Reducing tidal volume and increasing positive end-expiratory pressure with constant plateau pressure during one-lung ventilation: effect on oxygenation

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Editor’s key points

- Optimum ventilator strategies need to be evaluated for one-lung anaesthesia.
- This study investigated the effects of low tidal volume (VT) with limited plateau pressure.
- Using a cross-over design, it was shown that low VT combined with PEEP resulted in reduced oxygenation.
- Further study is needed to establish the ideal ventilator strategy.

Background. It is no longer safe to use large tidal volumes (VT) (>8 ml kg⁻¹) for one-lung ventilation (OLV), and limiting plateau pressure should be a major objective. Due to the specificity of OLV, the use of positive end-expiratory pressure (PEEP) remains controversial. This study determined whether at the same low plateau pressure, reducing VT and increasing PEEP were not inferior to larger VT and lower PEEP ventilation in terms of oxygenation.

Methods. This prospective, randomized, non-inferiority, cross-over trial included 88 patients undergoing open thoracotomy who received two successive ventilatory strategies in random order: VT (8 ml kg⁻¹ of ideal body weight) with low PEEP (5 cm H₂O), or low VT (5 ml kg⁻¹) with a high PEEP. Respiratory rate and PEEP were, respectively, adjusted to maintain constant ventilation and plateau pressure. The primary endpoint was the PaO₂/FIO₂ ratio under each ventilatory strategy.

Results. The non-inferiority of low-VT ventilation could not be established. The mean adjusted PaO₂/FIO₂ ratio was lower overall during low-VT ventilation, and differences between the two ventilatory modes varied significantly according to baseline (T0) PaO₂/FIO₂. Decreased oxygenation during low VT was smaller when baseline values were low. Systolic arterial pressure was not lower during low-VT ventilation.

Conclusion. During OLV, lowering VT and increasing PEEP, with the same low plateau pressure, reduced oxygenation compared with larger VT and lower PEEP. This strategy may reduce the risk of lung injury, but needs to be investigated further.

Keywords: lung compliance; oxygen consumption; pulmonary ventilation; surgery, thoracic

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During one-lung ventilation (OLV), an intrapulmonary shunt related to collapse of the non-dependent lung and increased atelectasis areas in the dependent lung result in hypoxaemia, which is a serious challenge for anaesthetists. Based on clinical trials in which the use of large tidal volumes (VT) during OLV can improve oxygenation, recommendations were made to keep VT as high as it is in two-lung ventilation (i.e. 10–12 ml kg⁻¹). As a result, it was no longer considered safe to use high-VT volumes during OLV, and limiting plateau pressure should be a major objective in the ventilatory setting of OLV. Although a reduction in VT should decrease the risk of ventilation-induced lung injury, this ventilatory strategy may lead to consistent alveolar derecruitment and atelectasis.

The application of positive end-expiratory pressure (PEEP), which minimizes lung collapse and prevents the repeated opening and collapse of lung units, may, paradoxically, impair intraoperative oxygenation during OLV. It may increase pulmonary vascular resistance and shift blood flow to the non-dependent lung. Additionally, the best level of PEEP to maintain oxygenation after reduction in VT during OLV remains unknown. The problem is not only the influence of VT, but also a subtle interaction between PEEP and VT.

The present study tested the hypothesis that at the same plateau pressure, reducing VT and increasing PEEP are not inferior to a higher VT with lower PEEP ventilation in terms of oxygenation. Thus, we conducted a prospective,
randomized, cross-over study to assess the non-inferiority of lower-V_{T} (5 ml kg\(^{-1}\) with a higher PEEP) compared with a regular-V_{T} strategy (8 ml kg\(^{-1}\) with 5 cm H\(_2\)O), with oxygenation as the endpoint.

**Methods**

**Study population**

This prospective, randomized, open-label, two-period, cross-over trial was carried out in the Department of Anaesthesia and Critical Care 2 at the University Hospital of Bordeaux, between November 2007 and January 2010. After approval by our institutional review board (Comité de Protection des Personnes Sud-Ouest et Outre Mer III) and registration in the NIH clinical trials registry (registration number on clinicaltrials.gov: NCT 00534690), 88 patients undergoing an elective open-chest thoracotomy for pulmonary resection were prospectively enrolled. According to our institutional review board, informed oral consent was obtained the day before surgery from all patients, and written consent agreements were documented in the medical records.

