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Perioperative Lung Protective Strategies

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Abstract

The traditional intraoperative ventilatory settings (tidal volume > 10 ml/kg ideal body weight) can be harmful even in patients with healthy lungs. In the operating theatre, safe anesthesia and optimization of oxygen delivery should be achieved while minimizing the deleterious effects of surgical trauma and avoiding iatrogenic complications. This review examines the mechanisms of perioperative lung injuries and particularly the injurious effects of mechanical ventilation. Protective lung strategies are discussed using a physiological approach, being mainly focused on the surgical patients with "healthy" lungs.

Introduction

Currently, the incidence of postoperative pulmonary complications (PPC) far outnumbers cardiovascular complications [1]. They vary from 10% to 70%, depending on their definition, study design (retrospective or prospective), 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 as part of the anesthesia emergence period and as the physiological response to surgery. Most of the 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, pneumonia, acute lung injury (ALI) or respiratory failure [7].

Predictive factors of 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. [9] have validated a 5-grade scoring system based on the therapeutic consequences and residual disabilities in relation to surgical operations. 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.

Mechanisms of Perioperative Pulmonary Injuries

Atelectasis

Collapsed lung areas or atelectasis develop in about 90% anaesthetized patients, irrespective of ventilatory control (spontaneous or mechanically supported) and of anesthesia type (intravenous agent, volatile anaesthetics or, combined general anesthesia and regional block) [10]. Atelectasis formation predominantly results from the reduction of lung volumes and from deficient or abnormal synthesis of surfactants that occur during anesthesia and could persist or even worsen after completion of the surgical procedure.

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 the relaxation of the respiratory muscles and the decrease in thoracic elastic recoil [11,12]. Ventilation with enriched oxygen mixture (FIO_2 > 80%) promotes the development of atelectasis as a result of complete absorption of O_2 in poorly ventilated lung regions. Depending on the duration of mechanical ventilation, 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 impedes lymphatic flow and may become a focus of infection in the postoperative period.

In obese patients, the healthy lungs are compressed by the "heavy" weight of the chest/abdominal wall, resulting in further aggravation of the restrictive pulmonary syndrome associated with anesthesia and surgery. Likewise, in acute lung diseases and heart failure, ongoing inflammation and fluid accumulation within the lung interstitium and the alveolar space, tissue tend to expel air/gas out of the alveoli and thereby promote the development of atelectasis.

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.

Surprisingly and for decades, anaesthetists have been taught to apply "unphysiological" large tidal volume (10 to 15 ml/kg) to prevent the development of atelectasis.

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Mechanical inflation of "physiological" low V_T (4-8 ml/kg) produces higher Ptp and may cause subtle lung injuries over several hours: neutrophil infiltration, rupture of alveolar-bronchial 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) over a prolonged time period, auto regulatory local responses are triggered in an attempt to maintain low pulmonary compliance while protecting the ECM against fluid overload (e.g., further macro-molecular fragmentation, activation of matrix metallo-protease and up regulation of collagen synthesis in the ECM) [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 up regulation of pro-inflammatory mediators (TNF-α and interleukin-8) associated with diffuse alveolo-capillary lesions has also been demonstrated in rabbits ventilated with large V_T under moderate hyperoxia (compared with normoxia/large V_T and hyperoxia/normal V_T) [21,22].

Mechanical ventilation induces alveolar injuries by repetitive opening and closing of unstable lung units due to the inactivation of surfactant and the excessive mechanical stress between atelelectatic areas and neighbouring areas with low ventilation/perfusion ratio [23,24].

With the pioneering experimental work of Dreyfuss et al. [25], 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 [25].

In anesthetized patients with healthy lungs, - besides "high" V_T and elevated inspiratory pressure -, other risk factors for lung injuries have been identified [26-29]. Fluid over hydration increases capillary hydrostatic pressure and promotes interstitial/alveolar edema particularly when lymphatics are disrupted. Additionally, 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 [30].

