Current concepts of protective ventilation during general anaesthesia

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Summary

Mechanical ventilation with high tidal volumes (V_T) has been common practice in operating theatres because this strategy recruits collapsed lung tissue and improves ventilation-perfusion mismatch, thus decreasing the need for high inspired oxygen concentrations. Positive end-expiratory pressure (PEEP) was not used routinely because it was thought to impair cardiovascular function. Over the past two decades there have been advances in our understanding of the causes and importance of ventilation-induced lung injury based on studies in animals with healthy lungs, and trials in critically ill patients with and without acute respiratory distress syndrome. Recent data from randomised controlled trials in patients receiving ventilation during general anaesthesia for surgery have demonstrated that lung-protective strategies (use of low V_T, use of PEEP if indicated, and avoidance of excessive oxygen concentrations) are also of importance during intraoperative ventilation.

Key words: mechanical ventilation; postoperative pulmonary complications; general anaesthesia; surgery

Introduction

More than 230 million surgical procedures are undertaken worldwide each year [1]. Complications after surgery are an important cause of mortality and morbidity; approximately 4% of patients who develop a postoperative complication die before hospital discharge, and those who survive often have reduced functional status [2, 3]. Development of postoperative pulmonary complications (PPCs) has a stronger impact on outcome of these patients; one in every five patients who develop one or more PPCs dies within 30 days of surgery, and the occurrence of PPCs is strongly associated with longer postoperative stay in hospital [2–4]. Advances in the understanding of the potential harmful effects of mechanical ventilation, resulting in so-called ventilation-induced lung injury (VILI) have led to the development of lung-protective strategies in patients with the acute respiratory distress syndrome (ARDS) [5]. Recently there have been a number of trials that suggest that certain lung-protective strategies could also benefit patients without ARDS, including those receiving intraoperative ventilation during general anaesthesia for surgery. These strategies include measures that prevent alveolar over-distension, decrease repeated alveolar opening and closing with each breath cycle, and prevent oxygen toxicity.

The scope of this narrative review is to summarise the rationale for lung-protective intraoperative ventilation strategies focusing on the potential benefits of tidal volume (V_T) reduction, use of positive end-expiratory pressure (PEEP) and avoidance of excessive oxygen concentrations (FiO_2).

Tidal volume

Historical rationale for tidal volume settings in the operating room

For many years, anaesthesiologists applied ventilation strategies with high V_T because this strategy re-opens lung regions that collapse with each breath at end-expiration, i.e. minimises atelectasis. This was seen as beneficial because it reduced ventilation-perfusion mismatch, thereby requiring lower FiO_2 [6]. While high tidal volumes were increasingly considered to be harmful in critically ill patients, in particular those with ARDS [6], use of high V_Ts during intraoperative ventilation was considered to be safe because of the relatively short duration (hours) of ventilation, compared with critically ill patients who could be ventilated for days to weeks.

Evidence for harm from high tidal volumes in animal models of ventilation

In the last few decades, animal research has convincingly demonstrated that ventilation with high V_T can induce VILI (fig. 1B) [7]. Animal studies frequently used a multiple-hit approach in which lung injury was first triggered by a pre-

ceding insult (e.g., systemic inflammation or sepsis, pneumonia or aspiration) and then amplified by the harmful effects of large V_T [8, 9]. However, several animal studies demonstrated that ventilation with high V_T alone – without a preceding hit – could induce VILI [10]. This suggested that intraoperative ventilation strategies that use high tidal volumes might be harmful. Of particular note, the animal models almost always used relatively short periods of ventilation ($\leq$12 hours), more closely simulating the clinical scenario of the operating room.

Evidence for harm from high tidal volumes in patients with ARDS

The harmful effects of ventilation with high V_T in patients with ARDS were not confirmed until the landmark ARDS Network trial in 2000, which demonstrated the beneficial effect of ventilation with low V_T (6 ml/kg predicted body weight, PBW) compared with conventional V_T (12 ml/kg PBW) [5]. Ventilation with low V_T resulted in decreased mortality and increased number of ventilator-free days [5]. Some clinicians and investigators were relatively slow to accept these findings, but subsequent trials and a meta-analysis convincingly confirmed the mortality reduction [11]. Currently, lung-protective ventilation with low V_Ts is considered standard of care for ARDS [11, 12].