Non-inclusion criteria were as follows: the ratio of forced expiratory volume in 1 s (FEV\(_1\)) over total lung capacity, and/or FEV\(_1\)<70% as predicted by age and height. This study was designed as an intra-individual comparison of two strategies of ventilation, with each patient being his/her own control.

**Perioperative management**

Pre-medications consisted of midazolam (5 mg) given orally. Preoperative medications were continued until the morning of surgery with the exception of angiotensin-converting enzyme inhibitors. Routine monitoring included an electrocardiogram, pulse oximetry, a capnogram, and arterial pressure. The bispectral index (BIS) was monitored continuously using a BIS monitor (Aspect Medical Systems, Newton, MA, USA). After pre-oxygenation, anaesthesia was induced with propofol (1–3 mg kg\(^{-1}\)), sufentanil (0.3 \(\mu\)g kg\(^{-1}\)), and cisatracurium (0.15 mg kg\(^{-1}\)). Anaesthesia was maintained with sevoflurane, and additional boluses of sufentanil were given intraoperatively, as necessary. End-tidal concentrations of sevoflurane were titrated to maintain BIS values at between 45 and 55 throughout the entire intraoperative period. Another bolus of cisatracurium was added at incision (0.10 mg kg\(^{-1}\)) and, if necessary, according to the response of the output from four supramaximal stimulations (30 mA) of the orbicularis muscle, which was estimated visually during surgery.

Patients were intubated with a left-sided double-lumen tube (DLT) (Broncho-part; Rush, Kermen, Germany: 39 F for males and 37 F for females). Fibreoptic bronchoscopy was systematically used to confirm the correct positioning of the DLT immediately after its blind insertion. Haemodynamic instability was defined as a decrease in systolic arterial pressure of \(>20\%\) and was treated, if necessary, with fluids, ephedrine, or both. The lungs were ventilated with a Zeus or Primus Ventilator (Drager, Lubeck, Germany) in a square-wave flow–volume-controlled mode and with an inspired oxygen fraction (F\(_{I\text{O}}\)) in order to obtain pulse oximetry of \(\geq92\%\).

Ideal body weight was calculated as previously reported and \(V_{T}\) was set at 8 ml kg\(^{-1}\), with the maximal plateau pressure (P\(_{plat}\)) limited to 32 cm H\(_2\)O. The inspiratory to expiratory time ratio was 1/2, with an end-inspiratory pause of 20%. Respiratory frequency was adjusted to maintain an end-tidal carbon-dioxide tension (E\(_{CO_2}\)) of between 4 and 4.6 kPa. PEEP was arbitrarily set at 5 cm H\(_2\)O. OLV was initiated immediately after skin incision without modifying the respiratory parameters, and the lumen of the non-ventilated lung was opened to room air. A 15 min period was allowed for stabilization of haemodynamic and respiratory parameters, and to reveal any unexpected OLV intolerances. After haemodynamic (non-invasive arterial pressure and heart rate measurements) and ventilatory (\(V_{T}\), P-peak, plateau and mean airway pressure, respiratory frequency, and compliance) baseline values (T0) were recorded, the patient was randomized according to the order of application of the two ventilatory strategies (Fig. 1): Group A patients were started with \(V_{T}\) at 8 ml kg\(^{-1}\) of ideal body weight and a PEEP of 5 cm H\(_2\)O; Group B patients were started with \(V_{T}\) at 5 ml kg\(^{-1}\) of ideal body weight and a PEEP level that kept the same plateau pressure as that recorded at T0. Each ventilatory strategy was switched from one to the other after 10 min and was systematically followed by new haemodynamic and respiratory recordings of all parameters. This relatively short study period was chosen to avoid increases in surgical time. By using this methodology, the delay between opening the chest and the end of the study period did not exceed 40 min (otherwise some vessels may be ligated). During the whole study period, F\(_{I\text{O}}\), and the inspiratory-to-expiratory time ratio remained unchanged. As the long end-expiratory pause could not be performed, intrinsic PEEP (iPEEP) during both ventilatory strategies could not be evaluated from the expiratory flow–time curve.