Some individuals are prone to develop ALI, given their deficient lung defence and repair mechanisms (e.g., antioxidant, heat shock protein, p75 receptor for tumour necrosis factor alpha [TNF-α]) that fail to counteract the inflammatory and oxidative responses to damaging insults [31]. 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 [32]. 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. Likewise, in patients undergoing oesophagectomy, SNP of the angiotensin-converting enzyme (D/D genotype) has been found to be highly predictive of major pulmonary complications [33].

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 demonstrating the injurious effects of large V_T [30].

Perioperative Lung Protective Strategies

Volatile anesthetics

Compared with intravenous hypnotics, volatile anaesthetics induce bronchodilatation and may inhibit the hypoxic pulmonary vasoconstriction (HPV) although no significant difference has been reported regarding blood oxygenation when anaesthetic administration is titrated to achieve a similar depth of anesthesia [34].

Based on experimental models of lung ischemia-reperfusion (I-R) and lipopolysacharide (LPS) or zymosan injuries, volatile anaesthetics such as isoflurane and sevoflurane have demonstrated potent immunomodulatory properties [35,36]. 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 post conditioning 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 anaesthetics [37].

Preliminary data obtained in patients undergoing thoracic surgery lend support to the anti-inflammatory effects of volatile anaesthetics, compared with propofol. 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) [38]. In another RCT, a reduction of inflammatory markers with a trend for fewer respiratory complications was found in patients anesthetized with sevoflurane anesthesia (sevoflurane vs propofol, n=40) [39].

Pressure or volume controlled ventilation

Mechanical ventilation can be classified as either volume controlled (VCV) or pressure controlled (PCV) depending on whether a predetermined V_t or predetermined peak inspiratory pressure (PIP) is set by the clinician and delivered by the ventilator. Airway resistance as well as resistance and compliance of the respiratory system (ventilator circuit and patient lung and thoraco-abdominal wall) both determine the amount of pressure necessary to deliver the tidal volume and the pattern of pressure-volume loops.

During VCV, inspiratory pressures should be closely monitored to prevent barotrauma whereas during PCV, alarms must be set for inspiratory volumes (low and high) to prevent hypoventilation or hyperventilation. Basically, during VCV, airway pressure increases in response to reduced respiratory compliance, increased airway 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 [40,41].

Several manufacturers have incorporated variable flow options as well as volume-targeted, pressure-regulated and time-limited ventilatory modalities in their machines. Accordingly, instead of providing an exact tidal volume each breath, a target volume is set and the ventilator will vary the PIP on a breath to breath basis to achieve that volume. As with PCV, the inspiratory time (T_i) limits the length

of the inspiratory cycle while offering the benefit that the set V_t will be achieved with the lowest possible PIP. Pressure regulated modes such as PRVC, Auto-flow (Draeger) or Average Volume Assured Pressure Support (AVAPS) from Philips can most easily be thought of as turning a volume mode into a pressure mode with the added benefit of maintaining more control over V_t with strictly pressure-control.

Regarding flow characteristics, gas may be delivered by the ventilator as a constant "square" or a "decelerating" wave. The maximal flow in the early part of the inspiratory phase under PCV was initially thought to provide more homogeneous distribution of gas mixture while avoiding alveolar distension and mitigating ventilation-perfusion mismatch [42].

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 [43,44]. Interestingly, the ventilation heterogeneity and patchiness in ventilation during steady-state VCV can be substantially reduced after the transition to PCV [45].

In thoracic surgery, recent interest has been focused on the use of PCV given potential benefits related to the attenuation of lung inflating pressures and the reduction of intrapulmonary shunt. However, conflicting results have been reported regarding the physiological and clinical effects of PCV and VCV. In two studies from Turkey, PCV provided significant reductions in both peak and plateau airway pressures (Ppeak, Ppl) that was associated with better oxygenation than in patients receiving PCV [46,47]. Interestingly, larger benefit was observed in patients with altered pulmonary function while gas exchange was slightly improved when a PEEP of 4 cm H_2O was applied. Although other investigators confirmed the lower Ppeak associated with PCV, they failed to replicate the reduction in Ppl neither any benefit in terms of oxygenation [48-51].

