BJA

British Journal of Anaesthesia, 121 (4): 899–908 (2018)

doi: 10.1016/j.bja.2018.04.021
Advance Access Publication Date: 2 June 2018
Respiration and Airway

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Intraoperative ventilation settings and their associations with postoperative pulmonary complications in obese patients

L. Ball[1,2,*], S. N. T. Hemmes[2,3], A. Serpa Neto[2,4], T. Bluth[5], J. Canet[6], M. Hiesmayr[7], M. W. Hollmann[3], G. H. Mills[8], M. F. Vidal Melo[9], C. Putensen[10], W. Schmid[7], P. Severgnini[11], H. Wrigge[12], M. Gama de Abreu[5], M. J. Schultz[2,13], P. Pelosi[1], and for the LAS VEGAS investigators[14], the PROVE Network[14], the Clinical Trial Network of the European Society of Anaesthesiology

[1]Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Policlinico San Martino, Genova, Italy, [2]Department of Intensive Care, Amsterdam, The Netherlands, [3]Department of Anaesthesiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [4]Department of Critical Care Medicine, Hospital Israelita Albert Einstein, São Paulo, Brazil, [5]Department of Anaesthesiology and Intensive Care Medicine, Pulmonary Engineering Group, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany, [6]Department of Anesthesiology and Postoperative Care, Hospital Universitari Germans Trias I Pujol, Barcelona, Spain, [7]Division Cardiac, Thoracic, Vascular Anesthesia and Intensive Care, Medical University Vienna, Vienna, Austria, [8]Operating Services, Critical Care and Anaesthesia, Sheffield Teaching Hospitals and University of Sheffield, Sheffield, UK, [9]Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, MA, USA, [10]Department of Anesthesiology and Intensive Care Medicine, University Hospital Bonn, Bonn, Germany, [11]Department of Biotechnology and Sciences of Life, ASST- Settelaghi Ospedale di Circolo e Fondazione Macchi, University of Insubria, Varese, Italy, [12]Department of Anesthesiology and Intensive Care Medicine, University of Leipzig, Leipzig, Germany and [13]Mahidol-Oxford Tropical Medicine Reseach Unit (MORU), Mahidol University, Bangkok, Thailand

*Corresponding author. E-mail: lorenzo.ball@edu.unige.it

[14] LAS VEGAS (the 'Local ASsessment of VEntilatory management during General Anesthesia for Surgery' study) and The PROVE Network; the PROtective VEntilation Network (www.provenet.eu) collaborators are listed in the online supplement (pp. 3–8).

Abstract

Background: There is limited information concerning the current practice of intraoperative mechanical ventilation in obese patients, and the optimal ventilator settings for these patients are debated. We investigated intraoperative

Editorial decision: 18 April 2018; **Accepted:** 18 April 2018

ventilation parameters and their associations with the development of postoperative pulmonary complications (PPCs) in obese patients.
Methods: We performed a secondary analysis of the international multicentre Local ASsessment of VEntilatory management during General Anesthesia for Surgery' (LAS VEGAS) study, restricted to obese patients, with a predefined composite outcome of PPCs as primary end-point.
Results: We analysed 2012 obese patients from 135 hospitals across 29 countries in Europe, North America, North Africa, and the Middle East. Tidal volume was 8.8 [25^{th}–75^{th} percentiles: 7.8–9.9] ml kg^{-1} predicted body weight, PEEP was 4 [1–5] cm H_2O, and recruitment manoeuvres were performed in 7.7% of patients. PPCs occurred in 11.7% of patients and were independently associated with age (P<0.001), body mass index ≥40 kg m^{-2} (P=0.033), obstructive sleep apnoea (P=0.002), duration of anaesthesia (P<0.001), peak airway pressure (P<0.001), use of rescue recruitment manoeuvres (P<0.05) and routine recruitment manoeuvres performed by bag squeezing (P=0.021). PPCs were associated with an increased length of hospital stay (P<0.001).
Conclusions: Obese patients are frequently ventilated with high tidal volume and low PEEP, and seldom receive recruitment manoeuvres. PPCs increase hospital stay, and are associated with preoperative conditions, duration of anaesthesia and intraoperative ventilation settings. Randomised trials are warranted to clarify the role of different ventilatory parameters in obese patients.
Clinical trial registration: NCT01601223.

Keywords: anaesthesia; general; obesity; postoperative complications; perioperative care

Editor's key points

- The optimum settings for mechanical ventilation in obese patients during surgery are uncertain.
- This secondary analysis of obese patients in the LAS VEGAS study examined ventilator settings and the association with postoperative pulmonary complications.
- High tidal volumes and low PEEP were often used, and recruitment manoeuvres were uncommon.
- Postoperative pulmonary complications were associated with several factors including use of high peak airway pressure, and recruitment manoeuvres performed by squeezing the reservoir bag.
- Data from prospective randomised trials are needed to confirm these findings.