Randomization of patients was computer-generated by the study statistician, and the randomization process was centralized: the randomization of each patient was conducted by the secured website of the Clinical Epidemiology Unit.

After completion of the two cross-over periods, each patient’s ventilatory settings were left to the discretion of the attending anaesthesiologist. All measurements were made during radial lymphadenectomy and before pulmonary-vessel ligation in the non-dependent lung. If Sp\(_{O_2}\), decreased to \(<92\%\) during the study period (after baseline recording), surgery was temporarily stopped to resume two-lung ventilation, and the event was recorded.

**Statistical analyses**

This non-inferiority cross-over trial compared two ventilation regimens (described above), which were both administered to all patients in a randomized order. The primary endpoint was the difference between the P\(_{A\text{O}_2}/F_{I\text{O}_2}\) ratios after 10
min for each ventilation regimen. The study was powered so that the non-inferiority of the low-$V_T$ strategy, compared with the high-$V_T$ standard strategy, could be ascertained in terms of the $P_{A_{O_2}}/F_{I_{O_2}}$ ratio outcomes. After clinical consideration, the non-inferiority margin was defined as a 15% change in the $P_{A_{O_2}}/F_{I_{O_2}}$ ratio obtained by conventional ventilation (standard $V_T$), which was estimated in a preliminary study conducted under the same conditions [152 (75)]. Based on this primary analysis, the bilateral 95% confidence interval (CI) for the difference between $P_{A_{O_2}}/F_{I_{O_2}}$ ratios, between low- vs high-$V_T$ regimens, was estimated. If the lower boundary of the 95% CI was above $-22.8$ ($-15\%$ of 152), the conclusion was that the low-$V_T$ regimen did not decrease oxygenation of the patients to a clinically relevant degree (i.e. the lower-$V_T$ regimen was not inferior to the standard ventilation regimen).

The study's sample size (80 patients) was computed to achieve 90% power in showing the non-inferiority of the new regimen, assuming a non-inferiority margin of $-22.8$ (nQuery Advisor software, v. 6.0).

A linear regression model was used to assess the effect of the treatment, the treatment period (first or second), and the treatment–period interactions. The latter aimed at checking the absence of a carry-over effect, which would have prevented valid analysis of the second treatment period. Covariates were introduced into the model whenever adjustment was needed. All statistical analyses were conducted by a biostatistician (C.G.) from the Clinical trial Unit/ Clinical Epidemiology Unit, using SAS® software v9.1.3 (SAS Institute Inc., Cary, NC, USA).

**Results**

Six patients were excluded from the analysis due to severe hypoxaemia (i.e. $S_{p_{O_2}}$ of $<92\%$), which occurred just after baseline recording (T0) and randomization (four patients in Group B and two in Group A). Continuous positive airway pressure, with pure oxygen, was used in the dependent lung. The perioperative characteristics of the analysed patients ($n=82$) are summarized in Table 1. Preoperative ventilatory function and surgical procedures were comparable between both groups (Table 1). Table 2 shows that $V_T$ reached the level planned by the protocol and that PEEP levels were different between both ventilatory strategies, whereas plateau pressure and minute ventilation were similar in both groups (Table 2).