Importantly, compared with VCV, although PCV has been shown to produce lower Ppeak within the ventilator circuit, the pressure distal to the tip of the endobronchial tube (bronchus and alveola) was found to be equivalent [52]. Altogether, the current state of knowledge does not provide evidence for superior clinical effects of PCV over VCV in deeply anesthetized/paralyzed patients with healthy lungs receiving full mechanical ventilation.

PEEP

Following anesthesia induction in the supine position, the FRC decreases and the progressive collapse of various amount of lung areas results in impaired blood oxygenation owing to ventilation-perfusion mismatch (V/Q).

The addition of PEEP, - by augmenting transpulmonary pressure at each exhalation -, prevents the collapse of the small airways and the fall in FRC, thereby it may minimize the propensity to develop atelectasis [11].

In patients with healthy lung, titrated levels of PEEP has been shown to restore lung volumes and thereby improve lung compliance while decreasing intrapulmonary shunting [53]. Nevertheless, depending on the level of PEEP and the presence of pathological lung conditions, PEEP has the potential to cause both harm and good. PEEP-induced increases 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 sheep model of ARDS, comparison of various methods based on pressure-volume curves and gas exchange for setting the optimal PEEP failed to show any significant difference: maximum dynamic compliance, maximum $PaO_2/PaCO_2$, minimum shunt and the lower/upper inflection points all yielded results that were statistically indistinguishable [54].

In morbidly obese patients, observation of the slope of the CO_2 expiratory curve might be helpful to titrate the optimal level of PEEP after a recruitment maneuver [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 CO_2 slope reflecting facilitated elimination of CO_2 as a result of the improved elastic properties of the respiratory system.

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 PaO_2/FIO_2 and lesser atelectatic areas, compared with mechanical ventilation without PEEP (or zero-PEEP, ZEEP) [56]. No relevant adverse effects (barotrauma and cardiovascular complications) were reported in the three trials that adequately measured these outcomes. In morbidly obese subjects, the addition of 10 cm H_2O of PEEP to mechanical ventilation has been shown to reduce respiratory elastance and to improve oxygen exchange [57].

Recruitment maneuver or alveolar recruitment strategy

Bendixen and coll. [58], first demonstrated the physiological rationale of a lung recruitment maneuver (RM) to correct oxygenation impairment during anesthesia. Single manual ventilation up to 40 cm H_2O was maintained for 15 s using the anesthesia bag while adjusting the expiratory valve. This pressure was equivalent to inflation up 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_2O) over 8 to 10 respiratory cycles (alveolar recruitment strategy [ARS]) or by applying continuous a positive airway pressure (CPAP) over 10-30 s [59].

To re-expand atelectatic areas, the lung opening pressure should be achieved 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_2O PEEP is more effective than ZEEP or PEEP of 5 cm H_2O for prevention of postoperative lung atelectasis and is associated with better oxygenation, shorter stay in the postanesthesia care unit (PACU), and fewer pulmonary complications in the immediate postoperative period [60-62]. Application of PEEP and RM was not accompanied by a significant reduction in mean arterial pressure (MAP), even after pneumoperitoneum and reverse Trendelenbourg position.

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 [63-65].

At the end of surgery and before extubation, a single recruitment maneuver is not sufficient to produce sustained improvement in oxygenation [66]. Presumably, temporary increase in Ptp fails to reexpand large areas of atelectasis, air flow being diverted to the most compliant part of the lung and causing alveolar overdistension. Performing vital capacity at regular time interval might be necessary to reverse small volume of collapsed lung areas.

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

Tidal volume

Based on experimental models of ALI/ARDS, the "open-lung" approach has been shown to minimize the bronchoalveolar strain using low V_T while maintenance of the FRC and prevention or re-expansion of atelectasis is achieved with the application of PEEP and periodic RMs [67,68]. 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) [69]. At similar PEEP levels, mechanical ventilation with lower V_T (< 8 ml/kg) was associated with a 25% reduction in hospital mortality.

Prophylactic utilization of low VT may limit pulmonary and systemic inflammation (lesser release of IL-8 and TNF in BALF and of plasma IL-6) in mechanically ventilated patients without pre-existing lung injury [70,71]. 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 [69].