Intraoperative ventilatory support in obese patients produces several challenges.[1] In addition to impaired oxygen reserve,[2] obese patients often have comorbidities,[3] resulting in impaired respiratory mechanics during ventilation[4,5] and increasing the risk of postoperative pulmonary complications (PPCs).[6,7] Moreover, obese patients have reduced functional residual capacity, which is further decreased by supine positioning and general anaesthesia.[5] Indeed, atelectasis is frequently seen during intraoperative ventilation in obese patients,[8] and is likely to play a role in the development of PPCs.[9] Several ventilator strategies have been suggested to improve the postoperative outcome of obese patients, including the use of higher levels of PEEP,[10] preoxygenation with continuous positive airway pressure (CPAP) followed by PEEP,[9–11] and intraoperative recruitment manoeuvres.[12]

There has been increasing interest in so-called 'lung-protective' ventilation strategies in surgical patients in recent years. However, the largest study describing intraoperative ventilation and its relationship with body weight was limited to a single country, included only 298 patients, and did not investigate the associations with PPCs.[13] Typical settings suggested to protect lungs from ventilation-induced lung injury include the use of low tidal volumes (V_T) and moderate PEEP levels with or without recruitment manoeuvres.[14] It is uncertain which of these measures have the largest protective effect, but a recent individual patient data meta-analysis suggests that V_T reduction has a greater protective effect compared with higher PEEP levels.[15] Whether this also applies to obese patients is uncertain. In another recent meta-analysis, higher PEEP with a single recruitment manoeuvre resulted in improved oxygenation and respiratory system compliance, and reduced intraoperative atelectasis among obese patients undergoing surgery.[16] However, the impact of these intraoperative strategies in the postoperative course is unclear.

In this study, we analysed intraoperative ventilation data in obese patients enrolled in the 'Local ASsessment of VEntilatory management during General Anesthesia for Surgery' (LAS VEGAS) study.[7]

Our aims were: (1) to describe how obese patients are ventilated during general anaesthesia for surgery; and (2) to investigate the associations between intraoperative ventilatory settings with the occurrence of PPCs. We hypothesised that obese patients receive non-protective ventilation strategies, and that the occurrence of PPCs depends on the intraoperative ventilation settings.

Methods

Study design

This was a secondary analysis of the LAS VEGAS study[7] focusing on obese patients, and carried out according to the recommendations of the strengthening the reporting of observational studies in epidemiology (STROBE) statement (www.strobe-statemenent.org).[17]

The LAS VEGAS study was a worldwide international multicentre prospective 7 day observational study describing intraoperative ventilation practice and associations between ventilatory parameters and the development of PPCs, conducted in early 2013. The LAS VEGAS study was co-funded and endorsed by the European Society of Anaesthesiology, which had no role in the study design nor data analysis and interpretation. The LAS VEGAS study was registered at www.clinicaltrials.gov (NCT01601223). Each participating centre applied for approval from the respective ethical review board, and written informed consent was obtained where required.

Inclusion and exclusion criteria

The LAS VEGAS study enrolled consecutive patients requiring invasive ventilation during general anaesthesia for surgery during 1 week in the participating centres. Exclusion criteria of the LAS VEGAS study were: age <18 yr, mechanical ventilation in the previous 30 days, obstetric procedures, surgical procedures outside the operating room, cardiothoracic surgery with one-lung ventilation, and interventions requiring cardiopulmonary bypass. For this secondary analysis we excluded patients with BMI<30 kg m^{-2}.

Data collected

In the LAS VEGAS study, the following data were collected: baseline characteristics and demographic data; details on the surgical procedure; the assess respiratory risk in surgical patients in Catalonia (ARISCAT) score[18]; hourly vital parameters and ventilation data, including V_T, PEEP, peak pressure, fraction of inspired oxygen (FiO_2), ventilatory frequency, performance and type of recruitment manoeuvres; end-tidal CO_2 ($etCO_2$); and SpO_2. Collection of hourly parameters started at induction of anaesthesia (T=0) and hourly until the end of anaesthesia, up to the 7th h of surgery (T=7). We also reported the proportion of patients receiving V_T<8 ml kg^{-1} predicted body weight with PEEP≥8 cm H_2O, a 'lung-protective' strategy proposed by experts.[19]

Recruitment manoeuvres were classified as 'recruitment by ventilator' if performed using a temporary increase in PEEP, V_T, inspiratory pressure, or a combination of these, or 'recruitment by bag squeezing' if the manoeuvre was performed during a disconnection from the ventilator for manual ventilation using a ventilation bag or balloon. Recruitment manoeuvres were further scored as 'rescue' if the manoeuvre was not part of the planned ventilation strategy, or 'planned' if it was part of routine ventilation practice (i.e. performed regularly, or at a fixed time point, without a clinical indication; see Supplementary Table S1). We also determined if PEEP was increased after the recruitment manoeuvres.

Outcomes

The primary endpoint was a composite outcome of PPCs, combining the following postoperative events: unplanned need for oxygen (i.e. postoperative supplementary oxygen that was not part of usual patient care), unexpected postoperative invasive or non-invasive mechanical ventilation, acute respiratory failure, acute respiratory distress syndrome, pneumonia, or pneumothorax. The occurrence of each type of PPC was monitored until hospital discharge, but maximum up to postoperative day 5. Detailed definitions of the composites of PPCs and intraoperative complications are provided in Supplementary Tables S2 and S3.

Secondary endpoints included in-hospital mortality, length of hospital stay, and hospital-free days and alive at Day 28, and the following predefined intraoperative complications: desaturation; rescue recruitment manoeuvres; need for airway pressure reduction; expiratory flow limitation; hypotension; use of vasoactive drugs; and onset of a new cardiac arrhythmia.

