targeted, pressure-limited, and time-cycled.
In ALI patients, variations in lung strain have been shown to be minimized by ventilating with PCV compared with VCV, although static mechanics, oxygenation, and hemodynamics remained similar. (35,36)

In patients undergoing thoracic surgery, conflicting results have been reported regarding the physiological and clinical effects of PCV and VC. Senturk and Tugrul group’s found significant reductions in both peak and plateau airway pressures (Ppeak, Ppl) that was associated with better oxygenation. (37,38) Larger benefits were found in patients with altered pulmonary function and gas exchange could be further improved when a PEEP of 4 cm H2O was applied. Although other investigators confirmed the lower Ppeak associated with PCV, they could not replicate the reduction in Ppl and the oxygenation benefits. (39-42) Interestingly, the lower Ppeak achieved with PCV is observed mainly in the respiratory circuit but the difference is not clinically relevant in the bronchus and in the alveola. (43)

Altogether, PCV offers no advantage over VCV in deeply anesthetized/paralyzed patients receiving full mechanical ventilation. During anesthesia emergence, pressure support ventilation (PSV) may offer lower work of breathing and improved comfort for patients with increased and variable respiratory demand. In addition, with assist mode of ventilation, recruitment of dependent collapsed lung areas and redistribution of pulmonary blood flow towards nondependent zone result in improved oxygenation and restoration of the FRC. (44-46)

3.3. PEEP

Following anesthesia induction and supine position, the FRC decreases and the progressive collapse of various amount of lung areas results in impaired blood oxygenation. Mechanical ventilation induces “low-volume” injuries by repetitive opening and closing of unstable lung units owing to the inactivation of surfactant and the excessive mechanical stress between atelelectatic areas and neighbouring areas with low ventilation/perfusion ratio (V/Q). (47,48,48a)

During mechanical ventilation, PEEP exerts a positive pressure in the lungs at each exhalation that may prevent the fall in FRC, the collapse of the small airways and thereby may reduce the development of atelectasis. In patients with healthy lung, appropriate PEEP levels restore lung volumes and thereby improve lung compliance and decrease intrapulmonary shunting. (11) Nevertheless, depending on the level of PEEP and the presence of lung pathological conditions, PEEP has the potential to cause both harm and good. PEEP-induced increase in intrathoracic pressure may decrease cardiac output, increase the risk of barotraumas and overdistend normal lung areas, causing additional physiological dead space, particularly in damaged lungs with heterogenous distribution.

In a meta-analysis of eight RCTs involving 330 surgical patients, positive pressure ventilation with PEEP resulted in favourable effects on day 1 postoperatively in terms of higher PaO2/FIO2 and lesser atelectatic areas, compared with mechanical ventilation without PEEP (or zero-PEEP, ZEEP). (49) No relevant adverse effects (barotrauma and cardiovascular complications) were reported in the three trials that adequately measured these outcomes. Adding an external PEEP resulted in improved respiratory mechanical properties in morbidly obese subjects. (49a)
3.4. Recruitment maneuver or alveolar recruitment strategy

Bendixen and coll., first demonstrated the physiological rationale of a lung recruitment maneuver (RM) to correct oxygenation impairment during anesthesia. (50) A single manual ventilation up to 40 cm H\textsubscript{2}O was maintained for 15 s using the anesthesia bag while adjusting the expiratory valve. This pressure was equivalent to inflation to vital capacity, and thus this maneuver was also called the vital capacity maneuver. More recently, it has been shown that this RM needs to be maintained for only 7–8 s in order to reexpand all previously collapsed lung tissue. Alternatively, atelectatic re-expansion can be performed either by stepwise increase of PEEP/inspiratory pressures (e.g., 0/10, 5/15, 10/20, 15/25 cm H\textsubscript{2}O) over 8 to 10 respiratory cycles (alveolar recruitment strategy [ARS]) or by applying continuous a positive airway pressure (CPAP) over 10-30 s. (51)

To re-expand atelectatic areas, the lung opening pressure should be overcome by temporary elevation of Ptp while at end-expiration, Ptp should remain higher than the closing airway pressure. In other words, RM re-expands collapsed pulmonary acini and subsequent re-collapse is prevented by titration of external PEEP.