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 [72-85].

Not surprisingly, no difference was observed between traditional and protective ventilatory approaches in patients undergoing minor/moderate surgical procedures, lasting less than 5h. In patients of higher surgical risk (major abdominal, thoracic and cardiac surgery), a protective ventilation" strategy (V_T 4-6 ml/kg PBW, PEEP with or without RM) was associated with a reduced expression of alveolar/systemic inflammatory markers, reduced procoagulant activity in the bronchoalveolar fluid, 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 [80,84,85]. After major noncardiac surgery, Lee et al. [1] reported fewer pulmonary complications and shorter intubation times in patients ventilated postoperatively with small V_T (6 vs 12 ml/kg) [80]. Michelet et al. [84] 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_2O PEEP (compared with 10 ml/kg V_T and ZEEP). More recently, Yang et al. [85] compared two ventilatory strategies during OLV in 100 patients scheduled for lobectomy (V_T 10 ml/kg, ZEEP and FIO_2 100% vs. V_T 6 ml/kg, 5cm H_2O PEEP and FIO_2 0.5). The combined endpoint of pulmonary dysfunction (PaO_2/FIO_2< 300 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.

FIO_2

In clinical anesthesia, hyperoxic ventilation (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 [86,87]. Absorption atelectasis and enhanced generation of O_2 derived free radicals have been incriminated as potential drawbacks of high FIO_2 levels.

Following anesthesia induction with 100% FIO_2, atelectatic areas may reach up to 5-10% of total lung volume whereas the amount of collapsed area is much less in those receiving less than 60% FIO_2.

Clinicians should be aware that, following pre-oxygenation at an FIO_2 of 1.0, 7 min elapse before SaO_2 decreases below 90%; in contrast, at an FIO_2 of 0.6, the time delay before O_2 desaturation is shorten to 3.5 min [88].

As a safety measure, pre-oxygenation with high FIO_2 (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 FIO_2 should be reduced at a level sufficient to ensure optimal O_2 delivery with SaO_2 > 96% [89]. During anesthesia emergence, hyper-oxygenation is highly discussable as it promotes atelectasis formation [90].

Normocapnia vs hypercapnia

Most anesthetists tend to hyperventilate their surgical patients. In a cohort study including 3,421 patients undergoing colonic resection or gynaecologic interventions, the median $etCO_2$ was 4.2 kPa and higher $etCO_2$ was a predictor of reduced hospital length of stay lending support to the non-deleterious (or even favourable) effects of short-term permissive hypercapnia [91].

The current recommendations for ventilatory settings are to target SaO_2 > 96% and end-tidal CO_2 ($etCO_2$) within a range of 4.8-5.5 kPa, using a V_T of 4-8 ml/kg PBW and pressure limited ventilation (< 30-35 cm H_2O).

Whenever possible, hypocapnia should be avoided given the risk of vasoconstriction of the cerebral vessels and the consequent neurocognitive dysfunction. On the other hand, hypercapnia can be better tolerated: although it may trigger the release of catecholamines causing an increase in oxygen consumption, it has been associated with improved O_2 tissue delivery and with attenuation of key effectors of the inflammatory response and lung neutrophil infiltration [92,93]. Currently, clinical evidence supports the use of permissive hypercapnia, particularly in ALI/ARDS, status asthmaticus, and neonatal respiratory failure [94].

Spontaneous ventilation

Controlled mechanical ventilation is obviously indicated in the acute phase of lung illness to ensure adequate alveolar ventilation and to reduce work of breathing without causing further lung injury. In contrast, during the resolution phase of lung disease, spontaneous breathing during mechanical ventilation has been shown to improve gas exchange by redistribution of ventilation to dependent, juxtadiaphragmatic lung regions and thereby it promotes alveolar

