Protocol and statistical analysis plan of a prospective randomized clinical trial of intraoperative tidal volume ventilation with 6 mL/kg per body weight and PEEP of 5 cmH_2O versus 10 mL/kg per body weight and PEEP of 5 cmH_2O in adult patients undergoing major surgery

LOW TIDAL VOLUME IN ANAESTHESIA FOR MAJOR GENERAL SURGICAL

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SUMMARY

INTRODUCTION: Mechanical ventilation is mandatory in patients undergoing general anaesthesia for major surgery. Tidal volumes higher than 10 mL/kg of predicted body weight (PBW) have been advocated for intraoperative ventilation, however, recent evidence suggests that low tidal volumes may benefit surgical patients. To date, the impact of low tidal volume compared to conventional tidal volume during surgery has only been assessed in clinical trials also combining different levels of positive-end expiratory pressure (PEEP) in each arm.

AIM: To assess the impact of low tidal volume compared to conventional tidal volume during general anaesthesia for surgery on the incidence of postoperative respiratory complications in adult patients receiving moderate levels of PEEP.

METHODS: Single center, two-arm, randomized clinical trial. In total, 1240 adult patients older than 40 years scheduled for at least 2 hours of surgery under general anaesthesia and routinely monitored with an arterial line will be included. Patients will be ventilated intraoperatively with moderate level of PEEP (5 cmH_2O) and randomly assigned to tidal volume of 6 mL/kg PBW (low tidal volume) or tidal volume of 10 mL/kg PBW (conventional tidal volume in Australia). The primary outcome will be the occurrence of postoperative respiratory complications, recorded as a composite endpoint of adverse respiratory events within the first seven postoperative days.

CONCLUSION: This is the first well-powered study comparing the effect of low and high tidal volume ventilation during surgery on the incidence of postoperative respiratory complications in adult patients receiving moderate levels of PEEP.

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INTRODUCTION

Mechanical ventilation is a mandatory intervention in patients undergoing general anaesthesia for major surgery. However, it has many potentially detrimental effects, the most dangerous being ventilator induced lung injury (VILI).[1] VILI can result from cyclic overstretching of aerated alveoli induced by the use of high tidal volume (*volutrauma*), from repeated opening and closing of peripheral airways induced by the use of insufficient levels of positive-end expiratory pressure (PEEP) (*barotrauma*), and from the direct use of high airway pressures (*barotrauma*).[1,2]

For several years, a high tidal volume strategy using tidal volumes higher than 10 mL/kg of predicted body weight (PBW) has been advocated for intraoperative ventilation.[3] The potential advantages of this strategy include reduced incidence of atelectasis, due to the maintenance of a high pressure in the airways, and a consequent reduction in the risk of perioperative hypoxaemia.[3] However, the potential benefits of a low tidal volume strategy first became apparent in studies in critically ill patients with acute respiratory distress syndrome (ARDS), where the use of low tidal volume is strongly associated with better clinical outcomes.[4] In addition, recent studies suggest that the use of high tidal volumes can initiate lung injury even in healthy lungs, especially during major surgery with its associated inflammatory response, making the lungs more prone to VILI.[5]

A recent multicentre clinical trial in France showed that, in a high-risk population, a bundle of care composed of low tidal volume, moderate levels of PEEP, and recruitment manoeuvres reduced the incidence of major complications in patients undergoing abdominal surgery compared to the use of

high tidal volume and no PEEP.[6] Nevertheless, this study compared a bundle of interventions and it is impossible to isolate which component was beneficial. A recent multicentre clinical trial sought to address this issue and compared the effect of a low PEEP strategy (< 2 cmH_20) with a high PEEP strategy (12 cmH_20) in patients undergoing major abdominal surgery and receiving low tidal volume ventilation.[7] In this study, the use of high levels of PEEP was not associated with better outcomes, suggesting that tidal volume may be more important in the prevention of complications.[7] Indeed, an individual patient meta-analysis including data from 21 studies supported this notion.[8]