Increasing evidence for harm from high tidal volumes in patients without ARDS

The finding that ventilation with low V_Ts benefits patients with ARDS evoked interest in lung-protective ventilation in patients without lung injury. One clinical trial published in 2010 found increased lung injury in a group ventilated with "high" V_T (10 ml/kg PBW) compared with "low" V_T (6 ml/kg predicted PBW) [13]. These findings were confirmed in a series of meta-analyses [7, 14–16] that also suggested that ventilation strategies with low V_T could hasten liberation from the ventilator. Despite the growing evidence for potential harm from high V_T in critically ill patients without ARDS, lung-protective ventilation is still not considered standard of care for critically ill patients who need ventilatory support but have healthy lungs. Nevertheless, a substantial reduction in V_T appears to have occurred in recent years [7, 14–18].

Increasing evidence for harm from high tidal volumes during intraoperative ventilation

Several small clinical trials of intraoperative ventilation suggested that V_T reduction could improve pulmonary mechanics and oxygenation [19, 20], reduce local production of inflammatory mediators [21], and shorten duration of postoperative ventilation [22]. As well, one meta-analysis suggested that intraoperative ventilation strategies that use low V_T could reduce the incidence of postoperative pulmonary complications [22].

Recently, three randomised controlled trials further increased the evidence for harm from intraoperative ventilation with high V_T [23–25]. An Italian single-centre randomised controlled trial showed that V_T reduction from 9 to 7 ml/kg PBW during abdominal surgery was associated with better postoperative pulmonary function [23]. A French multicentre randomised controlled trial showed

that there was a >60% reduction in postoperative pulmonary complications in patients undergoing abdominal surgery when a ventilation strategy using a V_T of 6 ml/kg PBW was compared with a V_T of 12 ml/kg PBW [24]. A Chinese randomised controlled trial in patients undergoing spinal fusion showed a very impressive benefit from reducing V_T from 10–12 ml/kg PBW to 6 ml/kg PBW [25]. Of note, in all three trials, lung-protective ventilation consisted of a bundle of measures: low V_T *with* higher levels of PEEP and recruitment manoeuvres; as such, it was impossible to conclude which protective measure caused most benefit. A recent individual patient data meta-analysis, including data from these three randomised controlled trials, suggested that benefit from lung-protection was best explained from V_T reductions, and not from higher levels of PEEP [26].

Present choices in tidal volume size in the operation room

One recently published observational study on intraoperative ventilation settings in a German university hospital [17], and one large report on intraoperative ventilation practices in a large number of American university hospitals, demonstrated increased use of low V_T during intraoperative ventilation: V_T nearly halved, to 7–8 ml/kg PBW [18]. One could pose the question as to whether this reduction in V_T can be considered "enough". It has been suggested that the "normal" V_T in mammals is $\approx$6.3 ml/kg PBW [27], and it is possible, but certainly not proven, that a further reduction of V_T during intraoperative ventilation would be better.

Positive end-expiratory pressure

Historical choices for PEEP settings in the operation room

Induction of anaesthesia, especially with the use of high FiO_2, causes atelectasis, which increases ventilation-perfusion mismatch [28]. Ventilation strategies that use low V_T
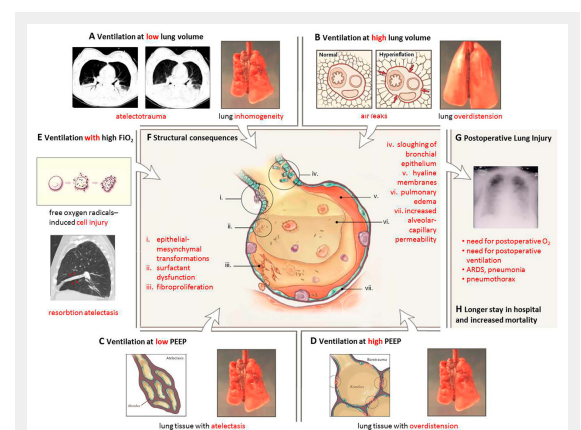

Figure 1

Postoperative pulmonary complications caused by forces generated by ventilation at low and high lung volumes, low and high PEEP and high FiO2 (Adapted from: Slutsky AS, Ranieri VM. Ventilator-Induced Lung Injury. N Engl J Med. 2013;369(22):2126–36. Copyright ©, Massachusetts Medical Society. Reprinted with permission.).

could further induce alveolar instability with cyclic opening and closing of alveoli with each breath (fig. 1A and C) [29]. PEEP may open those lung regions that collapse following induction of anaesthesia, and could maintain the alveoli open during the entire breathing cycle [28]. However, adverse effects such as cardiac compromise, mandating volume expansion and perhaps even vasoactive drugs [30], could outweigh these beneficial effects. Consequently many anaesthesiologists had reservations about using PEEP.

