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RESEARCH ARTICLE

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Intraoperative ventilator settings and their association with postoperative pulmonary complications in neurosurgical patients: post-hoc analysis of LAS VEGAS study

Chiara Robba^{1*}, Sabine N. T. Hemmes^{2,3}, Ary Serpa Neto^{2,4}, Thomas Bluth⁵, Jaime Canet⁶, Michael Hiesmayr⁷, M. Wiersma Hollmann³, Gary H. Mills⁸, Marcos F. Vidal Melo⁹, Christian Putensen¹⁰, Samir Jaber¹¹, Werner Schmid⁷, Paolo Severgnini¹², Hermann Wrigge¹³, Denise Battaglini^{1,14}, Lorenzo Ball^{1,14}, Marcelo Gama de Abreu⁵, Marcus J. Schultz^{2,15}, Paolo Pelosi^{1,14}, FERS for the LAS VEGAS investigators and the PROtective VEntilation Network and the Clinical Trial Network of the European Society of Anaesthesiology

Abstract

Background: Limited information is available regarding intraoperative ventilator settings and the incidence of postoperative pulmonary complications (PPCs) in patients undergoing neurosurgical procedures. The aim of this post-hoc analysis of the 'Multicentre Local ASsessment of VEntilatory management during General Anaesthesia for Surgery' (LAS VEGAS) study was to examine the ventilator settings of patients undergoing neurosurgical procedures, and to explore the association between perioperative variables and the development of PPCs in neurosurgical patients.

Methods: Post-hoc analysis of LAS VEGAS study, restricted to patients undergoing neurosurgery. Patients were stratified into groups based on the type of surgery (brain and spine), the occurrence of PPCs and the assess respiratory risk in surgical patients in Catalonia (ARISCAT) score risk for PPCs.

Results: Seven hundred eighty-four patients were included in the analysis; 408 patients (52%) underwent spine surgery and 376 patients (48%) brain surgery. Median tidal volume (V_T) was 8 ml [Interquartile Range, IQR = 7.3–9] per predicted body weight; median positive end–expiratory pressure (PEEP) was 5 [3 to 5] cmH₂O. Planned recruitment manoeuvres were used in the 6.9% of patients. No differences in ventilator settings were found among the sub-groups. PPCs occurred in 81 patients (10.3%). Duration of anaesthesia (odds ratio, 1.295 [95% confidence interval 1.067 to 1.572]; $p = 0.009$) and higher age for the brain group (odds ratio, 0.000 [0.000 to 0.189]; $p = 0.031$), but not intraoperative ventilator settings were independently associated with development of PPCs.

Conclusions: Neurosurgical patients are ventilated with low V_T and low PEEP, while recruitment manoeuvres are seldom applied. Intraoperative ventilator settings are not associated with PPCs.

Keywords: LAS VEGAS, Mechanical ventilation, Postoperative pulmonary complications, Neurosurgery

* Correspondence: kiarobba@gmail.com

¹Anaesthesia and Intensive Care, San Martino Policlinico Hospital, IRCCS for Oncology and Neurosciences, Largo Rosanna Benzi 8, 16131 Genoa, Italy
Full list of author information is available at the end of the article



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Background

Lung-protective ventilation strategies are increasingly used in surgical patients [1, 2]. Typical lung-protective strategies include the use of a low tidal volume (V_T) and a low plateau pressure (Pplat), with moderate positive end-expiratory pressure (PEEP) and use of recruitment manoeuvres (RM) if needed [1, 2]. Among these settings, a low V_T seems to have the most protective effects compared with moderate or high PEEP [3, 4].

However, lung-protective ventilation is rarely used in brain injured patients, in whom median V_T is generally 9 ml/kg of predicted body weight (PBW) [5]. The role of intraoperative ventilator settings and their potential impacts on the development of postoperative complications (PPCs) has been scarcely evaluated in neurological patients [6]. Typically, patients with neurosurgical pathologies have been excluded from most trials on protective intraoperative ventilation. This may be because lung-protective strategies could have detrimental effects on cerebrovascular physiology, and thus might be potentially contraindicated in acute neurosurgical patients [7]. Moreover, just few and inconclusive data exist regarding the ventilator settings applied in patients undergoing spinal surgery and the incidence of PPCs in this population [8, 9].