In obese patients undergoing laparoscopic bariatric surgery, intraoperative alveolar recruitment (vital capacity maneuver maintained for 8 s) followed by 10 cm H\textsubscript{2}O PEEP is more effective than ZEEP or PEEP of 5 cm H\textsubscript{2}O for prevention of postoperative lung atelectasis and is associated with better oxygenation, shorter PACU stay, and fewer pulmonary complications in the immediate postoperative period. (52-54) Application of PEEP and RM was not accompanied by a significant reduction in MAP, even after pneumoperitoneum and reverse Trendelenburg position. (54).

In these morbidly obese patients, observation of phase III slope of the CO\textsubscript{2} expiratory curve is helpful to titrate the optimal level of PEEP after a RM (55). The expiratory volumetric capnography is an easily traced parameter that provides aggregate information about gas exchange at the alveolar-capillary membrane, gas transport within airways, and respiratory mechanics. After a RM, the “best” PEEP is characterized by a flat slope because of improved elastic properties of the respiratory system and thereby lower resistance to CO\textsubscript{2} elimination. In a sheep model of ARDS, comparison of various methods based on P-V curves and gas exchange for setting the optimal PEEP failed to show any significant difference: maximum dynamic compliance, maximum PaO\textsubscript{2}/PaCO\textsubscript{2}, minimum shunt and the lower/upper inflection points all yielded results that were statistically indistinguishable. (56)

During OLV, application of a RM to the dependent lung results in significant improvement in blood oxygenation and respiratory mechanics (reduced dead space, improved compliance) that is accompanied by transient and slight hemodynamic disturbances (57-59).

Specific contraindication to RM should be mentioned: hemodynamic unstable patients (hypovolemic), light levels of anesthesia (patient-ventilator dysynchrony), bronchospastic airways, pneumothorax and bronchopleural fistula and increased intracranial pressure.

3.5. Tidal volume

Based on experimental models of ALI/ARDS, the “open-lung” approach has been shown to minimize the bronchoalveolar strain using low V\textsubscript{T} while maintenance of the FRC and prevention or re-expansion of atelectasis is achieved with the application of PEEP and periodic RMs. (60,61) Ventilatory management with pressure and volume limited ventilation was found to reduce mortality in ten trials including 1'749 critically adults with ARDS
(relative risk (RR) 0.84; 95% CI 0.70). At similar PEEP levels, mechanical ventilation with lower \( V_T < 8 \text{ ml/kg} \) was associated with a 25% reduction in hospital. In the ICU settings, such protective lung strategy have been associated with improved outcomes in terms of better survival, lesser barotrauma and shorter time on the ventilator in critically-ill patients.

In anesthetized patients with healthy lungs, besides “high” \( V_T \) and elevated inspiratory pressure -, other risk factors for lung injuries have been identified. Fluid overhydration increases capillary hydrostatic pressure and promotes interstitial/alveolar edema particularly when lymphatics are disrupted. Importantly, tissue trauma, ischemia-reperfusion, blood transfusion and exposure to extracorporeal devices may all concur to trigger a widespread inflammatory response with potential deleterious effects on the lungs.

Table 1 summarizes all RCTs including surgical patients that have questioned the impact of protective ventilatory settings (e.g., low \( V_T \) with PEEP, RM) on markers of inflammation (systemic and pulmonary), oxygenation and postoperative pulmonary complications.