Power calculation

The overall incidence of PPCs in the LAS VEGAS study was 10.4%.[7] Assuming at least the same incidence in obese patients, we needed to enrol 1500 obese patients to observe 150 events, and to be able to enter up to 15 covariates in a logistic regression model to determine the association with occurrence of a PPCs.[20]

Analysis plan

Patients with missing data concerning intraoperative ventilation parameters or outcome variables were excluded from the analysis. Patients were divided in obesity classes according to the World Health Organisation's definition (i.e. 30.0–34.9 kg m^{-2}, class I; 35–39.9 kg m^{-2}, class II; and ≥40 kg m^{-2}, class III).

Normality of distributions was assessed by inspection of quantile–quantile plots. Data are presented as medians (25th–75th percentiles) or proportions, when not otherwise specified. Differences between obesity classes over time in hourly collected variables were sought with a mixed linear model, including time points starting from 1 h after induction and excluding those with <25 patients per group. For all other descriptive statistics and multivariate models, repeated measurements at all time-points were aggregated using their median value over time. Time-to-event variables were graphed with Kaplan–Meier plots, and analysed with a mixed-effects Cox regression including the participating centre as random factor, to account for clustering. Differences between groups were analysed using with Fisher's (Freeman–Halton's), Mann–Whitney *U*-test, or Kruskal–Wallis test as appropriate, with Dunn *post hoc* correction for multiple comparisons. For mortality, the fragility index was also reported.[21]

A multivariate model was built to determine the associations between baseline data, obesity class, intraoperative V_T, PEEP level, peak pressure, FiO_2, and (type of) recruitment manoeuvres, and the development of PPCs. Main pre- and intraoperative factors known to affect incidence of PPC were included in the model to control for confounding factors.[18,22–25] All analyses were carried out with a mixed effects logistic regression that included a random effect to account for centre clustering. Only variables with *P*<0.20 in the univariate analysis entered the multivariate mixed model, then the model was refined with a backward stepwise variable selection process using the corrected Akaike information criterion (AICc), including V_T and PEEP with a forced-entry strategy. Further details on the variables entered in each model are provided in the online supplementary material. In a sensitivity analysis, the multivariate model was restricted to patients that underwent surgical procedures lasting ≥2 h.

In a *post hoc* analysis, PPCs were classified as 'mild' (i.e. only need for unplanned supplementary oxygen) or 'severe' (i.e. at least one other type of PPC), as previously reported in the LAS VEGAS study.[7] A multivariate model was developed with the same approach to identify factors associated with the incidence of severe PPCs. Because of the low number of observed severe PPCs, only variables that showed a significant association with all PPCs were entered into this model. Two other *post hoc* sensitivity analyses were performed to further investigate the association between recruitment manoeuvres and PPCs: a multivariate model excluding patients that underwent 'rescue' recruitment manoeuvres and a propensity score-matched cohort. The propensity score was estimated from a mixed-effects logistic regression including known non-modifiable risk factors for PPCs as fixed effects and centre number as random factor (details in the online supplement).

All analyses were performed with SPSS 21.0 (IBM, Chicago, IL, USA) and R 3.2.3 (The R Foundation for Statistical Computing, www.r-project.org). Statistical significance was considered for two-tailed $P<0.05$.

Results

Centres and patients

Patients came from 135 centres across 29 countries in Europe, North America, North Africa and Middle East. Supplementary Figure S1 illustrates the patients' inclusion flowchart: of 2012 obese patients, 1315, 449, and 248 were class I, II, and III, respectively. Patient characteristics and anaesthesia techniques are presented in Supplementary Table S4 and S5.

Ventilator settings and gas exchange

The most common ventilation mode was volume–controlled ventilation (Table 1). V_T was 525 (480–592) ml, resulting in 5.5 (4.9–6.3) ml kg^{-1} actual body weight, or 8.8 (7.8–9.9) ml kg^{-1} predicted body weight. PEEP was 4.0 (1.0–5.0) cm H_2O. Routine recruitment manoeuvres were performed in only 154/2012 (7.7%) patients, and in only 34/2012 (1.7%) patients PEEP was increased after the recruitment manoeuvre. Patients in higher obesity classes received higher V_T (Supplementary Fig. S2), higher PEEP levels, and received recruitment manoeuvres more frequently. In fact, 24.2% of patients received $V_T>10$ ml predicted body weight. Only 341/2012 (16.9%) patients received PEEP>5 cm H_2O, and as few as 31/2012 (1.5%) received both $V_T<8$ ml kg^{-1} predicted body weight and PEEP≥8 cm H_2O. There were no differences in FiO_2 and ventilatory frequency between the obese class groups, while the following changed significantly during the course of anaesthesia: V_T, PEEP, peak airway pressure, peak pressure minus PEEP, and FiO_2 (Fig. 1 and Supplementary Table S6). SpO_2 was lower in higher obesity classes, while $etCO_2$ in class I was lower than in class II and III (Supplementary Fig. S3). Nearly half (123/277) of the recruitment manoeuvres were classified as 'rescue' manoeuvres, while 66% (102/154) of the 'routine' and 50% (61/123) of the 'rescue' recruitment manoeuvres were performed by bag squeezing (Tables 1 and 2).

Outcomes

Out of 2012 patients, 236 (11.7%) developed one or more PPCs (Table 2), and the incidence was higher in higher obesity classes, being 10.3%, 12.2%, and 18.5% in class I, II, and III, respectively. No differences between obesity classes were observed in hospital length of stay and hospital-free days and alive at Day 28, but mortality was higher in class III patients (P=0.004, fragility index=2). As shown in Figure 2, hospital length of stay was 1 (0–4) days in patients without PPCs, while the occurrence of both mild and severe PPCs was associated with a longer hospitalisation: 3 (1–5) ($P<0.001$) and 3 (1–5) (P=0.014) days, respectively.