We therefore conducted a post-hoc analysis of the 'Local ASsessment of Ventilatory management during General Anaesthesia for Surgery-study' (LAS VEGAS), a conveniently sized international observational study in the operating rooms of patients receiving mechanical ventilation [10]. We focused on neurosurgical patients, including patients undergoing brain or spine surgery. The aims of this analysis were to assess which ventilator strategies were used in neurosurgical patients during general anaesthesia, and to assess the incidence of PPCs and risk factors (including type of surgery, ventilator settings, risk for PPCs) associated with the development of PPCs. The main hypothesis tested was that neurosurgical patients are ventilated with high tidal volume and low positive end expiratory pressure, and that intraoperative ventilator settings can have an effect on PPCs development.

Methods

LAS VEGAS study

This article is reported as per Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines (www.strobe-statement.org) (Electronic supplementary material ESM Table S1).

LAS VEGAS [8] was an international multicentre observational prospective study (registered at www.clinicaltrials.gov (study identifier NCT01601223)), endorsed and supported by the European Society of Anaesthesiology and the Amsterdam University Medical Centres,

location AMC, Amsterdam, The Netherlands. Details about the LAS VEGAS study collaborators, participating centres and hospital characteristics of participating centres are reported in ESM Tables S2a, b and S3.

All adult patients requiring invasive ventilation for surgical procedures in a time window of 7 days were included. Exclusion criteria were: age under 18 years, obstetric procedures, recent ventilation before surgery (< 28 days), surgical procedures not performed in the operating room, and interventions requiring cardiopulmonary bypass.

For this study, we restricted the analysis to patients receiving intraoperative ventilation for neurosurgical procedures (brain or spine surgery) (ESM Flow Chart).

Data collection

After inclusion, the following data were collected: patients' baseline and demographic characteristics; the assess respiratory risk in surgical patients in Catalonia (ARISCAT) score [11]; American Society of Anaesthesiologists (ASA) scale; details on the surgical procedure including intraoperative hourly vital parameters and ventilation data (mode of ventilation, fraction of inspired oxygen (FiO_2), V_T , PEEP, peak pressure (Ppeak), respiratory rate (RR)), end-tidal CO_2 (ETCO₂), oxygen saturation (SpO₂), number and type of recruitment manoeuvres, and intraoperative complications.

Recruitment manoeuvres were defined as 'rescue' when the recruitment manoeuvre was not part of the planned ventilation strategy and defined as 'planned' if it was part of routine ventilation practice (ESM Table S4). Mechanical power (MP) was calculated according to the following formula [12]: $0.098 \times V_T \times RR \times [P_{peak} \times (P_{plat} - PEEP)/2]$. Hourly data were collected starting at the induction of anaesthesia (T1/40) and then hourly until the end of anaesthesia, up to the 7th hour of surgery (T1/47).

Endpoints

The primary endpoint was to describe the current practice and ventilator strategies in patients undergoing neurosurgical interventions, in particular ventilator mode, V_T , PEEP, driving pressure, Ppeak and Pplat and RR, as well as mechanical power.

The secondary outcome was to assess the prevalence of PPCs and the association with preoperative and intraoperative variables including mechanical ventilator settings, type of surgery, ARISCAT score. Detailed definitions of the composites of PPCs and severe PPCs are provided in ESM Table S5. Intraoperative complications included desaturation, rescue recruitment manoeuvres, need for airway pressure reduction, expiratory flow limitation, hypotension and use of vasoactive drugs, onset of a new cardiac arrhythmia (ESM Table S6). The

occurrence of each type of PPC was monitored until hospital discharge, but maximum up to postoperative day 5.

Other secondary endpoints included the occurrence of severe PPCs, intraoperative complications, in-hospital mortality and length of hospital stay.

Statistical analysis

Patients were stratified into groups based on type of surgery (brain and spine), the occurrence of PPCs and risk for PPC according to ARISCAT (low risk [ARISCAT < 26] vs. moderate-to-high risk [ARISCAT \geq 26]). Continuous variables are expressed as mean \pm standard deviation (SD) or median (interquartile range [IQR]) per variable distribution. Discrete variables are presented as percentages. Baseline characteristics among type of neurosurgery were compared by either t-test, Wilcoxon rank-sum test, or chi-squared tests, as appropriate. The effect of type of neurosurgery on the incidence (per 10 P-days) of in-hospital PPC, severe PPC, and discharged alive was evaluated using log-rank test (stratified by centre); differences in survival probabilities and hospital discharge were depicted with an outcome-specific Kaplan-Meier plot.

