Accepted February 2015

REVIEW

How to ventilate patients without ARDS?

F.D. Simonis[1], A. Braber[2], H.P. Gelissen[3], J. Heidt[4], J. Horn[1], G. Innemee[4], E. de Jonge[5], N.P. Juffermans[1], P.E. Spronk[2], P.R. Tuinman[3], M. Vriends[4], R.B. de Wilde[5], A. Serpa Neto[1,6], M. Gama de Abreu[7], P. Pelosi[8], M.J. Schultz[1]

[1] Academic Medical Center, University of Amsterdam, the Netherlands: Department of Intensive Care & Laboratory of Experimental Intensive Care and Anaesthesiology, [2] Gelre Hospitals, Apeldoorn, the Netherlands: Department of Intensive Care, [3] VU Medical Center, Amsterdam, the Netherlands: Department of Intensive Care & REVIVE Research VUmc Intensive Care, [4] Tergooi, Hilversum, the Netherlands: Department of Intensive Care, [5] Leiden University Medical Center, Leiden, the Netherlands: Department of Intensive Care, [6] Hospital Israelita Albert Einstein, São Paulo, Brazil: Department of Critical Care Medicine, [7] University Hospital Carl Gustav Carus, Dresden, Germany: Department of Anesthesiology and Intensive Care, [8] IRCCS San Martino IST, University of Genoa, Genoa, Italy: Department of Surgical Sciences and Integrated Diagnostics

Correspondence

M.J. Schultz – marcus.j.schultz@gmail.com

Keywords - **mechanical ventilation; ventilation–associated lung injury; protective ventilation; tidal volume; positive end–expiratory pressure; oxygen fraction; intra–operative ventilation; intensive care unit; critical care; non injured lungs**

Abstract

Certain mechanical ventilation strategies could prevent the injury caused by this intervention. One element of so-called 'lung–protective' ventilation is the use of low tidal volumes. It is uncertain whether high levels of positive end-expiratory pressures have lung-protective properties as well. There are indications that high oxygen fractions of inspired air, or high blood oxygen targets, are harmful. This review summarises recently obtained clinical evidence for protective roles of low tidal volumes, high levels of PEEP, and low fractions of inspired oxygen in surgery patients, and critically ill patients without ARDS.

Introduction

Mechanical ventilation is increasingly recognised as a potentially dangerous intervention. Positive pressure ventilation can lead to an uneven distribution of aeration of the lungs, as such increasing the risk of overinflation at end-inspiration, repetitive opening and closing of lung units, and collapsed tissue throughout the respiratory cycle [1, 2]. Both overinflation and repeated opening and closing are considered to play a role in the development of what is known as 'ventilator-associated lung injury' [3]. In addition, there is a risk of oxygen toxicity, in particular when high fractions of inspired oxygen are used [4-6].

There is increasing interest for prevention of ventilation-associated lung injury. Convincing randomised controlled trial (RCT) evidence for benefit from 'protective ventilation', with low tidal volumes (to prevent overinflation) [7-9] and high levels of positive end-expiratory pressure (PEEP) (to prevent repeated opening and closing) [10-13] in patients with the acute respiratory distress syndrome (ARDS) dramatically changed ventilation practice in these patients. It remains uncertain whether patients without ARDS could also benefit from low tidal volumes and high levels of PEEP. Also, while observational studies suggest that high fractions of inspired oxygen are associated with worse outcome in different patient groups, RCT evidence showing a benefit from preventing high fractions of inspired oxygen is lacking.

This narrative review summarises recently obtained clinical evidence for protective roles of low tidal volumes, high levels of PEEP, and low fractions of inspired oxygen in surgery patients who receive short-lasting intraoperative ventilation during general anaesthesia, and critically ill patients who receive ventilation for respiratory failure other than ARDS.

Definitions

The definition of ARDS has recently changed from the American-European Consensus Criteria (AECC) [14] to the Berlin definition [9]. The new definition classifies ARDS into mild, moderate and severe ARDS. For clarity, throughout this review the Berlin definition is used, even though previous studies used the AECC definitions.

Studies of ventilation frequently use the term 'ventilator-induced lung injury' [15-17] and anaesthesiology studies frequently use the composite endpoint of 'postoperative pulmonary complications'

[18-21]. Throughout this manuscript we will use the terms 'lung injury' and '(postoperative) pulmonary complications'.
Finally, in the literature on ventilation the terms 'low' and 'lower' (e.g., low or lower tidal volumes, and low or lower fractions of inspired oxygen), and 'high' and 'higher' (e.g., high or higher levels of PEEP) are often used. In this manuscript we only use 'lower' and 'higher' for comparisons (e.g., between study arms).