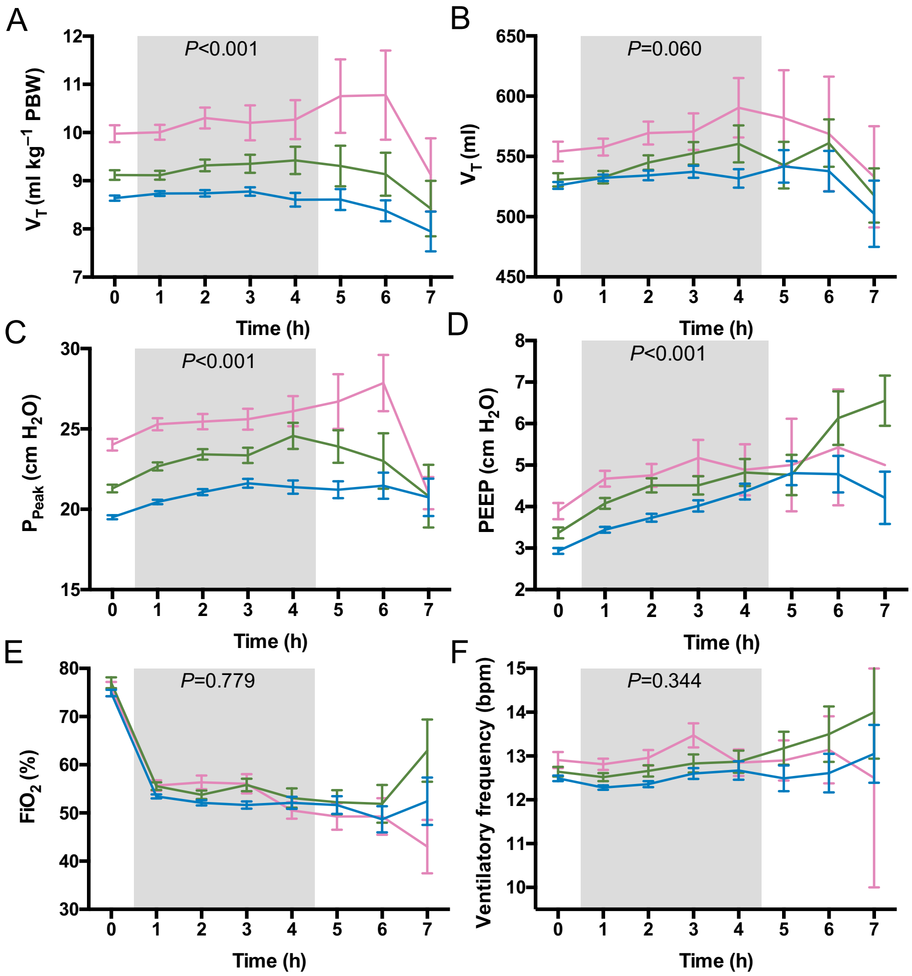
Intraoperative desaturation, rescue recruitment manoeuvres, need for airway pressure reduction, and expiratory flow limitation were more frequently reported in patients with higher obesity classes (Table 2).

Association between ventilator settings and development of PPCs

In the multivariate analysis, the following variables were associated with PPCs: age, obesity class III, obstructive sleep

Table 1 Intraoperative ventilator settings and parameters, in the entire cohort and in different obesity classes. $EtCO_2$, end-tidal CO2; FiO2, fraction of inspired oxygen; SpO_2, peripheral oxygen saturation. Values are median (25^{th} – 75^{th} percentile) or % (n/N). P-value refers to the between-groups Kruskal–Wallis, Fisher's, or χ^2 test, as appropriate

	All patients (n=2012)	Class I (n=1315)	Class II (n=449)	Class III (n=248)	P
Ventilation mode					
Volume-controlled ventilation	67.6 (1360/2012)	68.6 (902/1315)	66.1 (297/449)	64.9 (161/248)	0.754
Pressure-controlled ventilation	16.4 (330/2012)	16.0 (210/1315)	17.1 (77/449)	17.3 (43/248)	
Other modes	16.0 (322/2012)	15.4 (203/1315)	16.7 (75/449)	17.7 (44/248)	
Tidal volume					
Absolute (ml)	525.0 (480.0–592.0)	523.0 (475.0–587.0)	520.0 (480.8–590.0)	548.5 (490.0–600.0)	0.004
Per predicted body weight (ml kg^{-1})	8.8 (7.8–9.9)	8.6 (7.6–9.6)	8.9 (7.9–10.3)	9.8 (8.5–11.2)	<0.001
Per actual body weight (ml kg^{-1})	5.5 (4.9–6.3)	5.8 (5.3–6.4)	5.2 (4.6–5.8)	4.6 (4.0–5.3)	<0.001
Airway pressures					
PEEP (cm H_2O)	4.0 (1.0–5.0)	4.0 (0.0–5.0)	4.0 (2.0–5.0)	5.0 (2.0–6.9)	<0.001
Peak (cm H_2O)	21.0 (18.0–24.0)	20.0 (17.0–23.0)	22.0 (19.0–25.0)	25.0 (21.6–28.4)	<0.001
Compliance of the respiratory system					
Dynamic (ml cm H_2O^{-1})	30.8 (25.0–38.3)	31.8 (26.2–39.3)	29.4 (24.0–36.1)	27.8 (22.9–33.2)	<0.001
Static (ml cm H_2O^{-1})	36.7 (29.4–45.5)	38.0 (30.4–47.5)	35.0 (28.6–42.9)	33.1 (27.3–40.0)	<0.001
Ventilatory frequency (cycles min^{-1})	12.0 (12.0–13.5)	12.0 (12.0–13.0)	12.0 (12.0–14.0)	12.0 (12.0–14.0)	0.001
Minute ventilation (L min^{-1})	5.9 (6.6–7.3)	5.8 (6.5–7.2)	5.9 (6.6–7.3)	6.0 (7.1–7.8)	<0.001
Routine recruitment manoeuvres	7.7 (154/2012)	6.1 (80/1315)	9.1 (41/449)	13.3 (33/248)	
Not performed	92.3 (1858/2012)	93.9 (1235/1315)	90.9 (408/449)	86.7 (215/248)	<0.001
Ventilator	2.6 (52/2012)	1.9 (25/1315)	2.7 (12/449)	6.0 (15/248)	
Bag squeezing	5.1 (102/2012)	4.2 (55/1315)	6.5 (29/449)	7.3 (18/248)	
FiO_2 (%)	54.0 (48.0–70.0)	52.0 (46.5–70.0)	57.0 (50.0–72.5)	55.0 (50.0–70.4)	0.004
SpO_2 (%)	98.5 (97.5–99.5)	99.0 (98.0–100.0)	98.5 (97.5–99.0)	98.0 (97.0–99.0)	<0.001
$EtCO_2$ (kPa)	4.60 (4.20–4.93)	4.53 (4.20–4.91)	4.67 (4.27–5.05)	4.71 (4.27–5.11)	0.001