Not surprisingly, no difference was observed between traditional and protective ventilatory approach in patients undergoing minor/moderate surgical procedures, lasting less than 5h. In contrast, in higher risk of patients (major abdominal, thoracic and cardiac surgery), intraoperative “protective ventilation” strategies (\( V_T 4-6 \text{ ml/kg PBW}, \text{ PEEP with or without RM} \)) were associated with a reduced expression of alveolar/systemic inflammatory markers, reduced procoagulant activity in the BALF, better respiratory mechanical properties (dynamic compliance, airway resistance) and stable or improved oxygenation indices. In three of these RCTs, better clinical postoperative outcomes were reported in the group treated with the protective approach. After major noncardiac surgery, Lee et al. reported fewer pulmonary complications and shorter intubation times in patients ventilated postoperatively with small \( V_T \) (6 vs 12 ml/kg). Michelet et al. studied 52 patients undergoing oesophagectomy and observed lesser lung edema and better oxygenation index allowing earlier extubation among patients treated with low \( V_T \) (5 ml/kg) and 5 cm H\(_2\)O PEEP (compared with 10 ml/kg \( V_T \) and ZEEP). More recently, Yang et al., compared two ventilatory strategies during OLV in 100 patients scheduled for lobectomy (\( V_T 10 \text{ ml/kg, ZEEP} \) and FIO\(_2\) 100% vs. \( V_T 6 \text{ ml/kg, 5cm H}_2\text{O PEEP and FIO}_2\) 0.5). The combined endpoint of pulmonary dysfunction (\( \text{PaO}_2/\text{FIO}_2 < 300 \text{ mmHg, lung atelectasis} \)) was significantly lower in the “protective” group than the control group (4% vs. 22%).

Although these preliminary results support the scientific concept of the “open lung” approach, we are awaiting the results of well designed RCTs with sufficient power and relevant clinical endpoints.

3.6. FIO\(_2\)

In current practice, high FIO\(_2\) (>0.8) has been advocated for 2 reasons: 1) to prevent hypoxemia during anesthesia induction/emergence, by building up a large O\(_2\) store in the FRC and increasing the safety margin, 2) to promote the “killing” activity of PMN cells and prevent the occurrence of surgical site infection by increasing tissue PO\(_2\) during and shortly after surgery (80,81). The drawbacks of FIO\(_2\) relate to the enhanced formation of absorption atelectasis and the generation of O\(_2\) derived free radicals.

Following anesthesia induction, atelectatic areas appear within the first minutes in all patients on 100% FIO\(_2\) whereas it is much less in those receiving less than 60% FIO\(_2\). However, with pre-oxygenation at an FIO\(_2\) of 1.0, 7 min elapse before SaO\(_2\) decreases below
90%, at an FIO₂ of 0.6 whereas the time delay before O₂ desaturation is shorten to 3.5 min.(82)

As a safety measure, pre-oxygenation with high FIO₂ (80-100%) is recommended to ensure sufficient time in case of difficult airway management. After airway control with a laryngeal mask or an endotracheal tube, an early RM should be performed and FIO₂ should be reduced at a level sufficient to ensure optimal O₂ delivery with SaO₂ > 96%.(83) During anesthesia emergence, hyper-oxygenation is highly discussable as it promotes atelectasis formation.(84) During the ventilatory weaning period, RM and assisted ventilatory modes should be considered to improve aeration of the dependent part of the lungs with better matching of ventilation and blood flow.(45)

3.7. Normocapnia vs hypercapnia

The current recommendations for ventilatory settings are to target SaO₂ > 96% and end-tidal CO₂ (etCO₂) within a range of 4.8-5.5 kPa, using a V₁ of 4-8 ml/kg PBW and pressure limited ventilation (< 30-35 cmH₂O). The risks of hypocapnia are related to vasoconstriction of the cerebral vessels and consequent neurocognitive dysfunction. Hypercapnia has dual effects: it may trigger the release of catecholamines and increase oxygen consumption. On the other hand, clinical evidence supports the use of permissive hypercapnia, particularly in ALI/ARDS, status asthmaticus, and neonatal respiratory failure. Hypercapnia has been associated with improved O₂ tissue deliver, attenuation of key effectors of the inflammatory response and lung neutrophil infiltration (85, 86)

Interestingly, most anesthetists tend to hyperventilate their surgical patients. In a cohort study including 3’421 patients undergoing colonic resection or gynaecologic interventions, the median etCO₂ was 4.2 kPa and higher etCO₂ was a predictor of reduced hospital length of stay lending support to the non-deleterious (or even favourable) effects of short-term permissive hypercapnia. (87)

4. Alternate perioperative lung protective strategies

- Assist mode of ventilation: flow or pressure triggering; neurally-adjusted ventilatory assist
- Alternate mode of controlled ventilation: high-frequency oscillation, biologically variable ventilation
- Extracorporeal blood exchange devices allowing the lungs to heal while ventilated with a “protective” regimen
- Inhaled/aerosolized drugs with selective pulmonary vasodilating effects (e.g., nitric oxide, iloprost, sildenafil) or stimulating the epithelial fluid clearance (beta-adrenergic agonists, levosimendan)
- Goal-directed fluid and hemodynamic management
- Optimal analgesic regimen allowing early mobilization and chest physiotherapy
5. Conclusions and Practice points

Implementation of a bundle of scientifically based perioperative interventions represents an integral component of quality control and improved clinical care.