A multivariable regression model was built, with PPC as dependent variables. Because this outcome is binary (0/1), a logistic regression analysis was applied. Candidate covariates were chosen based on previous medical knowledge, independent of their *p*-value. From this preliminary selection, those variables with *P* < 0.20 in the univariate analysis were preferentially chosen for the stepwise procedure. Then, a reduced and parsimonious model was derived using backward stepwise selection. During this selection process, the linearity assumption for continuous variables was tested and transformed, if appropriate, with fractional polynomials (14). In all regression models, the Huber/White/sandwich estimator of variance correction was applied to account for any clustering effect due to centre sampling.

We set a two-sided *p* value of < 0.05 as the threshold for statistical significance. Stata 15.1 (Stata Statistical Software, release 15 [2017] (Stata Corp LP, College Station, TX, USA), and R (Version 3.5.3; R Foundation for Statistical Computing, Vienna, Austria) were used.

Results

A total of 784 patients were included in the analysis. Of these, 408 (52%) underwent spine surgery and 376 (48%) brain surgery. The characteristics of the patients according to subgroups are described in Table 1. Patients with moderate-to-high risk for PPCs- compared to those at low risk were older, with a higher incidence of co-morbidities (in particular chronic kidney failure), worse ASA physical status, and worse pre-hospital functional

status and preoperative conditions (as for laboratory tests and vital signs) (Table 1). Patients who developed PPCs were older, with more frequent co-morbidities (in particular respiratory and cardiological), worse ASA and preoperative functional status (Table 1).

Ventilation variables and intraoperative characteristics

Most of the patients underwent elective surgical procedure (72%), with a median surgical duration of 95 min (1st-3rd interquartile range IQR = 60–160) and median anaesthetic time of 126 min (IQR = 90–192.8 min). The most common ventilation mode was volume-controlled ventilation (VCV) (Table 2). VCV was more commonly used in patients undergoing brain surgery. Median V_T was 510 ml (Interquartile range, IQR 475–575), thus resulting in 8 ml/kg predicted body weight (IQR = 7.3–9). Median PEEP level was 5 cmH₂O (IQR 3–5), Ppeak was 18 cmH₂O (IQR = 15–21) and driving pressure was 12 (IQR = 11–15) cmH₂O (Table 2).

Routine RMs were performed in 54 patients (6.9%). Unplanned RMs occurred in 1.4% of cases. No statistical difference was found between the spine and brain surgery group or regarding the ventilator settings (Table 2, ESM Figure S1). EtCO₂ values were significantly lower in the brain surgery group compared with the spine surgery group (*p* = 0.001). Patients who developed PPCs received a higher amount of fluids compared to those with no PPCs (Table 2), but no differences were found in the ventilator settings between the two groups (Fig. 1).

Scatter plots showing the combinations of V_T with PEEP, driving pressure, Ppeak, and respiratory rate in patients who developed versus patients who did not develop PPCs, between the spine and brain group, and in patients with low risk [ARISCAT < 26] vs. moderate-to-high risk [ARISCAT \geq 26] are shown in Fig. 2, ESM Figures S2, S3.

Occurrence of PPCs, intraoperative complications and outcomes

Among the 784 patients included in the analysis, 81 (10.4%) developed PPCs (Table 2). PPCs occurred mainly on day 3. No differences between the surgical groups were found as for probability of PPCs occurrence and hospital length of stay (ESM Figure S4).

Patients with ARISCAT \geq 26 showed an increased probability of PPCs occurrence compared to patients at lower risk (HR 2.50; 95% CI 1.61–3.58, *p* < 0.000), and of longer hospital length of stay (HR 0.81; 95% CI 0.69.0.97, *p* = 0.019) (ESM Figure S4).