Protective ventilation in patients under general anaesthesia for surgery

Postoperative development of pulmonary complications is strongly associated with worse outcome in surgical patients [18,21,22]. Postoperative ARDS is the most feared postoperative pulmonary complication with reported incidences of up to 25% [23-25]. Intraoperative tidal volume size and level of PEEP are strong predictors of development of postoperative pulmonary complications.

Evidence for benefit from use of low tidal volumes

For many years, anaesthesiologists used high tidal volumes during intraoperative ventilation, as high tidal volumes open those parts of the lungs that collapse at the end of expiration. As such, this strategy prevented shunt, and thus hypoxaemia and the need for high fractions of inspired oxygen.
Three recently published RCTs of intraoperative ventilation tested the hypothesis that the use of low tidal volumes prevents postoperative pulmonary complications [19, 26, 27]. An Italian single-centre RCT showed that tidal volume reduction (from 9 to 7 ml/kg predicted body weight, PBW) prevented postoperative pulmonary dysfunction in patients scheduled for open abdominal surgery [26]. A French multicentre RCT (IMPROVE) confirmed these findings by showing that a reduction in tidal volume (from 12 to 6 ml/kg PBW) prevented almost two-thirds of postoperative pulmonary complications in patients scheduled for major open or closed abdominal surgery [19]. Similar results came from a Chinese single-centre RCT showing an even larger reduction of postoperative pulmonary complications with tidal volume reduction (from 12 to 6 ml/kg PBW) in patients scheduled for spinal fusion surgery [27].

Does ventilation with low tidal volumes mandate use of high levels of PEEP?

The abovementioned three RCTs of intraoperative ventilation actually studied the effects of *bundles* of protective ventilator settings, combining low tidal volumes *with* a high level of PEEP (6 to 8 cm H_2O [19], and 10 cm H_2O [26, 27]). The rationale behind using a bundle of low tidal volume and high levels of PEEP was that tidal volume reduction alone would promote atelectasis which could be prevented by use of high levels of PEEP, to stabilise those lung parts that tend to collapse [20,28].
A very recent international multicentre RCT (PROVHILO) of intraoperative ventilation in patients scheduled for open abdominal surgery compared a lower level of PEEP (< 2 cm H_2O) with higher levels of PEEP (12 cm H_2O) with recruitment manoeuvres in low tidal volume ventilation (tidal volumes of 8 ml/kg PBW) [29]. This RCT showed that the incidence of postoperative pulmonary complications was not dependent on the level of PEEP; instead, use of higher levels of PEEP was associated with intraoperative hypotension requiring more frequent fluid resuscitations and start of vasopressors. The results of this RCT thus suggest that the anaesthesiologist should not use high levels of PEEP in low tidal volume ventilation during general anaesthesia for surgery, at least not in non-obese patients who are to undergo major abdominal surgery – the population under study in PROVHILO.

What is the best fraction of inspired oxygen in patients undergoing ventilation during general anaesthesia for surgery?

Clinical studies investigating the association between intraoperative fractions of inspired oxygen and postoperative pulmonary function are lacking.

Protective ventilation in critically ill patients without ARDS

Investigations on the effects of protective ventilation in critically ill patients with respiratory failure other than ARDS are scarce. While tidal volume size has progressively decreased from higher than 12 ml/kg to 9 ml/kg PBW in intensive care units (ICUs) worldwide in recent years[30], observational studies still show impressive variation in tidal volume size, and tidal volumes remain far above that which is currently considered protective in ARDS patients [31-33] and preferred by respiratory therapists and intensivists [34].

Evidence for benefit of low tidal volumes

One large observational study showed that protocol-guided ventilation aiming at prevention of use of too high tidal volumes (> 12 ml/kg PBW) prevented lung injury by almost two-thirds of patients [35]. Two RCTs further tested the hypothesis whether tidal volume reduction would benefit critically ill patients [36, 37]. A North American single-centre RCT in surgical ICU patients who received ventilation because of respiratory failure other than ARDS showed that tidal volume reduction (from 12 to 6 ml/kg PBW) was associated with a lower incidence of pulmonary complications, and a shorter duration of ventilation [36]. A Dutch multicentre RCT in a mixed population of patients expected to need ventilation for longer than 48 hours because of respiratory failure other than ARDS showed that tidal volume reduction (from 10 to 6 ml/kg PBW) resulted in a lower incidence of ARDS [37]. These findings were confirmed in several meta-analyses that summarised the results of the abovementioned RCTs and several smaller mostly observational studies [16, 17, 38].