Our group recently reported that, in Australia, the use of high tidal volume (around 10 ml/kg PBW) is relatively common and that the average tidal volume during major abdominal surgery is approximately 10 ml/kg of PBW and that the standard level of PEEP used in the intraoperative period is 5 cmH_2O.[9] These findings suggest that in this setting a high tidal volume strategy in combination with moderate levels of PEEP is likely the most common strategy for intraoperative ventilation in Australia. The findings of our study imply that the control groups of previous randomized controlled trials of a low tidal volume strategy for intraoperative ventilation do not reflect the practice of intraoperative mechanical ventilation in Australia. To date, no suitably powered randomized clinical trial has assessed the isolated impact of tidal volume in surgical patients in the setting of a fixed moderate levels of PEEP.

The present study outlines the protocol and statistical analysis plan for a prospective randomized controlled trial comparing the effect of low tidal volume ventilation, using 6 ml/kg PBW, with conventional ventilation using 10 ml/kg PBW (as currently practiced in Australia) on the incidence of postoperative respiratory

complications in adult patients undergoing major surgery and receiving 5 cmH_2O of PEEP. Recruitment for the trial has now been completed but no data analysis has yet been undertaken. This trial is registered with ANZCTR (ACTRN12614000790640).

METHODS

Study design

Single centre, randomized superiority trial of low tidal volume ventilation compared to conventional ventilation in a tertiary teaching hospital affiliated to the University of Melbourne. The protocol was approved by the Austin Health Human Research Ethics Committee (HREC), and informed consent will be collected by local investigators for all patients before inclusion in the trial. No interim analyses is planned.

Study population

Inclusion criteria

Patients must satisfy all of the following inclusion criteria:

- Age ≥ 40 years; and
- Expected duration of ventilation for surgery ≥ 2 hours; and
- Need of an arterial line for routine monitoring during the surgery.

Exclusion criteria

Patients will be excluded from the study if any of the criteria listed below apply:

- Pregnancy or lactation; or
- Thoracic surgery; or
- Cardiac surgery; or
- Intracranial neurosurgery; or
- Need of nitrous oxide administration; or
- Previous enrolment in the trial.

Rationale for the inclusion and exclusion criteria

Older patients and longer expected duration of surgery are well known major risk factors for the development of postoperative respiratory complications,[11] thus, we

aimed to enrol an ‘enriched’ population where the rate of the primary outcome would be expected to be higher. In addition, the use of an arterial line during surgery also denotes a higher risk procedure, and permits sampling of arterial blood gases for evaluation of PaO_2.[9] The exclusion criteria are related to situations where: 1) ventilation practice differs markedly (one-lung ventilation in thoracic surgery and no ventilation during cardiopulmonary bypass in cardiac surgery); 2) the use of low tidal volume and consequent hypercapnia can induce harm (intracranial surgery); and 3) the outcome and management is expected to be different from usual (pregnancy and use of nitrous oxide).

Randomization and masking

A randomization list will be computed-generated by an independent investigator. Randomization will be conducted using sealed, sequentially numbered and opaque envelopes placed in the operating room and without any stratification factor. Patients who satisfy all inclusion criteria and have no exclusion criteria will be randomly assigned in a 1:1 ratio to either low tidal volume ventilation or conventional ventilation, using a permuted block method with random block sizes of 4, 6 or 10. Due to the nature of the intervention, blinding is not possible.

Intervention

General management such as the inspired fraction of oxygen (FiO_2), respiratory rate, general anaesthesia technique, fluid management, use of vasoactive drugs, analgesia plan, use of prophylactic antibiotics and anti-emetics agents will be at the discretion of the treating anaesthesiologist and in accordance with existing protocols for patients undergoing major surgery and equal for both groups. PBW will be calculated as 50 + 0.91*(height [cm] – 152.4) for males and 45.5 +

0.91*(height [cm] – 152.4) for females. Patients will be randomized to one of the following interventions:

Low tidal volume ventilation

Immediately after randomization, patients assigned to the low tidal volume group will be ventilated with volume-controlled ventilation, a tidal volume of 6 mL/kg PBW and PEEP of 5 cmH_2O. This allocated tidal volume target and PEEP will be maintained for the whole duration of the surgical procedure.