Time (h)	0	1	2	3	4	5	6	7
Class I	1305	1232	669	331	155	68	36	19
Class II	446	431	236	123	60	33	16	11
Class III	246	240	136	60	27	10	7	2
Total cases	1997	1903	1041	514	242	111	59	32

Fig 1. Mechanical ventilation settings over time. Blue line represents obesity class I, green line class II, and pink line class III. T 0 h represents the induction of general anaesthesia. *P*-values refer to the obesity class effect in a mixed effects model including obesity class, time, and an interaction term. Only the time-points highlighted in grey (i.e. those with at least 25 subjects) are included in the mixed model. Lines are means, error bars the standard error of mean. Except for the ventilatory frequency, the time factor was significant in all parameters ($P<0.05$). PBW, predicted body weight.

apnoea, duration of anaesthesia, peak pressure, routine recruitment manoeuvre with bag squeezing, and rescue recruitment manoeuvres both by bag squeezing and by the ventilator (Table 3).

Post hoc analyses

Of all PPCs, 76% were mild and 24% were severe. Rescue recruitment manoeuvres, obstructive sleep apnoea, and duration of anaesthesia were associated with development of severe PPCs (Table 3). In addition, routine recruitment manoeuvres by bag squeezing remained associated with the development of PPCs, when excluding patients that received ‘rescue’ recruitment manoeuvres (Supplementary Table S7). After propensity-score matching, ‘routine’ recruitment manoeuvres by bag squeezing remained associated with the development of PPCs (Supplementary Tables S8–10). The addition of a variable discriminating recruitment manoeuvres followed by a PEEP increase from those after which PEEP was left unchanged, did not change the results of the multivariate analysis ($P=0.98$ at the univariate analysis). Proportions of patients that developed PPCs in the different recruitment manoeuvres groups are shown in Supplementary Figure S4. In patients undergoing surgical procedures lasting ≥2 h, only obstructive sleep apnoea, duration of anaesthesia, ‘routine’ recruitment manoeuvres by bag squeezing and ‘rescue’ recruitment manoeuvres by the ventilator were associated with PPCs, while severe PPCs were associated with duration of

Table 2 Outcome measures. PPC, postoperative pulmonary complication. Values are median (25^{th}–75^{th} percentile) or % (*n*/*N*). P-value refers to the between-groups Kruskal–Wallis, Fisher (–Freeman–Halton), or χ^2 test, as appropriate. *Patients can have more than one type of PPC