The traditional intraoperative ventilatory settings ($V_t > 10 \text{ ml/kg PBW}$) can be harmful even in patients with healthy lungs. In the operating theatre, our task is provide safe anesthesia and to ensure satisfactory oxygen delivery while minimizing the deleterious effects of surgical trauma and avoiding iatrogenic complications (e.g., fluid overhydration, airway trauma, VILI, atelectasis, bronchoaspiration, toxic drug effects, hyperoxia/hypoxia).

To achieve these goals, I would recommend the following practical points:

- Pre-oxygenate with a high $\text{FiO}_2$ (> 80%) before anesthesia induction, allowing a large margin of safety in case of difficult airway management. During manual ventilation before tracheal intubation, a small positive pressure can be maintained throughout the whole respiratory cycle (inspiratory pressure less than 25 cmH$_2$O with 4-6 cmH$_2$O PEEP).

(During preoxygenation, CPAP has been advocated in morbidly obese patients and those requiring a rapid sequence induction, however this procedure is difficult to perform).

- After securing the airways (with a laryngeal mask, an ET or double-lumen tube):
  - a recruitment maneuver is performed (inspiratory P of 40 cmH$_2$O for 8-10 s)
  - a $V_t$ of 6-8 ml/kg (of predicted body weight) is selected with limitation of the $P_{pl} < 20 \text{ cm H}_2\text{O} (< 30-35 \text{ cm H}_2\text{O in damaged lungs or during OLV})$
  - PEEP is set empirically (4-6 cm H$_2$O) or titrated using the PV – $\text{CO}_2$ curves
  - $\text{FiO}_2$ can be reduced to levels sufficient to keep $\text{SaO}_2 > 96\%$ ($\text{FiO}_2 < 60\%$)

- Pressure or Volume controlled ventilation might be used in paralyzed patients. Apply assisted mechanical ventilation whenever possible and particularly at the end of surgery before tracheal extubation: patient’s respiratory efforts are triggered and assisted by the ventilator.

- The use of volatile anesthetic should be considered in patients with bronchospastic disease and may potentially confer additional protection to the lungs and other organs.

- Before extubation, a gentle recruitment maneuver is recommended; hyperoxygenation with 100% $\text{FiO}_2$ is not mandatory (50% to 70% is enough).

- In the postoperative period, voluntary deep breathing and early mobilization should be encouraged and will be facilitated if optimal analgesic techniques are provided without undue sedation and while cardiovascular homeostasis is maintained.

- Use of minimally invasive hemodynamic monitors for goal-directed fluid loading and titration of cardiovascular drugs. Monitoring the depth of anesthesia, cardiac output or using dynamic indices should be considered in major surgery or high-risk patients.
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Table 1: randomized controlled trials assessing the effects of different modes of ventilation