In crude analysis, the mean difference in $P_{A_{O_2}}/F_{I_{O_2}}$ between low and high $V_T$ was $-9.74$. Neither a period effect nor a period–treatment interaction was found: this means that the order of ventilatory strategy had no effect on oxygenation. Conversely, despite randomization, the baseline values of $P_{A_{O_2}}/F_{I_{O_2}}$ ratios at T0 were significantly different between treatment groups [174 (82) vs 152 (91)], and an interaction was observed between baseline values of $P_{A_{O_2}}/F_{I_{O_2}}$ and the effect of treatment. A statistical model that included baseline values of $P_{A_{O_2}}/F_{I_{O_2}}$, and the interaction between these and treatment, was built to compare changes between the treatment groups. Differences in $P_{A_{O_2}}/F_{I_{O_2}}$ ratios were then estimated according to five different selected baseline values (Fig. 2). The difference between low and high $V_T$ was $-14.7$ ($-30.4$ to $1.00$) for the median $P_{A_{O_2}}/F_{I_{O_2}}$ of 136 and was $-26.3$ ($-43.4$ to $-9.3$) for the 75th percentile when $P_{A_{O_2}}/F_{I_{O_2}}=204$ of baseline (Fig. 2).

As the 95% CI for the difference between treatments included the non-inferiority margin, regardless of the baseline value of $P_{A_{O_2}}/F_{I_{O_2}}$, the non-inferiority of the low-$V_T$ ventilatory strategy could not be established. The proportion of patients exhibiting a decrease in systolic arterial pressure of $>20\%$ was greater in the low-$V_T$ group (15% vs 10%). This difference was not significant after adjustment for appropriate covariates in the model ($P=0.25$). Fluid intake and vasopressor support were comparable between both ventilatory strategies.
Reducing $V_T$ and increasing PEEP during one-lung ventilation

Discussion

The major finding of this study is that during OLV, at the same plateau pressure level, a ventilatory strategy that reduces $V_T$ and increases PEEP is associated with a decreased $P_{A_CO_2}/F_{I_CO_2}$ ratio. However, the clinical consequence of this decrease seems to be moderate. Once OLV was tolerated and the patients had been randomized, $S_{P_{A_O_2}}$ remained >92% in all patients receiving both strategies; thus, none required OLV to be interrupted.

Many studies have focused on oxygenation during OLV using PEEP, alveolar recruitment manoeuvres, inhaled nitric oxide, almitrine, ventilator strategies, and even surgical lung compression. Some recent studies have evaluated different settings of $V_T$ and PEEP and have reported contradictory results for oxygenation. By comparing high $V_T$ vs low $V_T$, with two levels of PEEP and plateau pressures, Schilling and colleagues could not find any difference in oxygenation. However, Michelet and colleagues reported improved oxygenation using protective ventilation during OLV in patients undergoing oesophagectomy. However, the latter study focused on the influence of protective ventilation on systemic inflammation after oesophagectomy.

It is now generally admitted that higher-$V_T$ ventilation (i.e. $>8\text{ ml kg}^{-1}$) induces lung injuries during OLV. In our study, plateau pressure was relatively limited in both groups. It is known that for a given plateau pressure in patients with acute respiratory distress syndrome, PEEP has a greater influence on $P_{A_CO_2}$ than $V_T$ in improving alveolar recruitment. During OLV, we observed increased PEEP and decreased $V_T$ while plateau pressure remained constant, resulting in decreased oxygenation. This finding may be explained by the redistribution of pulmonary blood flow from over-distended lung units to the non-dependent lung, induced by increased mean alveolar pressure. We can assume that the best ventilation, in terms of oxygenation during OLV, can be visualized as a U-shaped curve in which too little $V_T$ and thus decreased alveolar pressure, will result in derecruitment of the dependent lung, and thus lead to hypoxaemia. Conversely, high $V_T$, high PEEP, or both, which induce high alveolar pressure, may then increase shunt to the non-dependent lung and also induce hypoxaemia.

The present study compared a classical and widely used OLV setting, $8\text{ ml kg}^{-1}$ with $5\text{ cm H}_2\text{O}$ PEEP, with a low $V_T$ of $5\text{ ml kg}^{-1}$ plus PEEP increased to maintained plateau pressure. The originality of our study comes from the choice of an oxygenation endpoint and from its design. The non-inferiority design was chosen according to the underlying hypothesis, and the study was powered accordingly. The cross-over trial design was chosen to reduce expected inter-subject variability in oxygenation, by making each patient serve as his/her own control. This design allowed adequate statistical power to conclude that at an equal plateau pressure, in a large number of patients undergoing OLV, a reduction in $V_T$ was not equivalent to standard $V_T$ in terms of oxygenation. One possible explanation is that the application of a higher level of PEEP, when $V_T$ is reduced, resulted in increased mean alveolar pressure and pulmonary vascular resistance. This underscores the important concept of an interaction between $V_T$ and PEEP during OLV.