	All patients (*n*=2012)	Class I (*n*=1315)	Class II (*n*=449)	Class III (N=248)	*P*
Intraoperative complications					
Desaturation	7.2% (145/2012)	5.7% (75/1315)	7.3% (33/449)	14.9% (37/248)	<0.001
Rescue recruitment manoeuvres	6.1% (123/2012)	5.5% (72/1315)	5.1% (23/449)	11.3% (27/248)	
Not performed	93.9% (1889/2012)	94.5% (1243/1315)	94.9% (426/449)	88.7% (220/248)	0.002
Ventilator	3.1% (62/2012)	2.5% (33/1315)	3.6% (16/449)	5.2% (13/248)	
Bag squeezing	3.0% (61/2012)	3.0% (39/1315)	1.6% (7/449)	6.0% (15/248)	
Need for airway pressure reduction	5.5% (110/2012)	4.1% (54/1315)	6.7% (30/449)	10.5% (26/248)	<0.001
Expiratory flow limitation	0.9% (18/2012)	0.7% (9/1315)	0.7% (3/449)	2.4% (6/248)	0.049
Hypotension	25.7% (517/2012)	24.9% (327/1315)	27.2% (122/449)	27.4% (68/248)	0.497
Use of vasoactive drugs	23.7% (477/2012)	23.2% (305/1315)	23.4% (105/449)	27.0% (67/248)	0.407
Onset of new arrhythmia	0.6% (12/2012)	0.7% (9/1315)	0.2% (1/449)	0.8% (2/248)	0.492
Postoperative outcome measures					
Composite outcomes					
Total PPC	11.7% (236/2012)	10.3% (135/1315)	12.2% (55/449)	18.5% (46/248)	0.001
Mild PPC (only unplanned O_2 therapy)	8.9% (179/2012)	8.1% (107/1315)	9.8% (44/449)	11.3% (28/248)	0.208
Severe PPC (excluding unplanned O_2 therapy only)	2.8% (57/2012)	2.1% (28/1315)	2.4% (11/449)	7.3% (18/248)	<0.001
Single outcomes*					
Unplanned O_2 therapy	10.0% (201/2012)	8.7% (115/1315)	11.1% (50/449)	14.5% (36/248)	0.015
Acute respiratory failure	1.8% (37/2012)	1.1% (14/1315)	1.8% (8/449)	6.0% (15/248)	<0.001
Need for mechanical ventilation	1.1% (23/2012)	1.1% (14/1315)	0.7% (3/449)	2.4% (6/248)	0.112
Acute respiratory distress syndrome	0.1% (2/2012)	0.1% (1/1315)	0.2% (1/449)	0.0% (0/248)	0.605
Pneumonia	0.4% (9/2012)	0.3% (4/1315)	0.2% (1/449)	1.6% (4/248)	0.028
Pneumothorax	0.0% (0/2012)	0.0% (0/1315)	0.0% (0/449)	0.0% (0/248)	>0.999
Other outcomes					
Hospital length of stay	1.0 (0.0–4.0)	1.0 (0.0–4.0)	1.0 (0.0–4.0)	1.0 (0.0–4.0)	0.983
In-hospital mortality	0.3% (6/2012)	0.2% (2/1315)	0.0% (0/449)	1.6% (4/248)	0.004
Hospital-free days at Day 28	26.0 (23.0–27.0)	26.0 (23.0–27.0)	26.0 (23.0–27.0)	26.0 (23.0–27.0)	0.926

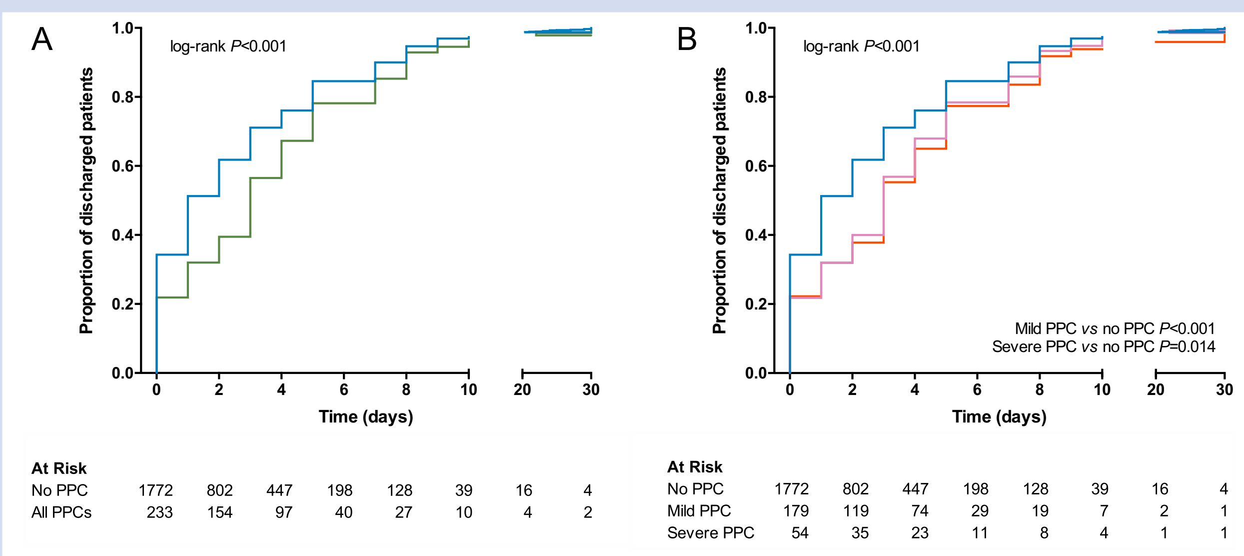


Fig 2. Kaplan–Meier plot for length of stay of all obese patients, stratified according to the type of postoperative pulmonary complication (PPC) developed. (a) no PPCs (blue line) *vs* all PPCs (green line). (b) No PPCs (blue line) *vs* mild (pink line) and severe (orange line) PPCs. Mild PPC: patients who required only oxygen therapy, not as part of the standard of care, without other PPCs. Severe PPC: patients who developed at least one of the following PPCs: acute respiratory failure, need for mechanical ventilation, acute respiratory distress syndrome, pneumonia, pneumothorax. *P*-values are calculated with a mixed effects Cox regression, including a random factor to account for centre clustering.