Authors	Publication Year	N	Types of Surgery	Ventilation strategy	Effects of low V_T Vs High V_T
Two Lung Ventilation					
Wrigge et al. [72]	2000	39	Visceral, orthopedic and Vascular	5ml/kg ZEEP vs 5ml/kg 10 cmH_2O PEEP vs 15 ml/kg 10 PEEP	Similar plasma cytokine levels
Wrigge et al. [73]	2004	30	Visceral	6 ml/kg 10 cmH_2O PEEP vs. 12-15 ml/kg ZEEP	Similar time course of cytokines in tracheal aspirate and plasma
Choi et al. [74]	2006	40	Visceral	6 ml/kg cmH_2O PEEP vs. 12 ml/kg ZEEP	↙Thrombin anti-thrombin complex ↗Activated Protein C in BALF ↙Thrombomoduline in BALF
Wolthuis et al. [75]	2008	40	Visceral	6 ml/kg 10 cmH_2O PEEP vs. 12 ml/kg ZEEP	Similar levels of TNF-α, IL-1, MIP-1 in BALF ↙IL-8 in BALF ↙Myeloperoxidase and elastase om BALF Similar levels of IL-6 and IL-8 in plasma
Reis-Miranda et al. [76]	2005	62	Cardiac	4-6 ml/kg 10 cmH_2O PEEP+RM vs. 6-8 ml/kg 3 cmH_2O PEEP	↙IL-8, IL-10 in plasma
Chaney et al. [77]	2005	25	Cardiac	6 ml/kg 10 cmH_2O PEEP vs. 12 ml/kg ZEEP	↗PaO_2/FIO_2 ↙Static lung compliance
Zupancich et al. [78]	2005	40	Post-cardiac	6 ml/kg 10 cmH_2O PEEP vs. 10-12 ml/kg 3 cmH_2O PEEP	↙IL-6 and IL-8 in BALF and plasma
Koner et al. [79]	2004	44	Cardiac	6 ml/kg 5 cmH_2O PEEP vs. 10 ml/kg ZEEP vs 10 ml/kg 10 cmH_2O PEEP	Similar plasma TNF-α and IL-1 Similar PaO_2/FIO_2
Lee et al. [80]	1990	103	General	6 ml/kg vs. 12 ml/kg	↙Pulmonary infection ↙Duration of mechanical ventilation
Wrigge et al. [81]	2005	44	Cardiac	6 ml/kg 10 PEEP vs.12 ml/kg ZEEP	↙TNF-α in BALF similar plasma cytokine levels
Weingarten TN et al. [82]	2009	40	Major open abdominal	6 ml/kg 12 PEEP vs. 10 ml/kg ZEEP	↗ PaO_2/FIO_2, ↗Compliance, ↙Raw ↙IL-8, ↙IL-6 in plasma (postop) Similar length of hospital stay
One- Lung Ventilation					
Wrigge et al. [81]	2004	32	Lung resection	6 ml/kg 10 cmH_2O PEEP vs. 12-15 ml/kg ZEEP	Similar time course of cytokines in tracheal aspirate and plasma
S chilling et al. [83]	2005	32	Lung resection	5 ml/kg ZEEP vs. 10 ml/kg ZEEP	↙TNF-α and sICAM in BALF Similar levels of albumin, elastase, IL-8, IL-10
Michelet et al. [84]	2006	52	Oesophagectomy	5 ml/kg 5 cmH_2O PEEP vs. 9 ml/kg ZEEP	↙IL-1, IL-6, IL-8 in plasma ↗PaO_2/FIO_2 and ↙lung water content ↙Duration of mechanical ventilation
Yang m et al. [85]	2011	100	Lung resection	6 ml/kg 5 cmH_2O PEEP, FIO_2 0.5+RM vs. 10 ml/kg ZEEP, FIO_2 1.0	↙Postoperaive 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

Table 1: Randomized controlled trials assessing the effects of different modes of ventilation.

recruitment. Moreover, during assisted ventilation, cardiovascular and sedative drug support can be reduced as a result of improved venous return and better patient-ventilator synchronization [95].

For various surgical procedures involving the limbs and the thoraco-abdominal wall, regional anesthetic blockade (e.g. perineural infiltration or neuraxial block) is sufficient to provide patient comfort. For intra-thoracic and intra-abdominal interventions, complete muscles paralysis is not always mandatory through the whole procedure; spontaneous ventilation can be maintained under light-to-moderate levels of sedation combined with systemic administration of short-acting opiate [96].