Evidence for benefit from high PEEP levels in animal models of ventilation

Atelectasis appears in a vast majority of larger mammals that receive general anaesthesia, with collapse of up to 15 to 20% of the dependent lung, worsened by the use of high FiO_2 and the use of muscle relaxation [31, 32]. Numerous preclinical studies have shown that ventilation strategies that used recruitment manoeuvres and PEEP could improve lung aeration, and thus improve oxygenation [33, 34]. However, PEEP could be detrimental by causing overdistention of nondependent lung regions (fig. 1D) [35].

Evidence for benefit from high PEEP levels in patients with ARDS

Independently, three well-performed randomised controlled trials in ARDS patients failed to show definitive benefit from ventilation strategies that used higher PEEP levels [36–38]; however, a meta-analyses of these trials suggested benefit from higher PEEP in ARDS patients who had lower PaO_2/FiO_2 ratios [39] Patients with moderate or severe ARDS who received ventilation with higher levels of PEEP had a lower mortality, and needed rescue therapies, such as inhaled nitric oxide, prone ventilation, extracorporeal membrane oxygenation, less frequently than patients who were ventilated with low levels of PEEP [39, 40] Patients with mild ARDS had no benefit from higher PEEP levels.

PEEP levels in critically ill patients without ARDS

There are only two small randomised controlled trials in patients without ARDS in which different levels of PEEP were compared. In one study, use of PEEP from 5 to 8 cm H_2O compared with zero PEEP resulted in a lower incidence of ventilator-associated pneumonia and a lower risk of hypoxaemia [41]. However, there were no differences in outcomes (incidence of ARDS or hospital mortality) [41]. In the other trial, the early application of 8 cm H_2O of PEEP in patients at high-risk for ARDS had no effect on the occurrence of ARDS or other associated complications [42]. In contrast, in the randomised controlled trial mentioned above comparing ventilation with a low V_T (6 ml/kg PBW) to high V_T (10 ml/kg PBW) in patients without ARDS [13], an independent association between use of higher levels of PEEP and the development of lung injury was noticed. Although there are no well-accepted recommendations on whether PEEP should be used in critically ill patients without ARDS, observational studies show increased use of PEEP in these patients [43–45].

PEEP during intraoperative ventilation

Atelectasis appears in the vast majority of patients during general anaesthesia for surgery and can persist for several days during the postoperative period. This is associated with an increased risk of postoperative infection and pulmonary complications [31]. The three randomised controlled trials (discussed above) of intraoperative protective ventilation compared bundles of lung-protection: low V_T *with* high levels of PEEP and recruitment manoeuvres, and high V_T *without* PEEP and recruitment manoeuvres [23–25]. As mentioned above, it was difficult, if not impossible, to conclude from these trials what led to the benefit of the lung-protective strategy: lower V_T *or* increased PEEP levels, *or* recruitment manoeuvres *or* all of the above. Of note, one large recent observational study suggested that use of low levels of PEEP during intraoperative ventilation with low V_Ts might be associated with increased risk of mortality [46]. One recent randomised controlled trial addressed the question of higher vs lower PEEP levels during intraoperative ventilation with low V_Ts [30]. In that trial, patients with a high risk for postoperative pulmonary complications, who were undergoing abdominal surgery, were randomised to intraoperative low V_T (8 ml/kg PBW) ventilation with no PEEP and no recruitment manoeuvres, or PEEP of 12 cm H_2O with recruitment manoeuvres. The 12 cm H_2O PEEP level was based on physiological studies showing that a PEEP of 10 to 12 cm H_2O was necessary to increase end-expiratory lung volume [47], to reduce atelectasis formation during surgery [48], and to improve compliance and oxygenation after surgery [49]. This trial showed no benefit from the higher PEEP strategy: occurrence of postoperative pulmonary complications was not affected. However, use of a higher level of PEEP was associated with intraoperative hypotension and need for vasoactive drugs. A recent individual patient data meta-analysis including data from several randomised controlled trials and observational trials of protective ventilation in the operating room suggested that high PEEP levels do not prevent postoperative pulmonary complications when low V_Ts are used [26].