Table 3 Multivariate mixed logistic regression including a random effect to account for centre clustering. The following variables were entered in the univariate model: sex, age, obesity class, smoking status, obstructive sleep apnoea, type of surgery, type of surgical incision, epidural analgesia, duration of anaesthesia, use of neuromuscular blocking agents, neuromuscular block antagonism, presence of residual curarisation, fluids per kg body weight, use of opiates, peak pressure, ventilation mode, positive end-expiratory pressure, fraction of inspired oxygen, tidal volume per kg predicted body weight, type of routine recruitment manoeuvres, type of rescue recruitment manoeuvres. CI, confidence interval; OR, odds ratio; PPC, postoperative pulmonary complication; WHO, World Health Organisation

Variable	All PPCs OR (95% CI), P-value	Severe PPCs OR (95% CI), P value
Age	1.02 (1.01–1.04), <0.001	Not in the model
Obesity WHO Class		
Class I	1 (Reference)	Not in the model
Class II	1.05 (0.71–1.54), 0.82	
Class III	1.65 (1.04–2.61), 0.033	
Obstructive sleep apnoea	2.25 (1.34–3.79), 0.002	2.36 (1.29–4.34), 0.006
Duration of anaesthesia (h)	1.36 (1.24–1.49), <0.001	1.20 (1.07–1.34), 0.001
Peak airway pressure (cm H_2O)	1.07 (1.04–1.11), <0.001	Not in the model
Routine recruitment manoeuvres		
Not performed	1 (Reference)	Not in the model
Ventilator	0.47 (0.16–1.43), 0.19	
Bag squeezing	2.00 (1.11–3.61), 0.021	
Rescue recruitment manoeuvres		
Not performed	1 (Reference)	1 (Reference)
Ventilator	2.08 (1.04–4.18), 0.040	2.75 (1.23–6.15), 0.014
Bag squeezing	2.56 (1.26–5.16), 0.009	2.57 (1.13–5.83), 0.025

anaesthesia and both types of 'rescue' recruitment manoeuvres (Supplementary Table S11).

Discussion

The main findings of this secondary analysis of the LAS VEGAS study are that: (1) obese patients frequently receive ventilation with V_T that cannot be considered lung protective, relatively low PEEP levels, while seldom receiving recruitment manoeuvres; (2) larger V_T, higher PEEP levels and recruitment manoeuvres are applied in the higher obesity classes; (3) older patients, those with OSAS and those with BMI>40 kg m^{-2} are at higher risk of developing PPCs; and (4) PPCs are associated with an increased length of hospital stay. Peak airway pressure, use of recruitment manoeuvres by bag squeezing, and 'rescue' recruitment manoeuvres were the only ventilation parameters that had an independent association with the development of PPCs.

The present analysis uses a large database of prospectively collected data concerning intraoperative ventilation settings and parameters and PPCs, the LAS VEGAS study.[7] To our knowledge, it is also the largest prospective observational study of intraoperative ventilation and outcomes in obese patients, providing a unique opportunity to study their associations in this patient category. Data were collected in several centres in many countries, making its findings representative for the current ventilatory management of obese patients.

The results of this secondary analysis suggest that a relevant proportion of obese patients undergoing anaesthesia for surgery is still ventilated with a high V_T per predicted body weight, with further increase in higher obesity classes. This could suggest that V_T is still not titrated according to the predicted body weight, as presently recommended in the literature[19]: 75% of the patients received a V_T>8 ml kg^{-1} predicted body weight, which is larger than can be considered lung protective.[14,19] This is in line with the previous report of a study conducted in France that included 298 obese patients.[13] The choice to ventilate with high V_T is unlikely to be the consequence of impairments in gas exchange, as both $etCO_2$ and SpO_2 were adequate in most patients. Notably, changes in ventilator settings over time were small and actually showed an increase in V_T during intraoperative ventilation, rather than, for instance, an increase in ventilatory frequency.

Most patients' lungs were ventilated with low or moderate PEEP levels, and only 25% of the patients received PEEP>5 cm H_2O. Routine recruitment manoeuvres were performed in <10% of patients, and most of the manoeuvres were 'routine'. Notably, the proportions of patients receiving 'routine' or 'rescue' recruitment manoeuvres was comparable to the whole LAS VEGAS cohort.[7] These findings suggest that 'rescue' recruitment manoeuvres are seldom necessary during intraoperative ventilation, and not more frequent in obese patients.

A recent meta-analysis of randomised controlled trials in obese patients reported high variability in intraoperative ventilatory strategies, and concluded that there is weak evidence to support use of high PEEP to prevent PPCs and improve outcome of these patients.[26] Nonetheless, the present analysis shows that high PEEP levels are seldom applied in daily practice.

The incidence of PPCs in class I obesity was comparable to that reported in the entire LAS VEGA cohort comprising obese and non-obese patients,[7] but higher in class II and class III obesity. Among patients' characteristics, age, BMI≥40 kg m^{-2}, and obstructive sleep apnoea were associated with PPCs. V_T and PEEP were not associated with the development of PPCs, which seems to be in contrast with previous findings.[14,27] However, the range of V_T and PEEP in the present cohort was rather narrow: only 5% of the patients were ventilated with 6 ml kg^{-1} predicted body weight, which is associated with improved outcome in a recent randomised controlled trial in abdominal surgery in France.[28] The proportion of patients receiving PEEP≥10 cm H_2O, a level commonly investigated in randomised controlled trials in obese patients,[1,11,26,28] was only 2%. Notably, most of the previous studies focused on abdominal surgery, while the present study used a cohort of patients including a wide variety of surgical procedures. This all might at least partially explain the discrepancies with other studies and the limited use of higher PEEP levels. Of note, one recent international multicentre randomised controlled trial[29] showed that higher PEEP did not affect the incidence of PPCs, but this was a trial in non-obese patients.