Conventional ventilation

Immediately after randomization, patients assigned to the conventional ventilation group will be ventilated with volume-controlled ventilation, a tidal volume of 10 mL/kg PBW and a PEEP of 5 cmH_2O. This allocated tidal volume target and PEEP will be maintained for the whole duration of the surgical procedure.

Data collection

A purposed built and design case report form (CRF) will be used for data collection. All data will be collected by trained research staff at study site directly from the clinical chart source data. Information recorded in the CRF will be required to accurately reflect the participant's medical and hospital notes. The study timelines, procedures and assessments are shown in **Table 1**. After the data collection is completed the database will be locked and only the principal investigator and the statistician responsible for the analyses will have access to it.

Study outcomes

Primary outcome

The primary outcome is the incidence of a composite outcome of postoperative respiratory complications, defined as positive if any component developed within the first 7 days after surgery. The following complications will be considered:

- Pneumonia (defined as need of antibiotics for a suspected respiratory infection and one or more of the following criteria: new or changed sputum, new or changed lung opacities, fever and/or white blood cell count > $12x10^9$/L);
- Bronchospasm (defined as newly detected expiratory wheeze treated with bronchodilators);
- Atelectasis (defined as lung opacification with a shift of the mediastinum, hilum or hemidiaphragm toward the affected area, and compensatory over-inflation in the adjacent non-atelectatic lung);
- Pulmonary congestion (defined as clinical signs of congestion, including dyspnoea, oedema, rales, and jugular venous distention, with or without chest x-ray demonstrating increase in vascular markings and diffuse alveolar interstitial infiltrates);
- Respiratory failure (defined as a postoperative PaO_2 < 60 mmHg on room air, a PaO_2 / FiO_2 ratio < 300 mmHg or arterial oxyhaemoglobin saturation measured with pulse oximetry < 90% and requiring oxygen therapy);
- Pleural effusion (defined as chest radiograph demonstrating blunting of the costophrenic angle, loss of sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures or [in supine position] a hazy opacity in one hemithorax with preserved vascular shadows);

- Pneumothorax (defined as air in the pleural space with no vascular bed surrounding the visceral pleura);
- Requirement for mechanical ventilation (defined as unplanned need of non-invasive or invasive ventilation).

All components of the primary outcome comprehending the assessment of chest X-rays or computed tomography will be adjudicated by assessors blinded to the treatment allocation.

Secondary outcomes

Secondary outcomes will include (according to the definition in **Table S1** in **Online Supplement**):

- Incidence of postoperative respiratory complications during hospital stay;
- Incidence of pulmonary embolism;
- Incidence of acute respiratory distress syndrome;
- Incidence of systemic inflammatory response syndrome;
- Incidence of sepsis;
- Incidence of acute kidney injury;
- Incidence of wound infection (superficial and deep);
- Rate of intraoperative need of vasopressor;
- Incidence of unplanned intensive care unit (ICU) admission;
- Rate of need for medical emergency team call;
- ICU length of stay;
- Hospital length of stay;
- Incidence of in-hospital mortality.

Sample size calculation

The sample size for this study has been calculated based on the incidence of postoperative respiratory complications of 10.8% observed in a previously study by our group.[10] A study population of 1240 patients will provide 80% power at a two-sided significance level of 0.05 to detect an absolute reduction in primary outcome of 3.4% allowing a dropout rate of 3%.

Statistical analyses

All statistical analyses will be conducted on an intention-to-treat basis, with patients analysed according to their assigned treatment arms, unless otherwise indicated (**Figure 1**). No or minimal losses to follow–up for the primary and secondary outcomes are anticipated. Complete–case analysis will be carried out for all the outcomes. However, if more than 5% of missing data were found for the primary outcome, a sensitivity analysis using multiple imputations and estimating–equation methods will be carried out.