Present choices in PEEP settings in the operation room

About 10 years ago, the recommendation was to use a 'sufficient' level of PEEP 'but at least 5 cm H_2O' to minimize atelectasis and maintain oxygenation [50]; more recently it was suggested that PEEP during intraoperative ventilation should be set at 6 to 8 cm H_2O [28]. However, the best level of PEEP during intraoperative ventilation remains highly uncertain. It could very well be that a minimum PEEP of 2 cm H_2O is sufficient in most patients, and that a further increase should be individualized, e.g., based on perioperative levels of oxygenation. It is also uncertain whether ventilation strategies that use higher levels of PEEP are beneficial in obese patients, or patients undergoing laparoscopic abdominal surgery, during which insufflation of gas in the abdominal cavity could induce more atelectasis.

Inspired fraction of oxygen

Historical choices in oxygen fractions settings in the operation room

Since PEEP was not widely used in the operating room, oxygenation was improved by using high inspired FiO_2 (despite the fact that this could induce reabsorption atelectasis) and/or high V_T (fig. 1E) [51]. It was also claimed that patients undergoing surgery could benefit from higher FiO_2 [52], as randomised controlled trials showed less postoperative nausea and vomiting, and a reduced risk of surgical site infection, in patients who were ventilated with FiO_2 as high as 80% [52, 53].

High oxygen fractions in animal models of ventilation

High FiO_2 may induce pulmonary injury that could at least in part be induced by increased oxidative stress via increased levels of reactive oxygen-derived free radicals, with an influx of inflammatory cells, increased permeability and endothelial cell injury [54]. In experimental models of lung injury, coexisting lung inflammation increases susceptibility to oxygen toxicity [55]. High FiO_2 induce the production of large amounts of reactive oxygen species that can overwhelm natural antioxidant defences and injure cellular structures [56]. Alterations in the permeability induced by lung injury increases the alveolar-capillary oxygen gradient increasing the risk of oxygen toxicity [57].

Potential harm from high oxygen fractions in critically ill patients who need ventilatory support

It has been suggested that normoxia should be the target in patients with ARDS, as this might prevent neurocognitive dysfunction in those who survive [54]. However, there is some evidence that both ventilation with high FiO_2 and high levels of blood oxygenation are associated with increased mortality in critically ill patients [57, 58], an effect that appeared to be independent of other factors such as disease severity. Similar associations were found in patients following resuscitation from cardiac arrest [59], patients with ischaemic stroke [60], and traumatic brain injury [61]. Two recent systematic reviews and meta-analyses found that arterial hyperoxia was associated with worse hospital outcome in various subsets of critically ill patients [61–63].

Evidence for harm from high oxygen fraction during intraoperative ventilation

At present, there are no sufficiently powered studies that have investigated the effects of higher FiO_2 on the occurrence of postoperative pulmonary complications.

Present choices in inspired fraction of oxygen in the operation room

The above mentioned recently published observational studies on intraoperative ventilation settings in one university hospital in Germany [17] and in a large number of university hospitals in the USA [18] show increased use of higher FiO_2 during intraoperative ventilation: for example, FiO_2 doubled to 80% in neurosurgery patients [17]. One could pose the question as to whether this increased use of higher FiO_2 is safe, given some evidence for harm in non-surgical patients.

Consequences and future directions for research

The harmful effects of high V_T mechanical ventilation in patients under short-term ventilation during general anaesthesia for surgery are now recognised (fig. 1G) [64, 65]. Recent findings suggest that higher levels of PEEP (10–12 cm H_2O) do not protect against postoperative pulmonary complications, and may even cause harm, at least in nonobese patients. And finally, we are uncertain as to whether higher FiO_2 is beneficial or harmful in surgical patients.

Several clinical trials addressing intraoperative ventilation are currently ongoing. The PROVE Network investigators initiated an international multicentre randomised controlled trial in obese patients at high risk for postoperative pulmonary complications during abdominal surgery. The Protective Ventilation With Higher Versus Lower PEEP During General Anesthesia for Surgery in Obese Patients (PROBESE) trial will compare higher and lower levels of PEEP during low V_T ventilation [66].

It is uncertain whether intraoperative ventilation with higher levels of PEEP is protective during general anaesthesia for surgical procedures other than abdominal surgery, such as thoracic surgery. A large randomised controlled trial comparing protective with conventional ventilation (V_T of 5 ml/kg PBW plus PEEP vs V_T of 10 ml/kg PBW without PEEP) in surgery for lung cancer is ongoing [67]. The PROVE Network investigators are also planning a trial in patients receiving one-lung ventilation for thoracic surgery (Protective Ventilation With Higher Versus Lower PEEP During General Anesthesia for Thorax Surgery, PROTHOR) [68], and they are planning a trial in patients undergoing laparoscopic abdominal surgery. These two randomised controlled trials will compare low V_T ventilation with different levels of PEEP. What are presently lacking are well-performed randomised controlled trials of different levels of FiO_2 during intraoperative ventilation.