The contribution of recruitment manoeuvres to the benefits of intraoperative protective ventilation remains unclear.[30] While the present analysis shows that recruitment manoeuvres are seldom performed, despite a pathophysiological rationale and some evidence supporting the use of recruitment manoeuvres in obese patients,[26] most recruitment manoeuvres were performed by bag squeezing. Bag squeezing could have several pitfalls that may discourage its use, in favour of manoeuvres consisting of stepwise transient changes of ventilator settings: bag squeezing requires a switch of the adjustable pressure limiting valve,[14,31] causing a temporary pressure decrease in the lungs if the tracheal tube is not clamped. This could result in de-recruitment of parts of the lungs; second, in general the operator has poor control over the pressure increase time and the maximum achieved pressure level, and in animal models of lung injury recruitment manoeuvres consisting of an abrupt increase of pressure resulted in increased lung inflammation.[32] Consequently, ventilator-based manoeuvres have recently been proposed as a preferred technique[14,31] and are always used in randomised controlled trials.[29]

In this cohort, use of 'routine' ventilator manoeuvres *per se* was not associated with an increased risk for PPCs, while use of bag squeezing was associated with the occurrence of PPCs. This finding was robust to centre-clustering correction, and the *post hoc* sensitivity analyses. The analysis suggests that this association was not limited to patients that received bag squeezing as a rescue measure, but also to those that underwent recruitment as a prophylactic strategy. This is the first report suggesting a direct effect on outcome of a specific recruitment manoeuvre technique, worthy of further investigation in preclinical and clinical studies. We hypothesise that, as was previously suggested,[14,31] ventilator-based recruitment manoeuvres allow a better control of peak pressure, and a smoother increase in airway pressures, which both could reduce lung injury. However, despite the complex statistical analysis adopted to correct for potential confounders, it must be stressed that the association reported in this study does not necessarily imply causality.

The most common PPC was unplanned need for supplementary oxygen. It has been argued that this complication should not be part of a composite of pulmonary endpoints, as this complication is usually suggested to be a mild complication only.[33] However, we found an association between unplanned need for supplementary oxygen and an increase in the length of stay, comparable to that observed for other PPCs, as recently reported in a large observational study in the USA.[34] Also, one could consider that need for supplementary oxygen is a consequence of postoperative atelectasis,[35] therefore providing a rationale for considering this event as a PPC when planning future clinical trials. Of note, an international randomised controlled trial (PROBESE) that currently investigates if high PEEP levels with recruitment manoeuvres protect against PPCs in obese patients during mechanical ventilation with low V_T, also included the need for supplementary oxygen in the PPC composite endpoint.[36] The importance of the postoperative period in outcomes after general anaesthesia in the obese is suggested by recent evidence which suggests lung protection strategies might consider include the postoperative period as well.[37]

The present analysis has several limitations. First, this was an unplanned secondary analysis of a larger study. To account for this, we developed a cautious statistical model, trying to compensate for potential confounding factors. Second, the observational design of the LAS VEGAS study has the intrinsic limitation of being unable to assess definitively causality, but rather only to observe associations. This is of particular relevance in studies concerning intraoperative mechanical ventilation, where the same factors that the clinicians use to overcome intraoperative gas exchange impairments, namely V_T and PEEP, have been linked themselves to the development of PPCs. Third, as the LAS VEGAS study mainly focused on intraoperative ventilation settings, we had limited or no information on certain modifiable risk factors or procedures known to affect the incidence of PPCs in obese patients, such as type of opioids and their use in the perioperative period,[38] use of nitrous oxide,[39] the clinical management and compliance to therapy of patients with obstructive sleep apnoea,[25] the use of perioperative CPAP[40] and patient positioning.[41]

In conclusion, during general anaesthesia for surgery, obese patients are frequently ventilated with high V_T, and low PEEP levels, and recruitment manoeuvres are seldom used. The incidence of PPCs is high and increases the length of hospital stay. Development of PPCs is associated with age, obstructive apnoeas, BMI$\geq$40 kg m^{-2}, duration of anaesthesia, high peak airway pressures and recruitment manoeuvres performed by bag squeezing. Randomised controlled trials are warranted to assess further whether ventilation strategies affect outcome in obese patients.

Authors' contributions

Full access to the database and take responsibility for the integrity of data: L.B., A.S.N.
Study design: L.B., A.S.N., T.B., M.G.A., M.J.S., P.P., S.N.T.H.
Interpretation of results: S.N.T.H., A.S.N., J.C., M.H., M.W.H., G.H.M., M.F.V.M., C.P., W.S., P.S., H.W., M.G.A., P.P., M.J.S.
Manuscript draft: L.B., A.S.N., T.B., M.G.A., M.J.S., P.P., S.N.T.H.
Statistical analysis: L.B., A.S.N.
Steering committee of the LAS VEGAS study: S.N.H., A.S.N., J.C., M.H., M.W.H., G.H.M., M.F.V.M., C.P., W.S., P.S., H.W., M.G.A., P.P., M.J.S.
Data collection: S.N.T.H., A.S.N., J.C., M.H., M.W.H., G.H.M., M.F.V.M., C.P., W.S., P.S., H.W., M.G.A., P.P., M.J.S.
Revising paper: all authors.

Acknowledgements

M.F.V.M. was supported by National Institutes of Health − National Heart, Lung, and Blood Institute (NIH-NHLBI) grant 1R34HL123438.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.bja.2018.04.015.

Declaration of interest

The authors declare that they have no conflicts of interest.

Funding

European Society of Anaesthesiology.

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Handling editor: J.P. Thompson