Hypothesis tests will be two–sided with a significance level of 0.05. In addition to the unadjusted *p*–values for secondary outcomes, a Holm–Bonferroni procedure will be applied to control for multiple testing [12]. Analyses will be performed using the R (R Core Team, 2016, Vienna, Austria) program.

Baseline characteristics

A description of the baseline characteristics of the trial participants will be presented by treatment group (**Table 2**). Discrete variables will be summarized as numbers (%). Percentages will be calculated according to the number of trial participants for whom data are available. Where values are missing, the denominator will be stated in the table and no assumptions or imputations will be made. Continuous variables will be summarized by either means and standard

deviations (SD) or medians and interquartile ranges (IQR), according to the observed distribution of the variable.

Intraoperative characteristics

Intraoperative characteristics including ventilation practice will be reported according to the **Table 3**, and **Table S2**, **S3** and **S4** in **Online Supplement**. Absolute differences between the groups with the respective 95% confidence interval will be calculated as mean differences from an independent *t*-test for continuous variables and risk differences derived from a generalized linear model considering a binomial distribution with an identity-link.

Proposed additional figures

Figure 2 – Incidence of Composite of Respiratory Complications According to Pre-specified Subgroups

Figure S1 – Forest Plot Showing the Results of the Sensitivity Analysis for the Primary Outcome Individual component analysis, count analysis, common effect test and average relative effect test.

Primary outcome

The effects of the intervention on incidence of postoperative respiratory complications will be reported as number and percentages and estimated with risk ratio and 95% confidence intervals calculated with Wald's likelihood ratio approximation test and with $\chi 2$ tests for hypothesis testing (**Table 4**). In addition, a generalized linear model with binomial distribution and with an identity–link function will be used to derive risk difference with 95% confidence interval.

Secondary outcomes

The effects of the intervention on binary secondary outcomes will be reported as number and percentages and estimated with risk ratio and 95% confidence

intervals calculated with Wald's likelihood ratio approximation test and with $\chi 2$ tests for hypothesis testing (**Table 4**). In addition, a generalized linear model with binomial distribution and with an identity–link function will be used to derive risk difference with 95% confidence interval. The effects of the intervention on length of ICU and hospital stay will be estimated with generalized linear models considering distributions that will fit a possible heavy right–tailed distribution without zero (such as truncated Poisson, gamma distribution or inverse Gaussian), choosing the best fit according to model's deviance. In addition, a Holm–Bonferroni correction to control the family–wide error rate to the *p*–values for all 13 secondary outcomes will be done and presented in a Table.

Subgroup analyses

The effects of the intervention on pre-specified subgroups will be assessed using generalized linear models considering a binomial distribution with an interaction between each subgroup and the study arm as fixed-effect. All such subgroup analyses will be exploratory, and the potentially reduced power of such tests to find evidence of significant interactions is acknowledged. These results will be reported as a forest plot. The specific subgroups that will be considered are:

- Abdominal vs. Non-abdominal surgery;
- Open vs. Laparoscopic surgery;
- Body mass index > 35 kg/m^2 vs. Body mass index ≤ 35 kg/m^2;
- Higher vs. Lower risk for respiratory complications.

Sensitivity analyses

As a sensitivity analysis, the effect of the intervention on primary outcome will be re-estimated using a generalized linear model with binomial distribution with additional adjustment for age, gender, baseline SpO_2, body mass index and

ARISCAT score, plus any variables with substantial imbalance across treatment arms at baseline.