In conclusion, during intraoperative ventilation, V_T should be kept low, perhaps 6 to 8 ml/kg PBW, but maybe even lower. It is less certain whether surgery patients benefit from levels of PEEP >2 cm H_2O; it could be beneficial in individual patients, but it comes at a price of more haemodynamic compromise. Finally, there is a paucity of clinical data addressing the oxygen fraction to utilise during surgery.

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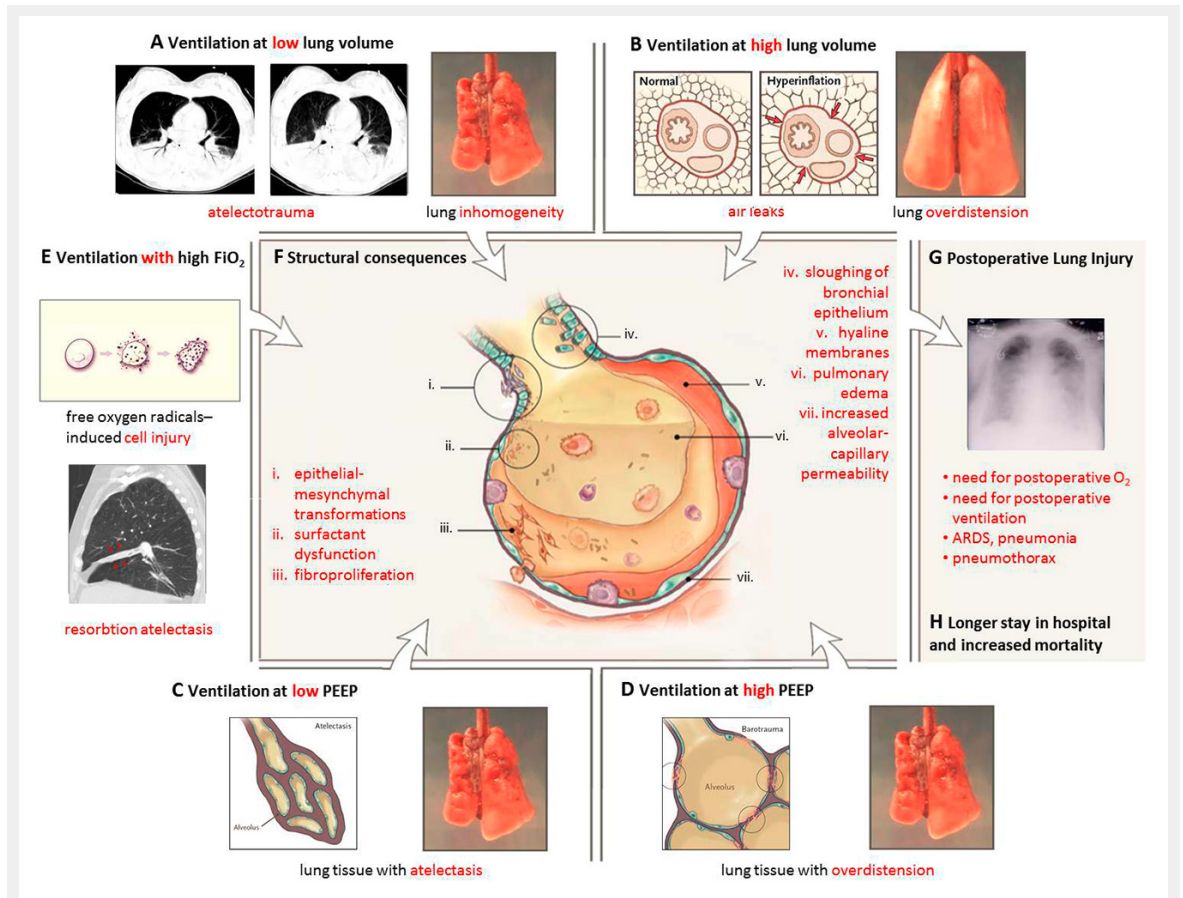## Figures (large format)

Figure 1

Postoperative pulmonary complications caused by forces generated by ventilation at low and high lung volumes, low and high PEEP and high FiO2 (Adapted from N Engl J Med. Slutsky AS, Ranieri VM. Ventilator-Induced Lung Injury. 2013;369(22):2126–36. Copyright ©, Massachusetts Medical Society. Reprinted with permission.).