Depending on lung mechanics and the perfusion status of each individual patient, ventilation strategies need to be adjusted to keep the lung open without impeding perfusion and to minimize alveolar damage. Measuring the shunt...
would have been useful, but was too invasive. We observed that a decreased $P_{A, O_2}/F_{I, O_2}$ ratio was of particular concern to patients with higher baseline $P_{A, O_2}/F_{I, O_2}$ ratios, as shown in Figure 2. Unfortunately, no specific measurements were done to provide a physiological explanation for these observations. However, although the global tendency leans towards a decrease in $P_{A, O_2}$, which gives statistically significant results, clinically, no patient required OLV to be interrupted for specific management of hypoxaemia, as $Sp_{O_2}$ remained $>92\%$ during the low-$V_T$ procedure.$^{1,2}$ A change in $P_{A, O_2}/F_{I, O_2}$ ratios represents a much more sensitive endpoint for ventilatory settings than $Sp_{O_2}<92\%$. However, both criteria provide information on decreases in oxygenation, and within safe ranges.

Once $V_T$ is reduced, respiratory frequency needs to be increased to maintain constant minute ventilation, which, in turn, leads to increased dead-space ventilation. This may explain the slight increase in $P_{A, CO_2}$ in the low-$V_T$ group.

In the present study, iPEEP may have increased in the dependent lung due to the higher respiratory rate and level of PEEP that was used during the study period. As this may result in a shunt increase, the occurrence of dynamic hyperinflation could be of great importance.$^{13,25}$ We did not observe any dynamic hyperinflation when PEEP was increased as plateau pressure remained stable. This can be partly explained by the exclusion of patients with airway obstruction diseases ($FEV_1<70\%$).$^{17}$

During low-$V_T$ ventilation, increased mean alveolar pressure may have caused decreased right ventricular preload or increased right ventricular output impedance.$^{26}$ After adjustment of appropriate covariates, systolic arterial pressure was not different between the groups, and fluid intake and vasopressor support were comparable.

Unfortunately, we did not compare the atelectasic areas using tomodensitometry during both strategies, as it was not feasible in the operating theatre during lung resection. Whether one strategy is better than the other, in terms of gas distribution with different tidal recruitments, end expiratory-lung volumes, atelectasis areas, and lung injuries caused by mechanical stress, will need to be investigated in further studies.$^{27}$

This study has several limitations. First, the time of each ventilatory strategy was relatively short because $P_{A, O_2}$ may progressively decrease during 30 min of OLV.$^{19,28}$ Thus, in order to confirm our results, a study that compares both methods for a longer time is needed. However, we were able to compare both strategies using the same timing and the same patients: thus, comparisons were possible. Consequently, we consider that our findings are clinically relevant. Secondly, our study focused on intraoperative oxygenation. The impact of ventilatory strategies on lung injury, by measuring alveolar cytokine in a broncho-alveolar lavage, tomodensitometric evaluation of alveolar recruitment by atelectasis areas, or both, would be interesting to investigate further.$^{29}$ Thirdly, our study was not blinded. Six patients were excluded for severe hypoxaemia and patients with chronic obstructive pulmonary disease were also not included. This limits the generalization of our results to patients who are probably mostly affected by decreased oxygenation in the low-$V_T$–high-PEEP strategy.

**Conclusion**

Hypoxaemia is a constant threat during OLV, and ventilation strategies are crucial to decrease the incidence of hypoxaemia. At the same plateau pressure, an increase in
end-expiratory pressure with decreased $V_t$ and increased PEEP worsened oxygenation.

The $\text{PaO}_2/\text{FiO}_2$ ratio decreased, but stayed within a clinically acceptable range and did not lead to interruption of OLV.

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**Declaration of interest**

None declared.

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