What is the best level of PEEP in ICU patients without ARDS?

Clinical studies investigating the association between levels of

PEEP and development of lung injury in ICU patients who do not have ARDS are lacking.

Evidence for benefit of low fractions of inspired oxygen

Observational studies show excessive oxygen use or 'liberal' oxygen therapy to be common in ventilated ICU patients [5] and that nurses and physicians often accept 'unnecessary' hyperoxia [4]. Longstanding hyperoxia, though, could be injurious [39] and high fractions of inspired oxygen are potentially toxic too. Notably, high fractions of inspired oxygen and high levels of PaO_2 are independently associated with increased mortality in ICU patients [4]. Associations between high levels of PaO_2 and worse outcome have also been found in several other patient populations [40-43]. However, the administration of high fractions of inspired oxygen is still a cornerstone of shock management to correct the deficit oxygen level. Based on current evidence it can be advised that oxygen therapy should be the treatment to avoid both hypoxaemia and hyperoxia [6], but which fractions of inspired oxygen to use and what PaO_2 levels to aim for is at present uncertain.

Discussion

There has been a paradigm shift from *treating* ARDS to *prevention* of ARDS (i.e., from *reducing* further harm by using protective ventilation to *preventing* harm by using protective ventilation) [17]. There is growing evidence for using low tidal volumes, low levels of PEEP and maybe also low fractions of inspired oxygen in patients without ARDS.

Recommendations

For patients suffering from ARDS it is currently standard of care to use low tidal volumes (4 to 8 ml/kg PBW), to use moderate levels of PEEP (5 to 10 cm H_2O) in patients with mild ARDS, and to restrict the use of high levels of PEEP (≥ 10 cm H_2O) to patients with moderate or severe ARDS (*figure 1*). Based on the currently available evidence we suggest using low tidal volumes (6 ml/kg PBW) in critically ill patients without ARDS, and moderate tidal volumes (< 8 ml/kg PBW) during intraoperative ventilation. Although convincing evidence is lacking, we advise to use low levels of PEEP in these patient groups. It is difficult to advise on which fraction of inspired oxygen to use, but we favour the use of the titration tables for fraction of inspired oxygen and level of PEEP in patients with ARDS, and to use the lowest possible fraction of inspired oxygen in patients without ARDS, both in the intensive care unit and in the operation room. From a physiological view it may seem paradoxical to allow use of tidal volumes of up to 8 ml/kg PBW in patients with ARDS, higher than those suggested to be safe in critically ill patients without ARDS. Indeed, in general patients with ARDS do have less open lung tissue for ventilation than critically ill patients without ARDS and surgery patients receiving intraoperative ventilation. Use of tidal volumes > 6 ml/kg PBW, however, should be seen as a rescue for those patients who suffer from severe dyspnoea or have unacceptable acidosis, a common problem in these patients, while almost never a problem in critically ill patients without ARDS. According to this rational it could also be that tidal volumes with intraoperative ventilation can be further reduced.

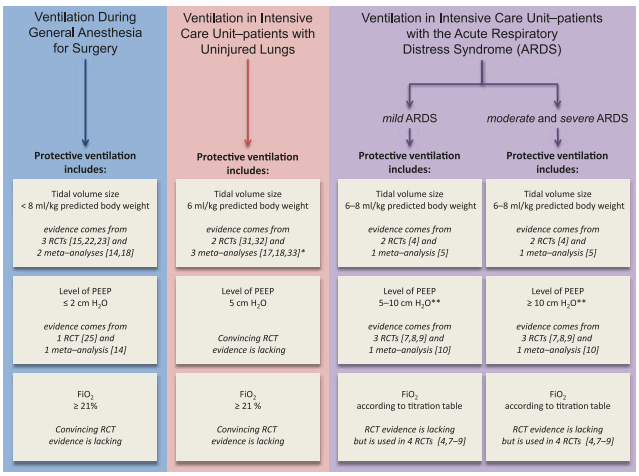

Figure 1. Recommendations for ventilator settings in patients receiving intraoperative ventilation, patients in the ICU without ARDS, and patients with ARDS

Legend:

* studies of ventilation in patients with uninjured lungs included in the meta-analyses suffered from some methodological shortcomings making it difficult to draw firm conclusions;

** tidal volumes higher than 6 ml/kg PBW in patients with ARDS are only allowed in case of severe dyspnoea and/or unacceptable acidosis (see discussion);

*** high rather than low levels of PEEP are advised for patients with moderate or severe ARDS; in the randomised controlled trials levels of PEEP were typically ≥10 cm H2O in patients with moderate or severe ARDS. PEEP: level of positive end-expiratory pressure, FiO2: fraction of inspired oxygen.