Since the primary outcome of the present study is a composite one, the choice of the statistical method is an important part of design because various methods provide different power, depending on the situation. In addition to the standard analysis described above, the following analyses will be performed to test the robustness of the trial findings:

- Count analysis: the number of positive component events (i.e., ‘count’) across the composite will be assessed. The groups will be compared on the count using a Wilcoxon rank–sum test, and the odds ratio with the 95% confidence interval will be assessed with a proportional odds logistic regression model;
- Individual component analysis: the effect of the intervention in each component will be analysed using a generalized linear model using a Bonferroni correction for multiple comparisons. The 99.37% Bonferroni–corrected confidence intervals will be reported (1 – 0.05/8 = 0.9937);
- Common effect test: A multivariate (i.e., multiple outcomes per subject) generalized estimating equations (GEE) model will be used to estimate a common effect odds ratio across the components;
- Average relative effect test: The average relative effect test will be assessed by averaging the component-specific treatment effect from the distinct effects model, and testing whether the average is equal to zero. In the GEE distinct effect model a distinct treatment effect is estimated for each component;

- Heterogeneity of treatment effect: Heterogeneity of treatment effect across components will be assessed by a treatment–by–component interaction test in the distinct effects GEE model.

Consenting and ethical compliance

All patients will give their consent before their inclusion in the study. Two situations may result in cessation of trial treatment:

- Patient or legal surrogate may decline consent to continue trial treatments; or
- Patient or legal surrogate may withdraw consent to continue in the trial.

In both cases, trial specific treatments will be interrupted and the patient will continue therapy as prescribed by the treating anaesthesiologist. When this situation occurs, consent for data collection will be sought, and if this is declined, the patient's data will be removed from the website and not analysed, apart from data related to randomisation and consent.

Data safety monitoring board

No monitoring by an independent monitoring board will be done.

CONCLUSION

The present study is a single centre Australian and New Zealand College of Anaesthetists funded randomised clinical trial designed to recruit a total of 1240 patients comparing a low tidal volume ventilation with 6 mL/kg of PBW with a conventional ventilation with 10 mL/kg PBW in adult patients undergoing general anaesthesia for major surgery who are expected to last at least 2 hours and receiving a PEEP of 5 cmH_2O.

LEGEND TO FIGURES

Figure 1 – Flowchart of inclusion

ITT: intention to treat

Table 1 – SPIRIT diagram, study timelines and procedures

	Pre randomization		Perioperative		Post randomization		
	Preoperative	**Randomization**	**Intraoperative**	**PACU**	**Once daily**	**07 days**	**Hospital discharge**
Enrolment							
Eligibility screening							
Allocation							
Baseline data							
Informed consent							
Interventions							
Low tidal volume							
Conventional tidal volume							
Measurements							
Ventilatory variables							
Arterial blood gases							
Vital signs							
Anaesthesia characteristics							
Outcomes							
Respiratory complications							
Pulmonary embolism							
Acute respiratory distress syndrome							
SIRS							
Sepsis							
Acute kidney injury							
Wound infection							
Intraoperative need of vasopressor							
Unplanned ICU admission							
Need for MET call							
ICU length of stay							
Hospital length of stay							
In-hospital mortality							

PACU: post-anaesthesia care unit; SIRS: systemic inflammatory response syndrome; ICU: intensive care unit; MET: Medical Emergency Team

Table 2 – Baseline characteristics of the included patients

	Low Tidal Volume Ventilation (*n* =)	Conventional Ventilation (*n* =)
Age, years		
Male gender		
Body weight, kg		
Actual		
Predicted		
Body mass index, kg/m^2		
ARISCAT risk score		
Low		
Moderate		
High		
Preoperative SpO_2, %		
Preoperative HCO_3, mmol/L		
Preoperative hemoglobin, g/dL		
Preoperative creatinine, µmol/L		
Co-morbidities		
Diabetes mellitus		
Hypertension		
Coronary artery disease		
Chronic renal disease		
Chronic liver disease		
Current smoker		
COPD		
Asthma		
Interstitial lung disease		
Bronchiectasis		
Obstructive sleep apnea		
Obesity*		
Recent LRTI		
Type of surgery		
General		
Abdominal		
Open		
Laparoscopic		
Orthopaedics		
Peripheral		
Spine		
ENT / Plastic / Maxillofacial		
Other		

Data are presented as mean ± standard deviation or N (%)