| Authors          | Publication year | N   | Type of Surgery       | Ventilation strategy                                                                 | Effects of low \( V_T \) vs High \( V_T \)                                                                 |
|------------------|------------------|-----|-----------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| **Two Lung Ventilation** |                 |     |                       |                                                                                      |                                                                                                           |
| Wrigge et al. [66] | 2000             | 39  | Visceral, Orthopedic and Vascular | 5 ml/kg ZEEP vs 5 ml/kg 10 cm\( H_2 \)O PEEP vs 15 ml/kg 10 PEEP                   | • similar plasma cytokine levels                                                                          |
| Wrigge et al. [67] | 2004             | 30  | Visceral              | 6 ml/kg 10 cm\( H_2 \)O PEEP vs 12-15 ml/kg ZEEP                                     | • similar time course of cytokines in tracheal aspirate and plasma                                          |
| Choi et al. [68]  | 2006             | 40  | Visceral              | 6 ml/kg cm\( H_2 \)O PEEP vs 12 ml/kg ZEEP                                         | • \( \Uparrow \) Thrombin anti-thrombin complex                                                          |
| Wrolhuis et al. [69] | 2008             | 40  | Visceral              | 6 ml/kg 10 cm\( H_2 \)O PEEP vs 12 ml/kg ZEEP                                     | • \( \Uparrow \) Similar levels of TNF-\( \alpha \), IL-1, MIP-1 in BALF                                |
| Reis-Miranda et al. [70] | 2005             | 62  | Cardiac               | 6-8 ml/kg 10 cm\( H_2 \)O PEEP + RM vs 6-8 ml/kg 3 cm\( H_2 \)O PEEP               | • \( \Uparrow \) IL-8, IL-10 in plasma                                                                     |
| Chaney et al. [71] | 2005             | 25  | Cardiac               | 6 ml/kg 10 cm\( H_2 \)O PEEP vs 12 ml/kg ZEEP                                     | • \( \Uparrow \) PaO\( _2 \)/FiO\( _2 \)                                                                 |
| Zupancich et al. [72] | 2005             | 40  | Post-cardiac          | 6 ml/kg 10 cm\( H_2 \)O PEEP vs 10-12 ml/kg 3 cm\( H_2 \)O PEEP                   | • \( \Uparrow \) IL-6 and IL-8 in BALF and plasma                                                         |
| Koner et al. [73]  | 2004             | 44  | Cardiac               | 6 ml/kg 5 cm\( H_2 \)O PEEP vs 10 ml/kg ZEEP                                     | • similar plasma TNF-\( \alpha \) and IL-1                                                               |
| Lee et al. [74]   | 1990             | 103 | General               | 6 ml/kg vs 12 ml/kg                                                               | • \( \Uparrow \) Duration of mechanical ventilation                                                       |
| Wrigge et al. [75] | 2005             | 44  | Cardiac               | 6 ml/kg 10 PEEP vs 12 ml/kg ZEEP                                                  | • \( \Uparrow \) Similar plasma cytokine levels                                                          |
| Weingarten TN et al. [76] | 2009             | 40  | Major open abdominal  | 6 ml/kg 12 PEEP vs 10 ml/kg ZEEP                                                  | • \( \Uparrow \) PaO\( _2 \)/FiO\( _2 \), \( \Uparrow \) Compliance, \( \Uparrow \) Raw                 |
| **One-Lung Ventilation** |                 |     |                       |                                                                                      |                                                                                                           |
| Wrigge et al. [67] | 2004             | 32  | Lung resection        | 6 ml/kg 10 cm\( H_2 \)O PEEP vs 12-15 ml/kg ZEEP                                 | • \( \Uparrow \) Similar time course of cytokines in tracheal aspirate and plasma                          |
| Schilling et al. [77] | 2005             | 32  | Lung resection        | 5 ml/kg ZEEP vs 10 ml/kg ZEEP                                                      | • \( \Uparrow \) TNF-\( \alpha \) and sICAM in BALF                                                       |
| Michelet et al. [78] | 2006             | 52  | Oesophagectomy        | 5 ml/kg 5 cm\( H_2 \)O PEEP vs 9 ml/kg ZEEP                                       | • \( \Uparrow \) IL-1, IL-6, IL-8 in plasma                                                               |
| Yang M et al. [79] | 2011             | 100 | Lung resection        | 6 ml/kg 5 cm\( H_2 \)O PEEP, FiO\( _2 \) 0.5 + RM vs 10 ml/kg ZEEP, FiO\( _2 \) 1.0 | • \( \Uparrow \) Postoperative pulmonary dysfunction (PaO\( _2 \)/FiO\( _2 \) < 300 mmHg, atelectasis)         |

BALF, bronchoalveolar lavage fluid; RM, recruitment maneuver; IL, Interleukin; PEEP, positive end expiratory pressure; ZEEP, zero end expiratory pressure; TNF, tumor necrosis factor; IL-x, PaO\( _2 \)/FiO\( _2 \), ratio of arterial oxygen pressure to fractional inspiratory oxygen pressure.