During anesthesia emergence, pressure support ventilation (PSV) may provide 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 [97,98].

Postoperatively, two types of noninvasive ventilation (NIV) are commonly used: continuous positive airway pressure (CPAP) and noninvasive positive pressure ventilation (NPPV) which delivers two levels of positive pressure (pressure support ventilation + positive end-expiratory pressure). There are two main indications for NIV: first, "prophylactic" application in high-risk patients (elderly, obese, COPD, heart failure) in order to prevent postoperative acute respiratory failure from developing and, second, "curative" application of NIV once ARF has occurred to avoid endotracheal intubation while alleviating respiratory insufficiency.

Although there is some evidence of the effectiveness of NIV in preventing post-extubation ERF, the benefits in the treatment of ongoing ARF are still debatable [99].

When applying NIV in surgical patients, clinicians should also considered the hemodynamic effects of positive pressure to the cardiovascular system, which can be favorable on the impaired left heart and deleterious on the diseased right heart [100].

Alternate Perioperative Lung Protective Strategies

Newer technological modalities including extracorporeal membrane oxygenation (ECMO) and pumpless extracorporeal lung assist (PECLA) are being increasingly introduced in critical care settings as rescue therapies in acute respiratory failure unresponsive to conservative measures. As arterio-venous or veno-venous ECMO or PECLA provide gas exchange, the exposure time of the lungs to high

stress and/or strain can be minimized by switching the ventilatory settings to a protective regimen (low V_T with PEEP) enabling the lung to rest and to heal [101].

Prehospital use of statin (particularly with aspirin) has been shown to confer lung protection in various experimental models of ALI as well as in septic patients [102,103]. Likewise, angiotensin-converting enzyme inhibitors such as enalapril have emerged as strong candidates in lung protection given their ability to block the LPS-induced anti-inflammatory effects [104]. Finally, preliminary clinical data suggest that the administration of inhaled beta 2-adrenergic agonists may accelerate the resorption of lung edema by enhancing active sodium and water transport in alveolar pneumocytes [105].

Although restrictive fluid regimen has been advocated, - particularly in thoracic surgery -, clinically "silent" hypovolemic state and the need for vasopressors have been associated with the development of postoperative acute kidney injury [106]. Nowadays, new hemodynamic monitoring tools enable clinicians to titrate the amount of fluid infused to achieve adequate tissue O_2 delivery while avoiding excess in intrathoracic blood volume (LiDCO system) or extra vascular lung water (PiCCO system). Monitoring stroke volume and/or respiratory-induced variation in pulse pressure variation allows a goal-directed fluid and cardiovascular drug therapy that may contribute to avoid over hydration while improving gas exchange and tissue oxygen delivery [107].

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 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 over hydration, airway trauma, VILI, atelectasis, bronchoaspiration, toxic drug effects, hyperoxia/hypoxia).

To achieve these goals, the following key items should be considered:

- Pre-oxygenate with a high 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 cm H_2O with 4-6 cm H_2O PEEP). In morbidly obese patients and in those requiring a rapid sequence induction, CPAP has been advocated during preoxygenation.
- After securing the airways (with a laryngeal mask, an ET or a double-lumen tube):
  - a recruitment manoeuvre is performed (inspiratory P of 40 cm H_2O for 8-10 s)
  - a V_T of 6-8 ml/kg (of predicted body weight) is selected with limitation of the Ppl < 20 cm H_2O (< 30 cm H_2O in damaged lungs or during OLV)
  - PEEP is set empirically (4-6 cm H_2O, 10 cm H2= in morbidly obese) or titrated using the PV loops or CO_2 curves
  - FIO_2 can be reduced to levels sufficient to keep SaO_2 > 96% (FIO_2 < 60%)
- 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.

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.

- Before extubation, a gentle recruitment maneuver is recommended; hyper oxygenation with 100% 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. In high risk patients, NIV techniques may reduce the risk of postoperative acute respiratory failure and the need of re-intubation.
- Use of minimally invasive hemodynamic monitors for is useful 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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