Future studies

The abovementioned PROVHILO trial compared high with low levels of PEEP with ventilation during general anaesthesia, but restricted inclusion to non-obese patients scheduled for major abdominal surgery [29]. PROVHILO, therefore, cannot exclude that high levels of PEEP could be beneficial in obese or severely obese patients. Therefore, the PROVE Network investigators initiated an international multicentre RCT in obese patients scheduled for abdominal surgery and at high risk for postoperative pulmonary complications (Technische Universität Dresden. Protective Ventilation With Higher Versus Lower PEEP During General Anesthesia for Surgery in Obese Patients (PROBESE); available from http://clinicaltrials.gov NLM Identifier: NCT02148692). It is also uncertain whether high levels of PEEP could benefit patients scheduled

for surgical procedures other than major abdominal surgery, such as thoracic surgery. Results of a French RCT comparing intraoperative ventilation with low tidal volumes and high PEEP vs. high tidal volumes with low PEEP in surgery for lung cancer surgery are awaited (Assistance Publique - Hôpitaux de Paris. Pulmonary Surgery and Protective Mechanical Ventilation (VPP); available from: http://clinicaltrials.gov NLM Identifier: NCT00805077). The PROVE Network investigators are planning an international RCT in patients scheduled for thoracic surgery (The PROVE Network. Protective ventilation during thoracic surgery (PROTHORAX); https://sites.google.com/site/proveneteu/provenet-studies).

The number of RCTs suggesting that clinicians should use low tidal volumes in patients without ARDS is small, and the RCTs suffer from several methodological shortcomings. In addition, there are several arguments against unlimited use of low tidal volumes in critically ill patients, i.e., irrespective of the presence of ARDS. First, ventilation with low tidal volumes could promote atelectasis [44]. Second, low tidal volume ventilation could increase the risk of patient-ventilator asynchrony [45, 46] and the increased efforts of patients with spontaneous ventilation using low tidal volumes could cause fatigue and induce *pendelluft*, thereby increasing the risk of lung injury [47]. All of these could offset the potential beneficial effects of low tidal volume ventilation as found in patients with ARDS. At present, two large RCTs are being conducted: the Protective Ventilation in Patients without ARDS at Start of Ventilation (PReVENT-NL) trial, and the Preventive Strategies in Acute Respiratory Distress Syndrome (EPALI) trial. PReVENT is a Dutch multicentre RCT comparing ventilation with low tidal volumes (between 4 and 6 ml/kg PBW) with ventilation using conventional tidal volumes (between 8 and 10 ml/kg PBW) and maximal plateau pressure of 25 cm H2O in critically ill patients without ARDS (Academic Medical Center - University of Amsterdam. Available from: http://clinicaltrials.gov NLM Identifier: NCT02153294). EPALI is a Spanish RCT comparing ventilation with lower tidal volumes (≤ 6 ml/kg PBW) with ventilation using conventional ventilation (8 ml/kg PBW) in critically ill patients at risk for ARDS (Corporacion Parc Tauli. Available from: http://clinicaltrials.gov NLM Identifier: NCT02070666). The primary endpoint in PReVENT is the number of ventilator-free days and being alive at day 28; the primary endpoint in EPALI is development of ARDS.

We need randomised controlled trials to determine what is the safest fraction of inspired oxygen, both in critically ill patients without ARDS, and patients receiving intraoperative ventilation. We may even need better evidence for the currently used titration tables for fraction of inspired oxygen and level of PEEP in patients with ARDS. As far as we know, there are currently no planned trials on this subject.

Conclusions

There is convincing evidence that use of low tidal volumes during intraoperative ventilation protects against postoperative pulmonary complications. Whether use of low tidal volumes should be part of protective ventilation in ICU patients without ARDS is less certain, but the evidence so far suggests that these patients could also benefit from tidal volume reduction. Recent findings suggest that intraoperative ventilation with low tidal volumes does not mandate high levels of PEEP in non-obese patients scheduled for abdominal surgery. Finally, it is uncertain what fractions of inspired oxygen should be used in ventilation in the operation room and in the ICU, but several studies suggest worse outcome in ventilated ICU patients who receive high fractions of inspired oxygen.

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