ARISCAT: Assess Respiratory Risk in Surgical Patients in Catalonia; COPD: chronic obstructive pulmonary disease; ENT: ear, nose and throat surgery; HCO_3: bicarbonate; LRTI: lower respiratory tract infection; SpO_2: pulse oximetry; TAP: transversus abdominis plane

* defined as BMI > 30 kg/m^2

Table 3 – Intraoperative characteristics, ventilation and oxygenation

	Low Tidal Volume Ventilation (*n* =)	Conventional Ventilation (*n* =)	Absolute Difference (95% CI)	*p* value
Tidal volume				
Absolute, mL				
Adjusted, mL/kg PBW[a]				
PEEP, cmH_2O				
Peak pressure, cmH_2O				
Highest				
Respiratory rate, bpm				
Lowest				
Highest				
SpO_2, %				
Lowest				
Highest				
FiO_2, %				
Highest				
$etCO_2$, mmHg				
Highest				
ABG analysis after induction				
pH				
PaO_2, mmHg				
$PaCO_2$, mmHg				
HCO_3, mmol/L				
PaO_2 / FiO_2				
Base excess				
Lactate, mmol/L				
Hypoxemia[*]				
Acidosis[**]				
Hypercapnia[***]				
ABG analysis prior closure				
pH				
PaO_2, mmHg				
$PaCO_2$, mmHg				
HCO_3, mmol/L				

PaO_2 / FiO_2	
Base excess	
Lactate, mmol/L	
Hypoxemia*	
Acidosis**	
Hypercapnia***	
Duration of surgery, minutes	
Use of regional anaesthesia	
Spinal local anaesthesia	
Spinal opioid	
Epidural	
Paravertebral block	
TAP / Abdominal block	
Peripheral limb block	

Data are presented as mean ± standard deviation or N (%)
ABG: arterial blood gas; CI: confidence interval; $etCO_2$: end-tidal carbon dioxide; FiO_2: inspired fraction of oxygen; HCO_3: bicarbonate; PaO_2: partial pressure of oxygen. $PaCO_2$: partial pressure of carbon dioxide; PBW: predicted body weight; PEEP: positive end-expiratory pressure; SpO_2: pulse oximetry
a PBW was calculated as 50 + 0.91 x (height [cm] – 152.4) for men and 45.5 + 0.91 x (height [cm] – 152.4) for women.
* defined as PaO_2 < 60 mmHg
** defined as pH < 7.30
*** defined as PaCO2 > 60 mmHg

Table 4 – Primary and secondary outcomes

	Low Tidal Volume Ventilation (*n* =)	Conventional Ventilation (*n* =)	Effect Estimate (95% CI)	Absolute Difference (95% CI)	*p* value
Primary outcome					
Composite respiratory complications within seven days			RR	RD	
Components of the primary outcome					
Pneumonia			RR	RD	
Respiratory failure			RR	RD	
Pleural effusion			RR	RD	
Atelectasis			RR	RD	
Pneumothorax			RR	RD	
Bronchospasm			RR	RD	
Pulmonary congestion			RR	RD	
Unplanned non-invasive or invasive ventilation			RR	RD	
Secondary outcomes					
Composite respiratory complications during hospital stay			RR	RD	
Pulmonary embolism			RR	RD	
Acute respiratory distress syndrome					
SIRS			RR	RD	
Sepsis			RR	RD	
Acute kidney injury			RR	RD	
Wound infection			RR	RD	
Superficial			RR	RD	
Deep			RR	RD	
Intraoperative need of vasopressor			RR	RD	
Unplanned ICU admission			RR	RD	
Need for MET call			RR	RD	
Length of stay					
In ICU, days			MD	MD	
In hospital, days			MD	MD	
In-hospital mortality			RR	RD	

Data are presented as mean ± standard deviation or N (%)

CI: confidence interval; HR: hazard ratio; ICU: intensive care unit; MD: mean difference; MET: medical emergency team; RR: risk ratio; PACU: post-anesthesia care unit; RD: risk difference

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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