Intraoperative episodes of hypotension and the need for vasoactive drugs during the procedure were frequent, especially in the spine group compared to the brain group (38.7% vs 31.2% for hypotension; *p* = 0.028 and 34.6% vs 27.7% for vasoactive drugs, *p* = 0.04,

Table 1 Pre-Operative Characteristics of the Patients According to Subgroups

	All Patients	Brain	Spine	<i>p</i> value	All patients	PPC	No PPC	<i>p</i> value	All patients	ARISCAT < 26	ARISCAT ≥ 26	<i>p</i> value
n (%)	784 (100)	376 (48)	408 (52)		777 (100.0)	81 (10.4)	696 (89.6)		548 (73.3)	200 (26.7)	748 (100.0)	
Demographics												
Age, years, mean (SD)	53 (16)	52 (16)	54 (15)	0.104	53 (16)	59 (15)	52 (16)	0.000	50 (15)	51 (15)	63 (16)	0.000
Gender, n (%)												
Male	392 (50)	183 (48.7)	209 (51.2)	0.060	392 (50.5)	37 (45.7)	355 (51.0)	0.072	285 (52.0)	97 (48.5)	382 (51.1)	0.065
Ethnicity, n (%)												
Black	2 (0.3)	0 (0.0)	2 (0.5)		2 (0.3)	2 (2.5)	0 (0.0)		1 (0.2)	1 (0.5)	2 (0.3)	0.663
Caucasian	709 (90.4)	340 (90.4)	369 (90.4)		704 (90.6)	71 (87.7)	633 (90.9)		493 (90.0)	183 (91.5)	676 (90.4)	
Asian	4 (0.5)	1 (0.3)	3 (0.7)		4 (0.5)	1 (1.2)	3 (0.4)		4 (0.7)	0 (0.0)	4 (0.5)	
Other	33 (4.2)	13 (3.5)	20 (4.9)		33 (4.2)	2 (2.5)	31 (4.5)		26 (4.7)	6 (3.0)	32 (4.3)	
Anthropometry												
Height, cm, mean (SD)	170 (10)	170 (10)	170 (9)	0.416	170 (10)	169 (10)	170 (10)	0.421	170 (10)	169 (10)	170 (10)	0.243
Weight, kg, mean (SD)	79 (17)	80 (18)	78 (16)	0.309	79 (17)	80 (18)	79 (17)	0.597	79 (17)	79 (17)	79 (17)	0.677
BMI, kg/m ² , mean (SD)	27.3 (5.8)	27.7 (6.6)	27.0 (4.9)	0.148	27.3 (5.8)	28.3 (6.5)	27.2 (5.7)	0.141	27.3 (6.0)	27.4 (5.0)	27.3 (5.8)	0.874
Co-morbidities, n (%)												
Co-morbidities	161 (20.5)	84 (22.3)	77 (18.9)	0.230	160 (20.6)	30 (37.0)	130 (18.7)	0.000	98 (17.9)	59 (29.5)	157 (21.0)	0.001
COPD	47 (6.0)	21 (5.6)	26 (6.4)	0.643	47 (6.0)	8 (9.9)	39 (5.6)	0.127	32 (5.8)	15 (7.5)	47 (6.3)	0.407
Respiratory	19 (2.4)	8 (2.1)	11 (2.7)	0.605	19 (2.4)	5 (6.2)	14 (2.0)	0.022	12 (2.2)	7 (3.5)	19 (2.5)	0.313
Liver cirrhosis	4 (0.5)	2 (0.5)	2 (0.5)	0.935	4 (0.5)	0 (0.0)	4 (0.6)	0.494	3 (0.5)	1 (0.5)	4 (0.5)	0.937
Chronic kidney failure	16 (2.0)	4 (1.1)	12 (2.9)	0.063	16 (2.1)	4 (4.9)	12 (1.7)	0.054	6 (1.1)	9 (4.5)	15 (2.0)	0.003
Heart failure	45 (5.7)	27 (7.2)	18 (4.4)	0.096	45 (5.8)	10 (12.3)	35 (5.0)	0.008	29 (5.3)	14 (7.0)	43 (5.7)	0.374
Neuro disease	12 (1.5)	8 (2.1)	4 (1.0)	0.191	12 (1.5)	2 (2.5)	10 (1.4)	0.476	11 (2.0)	1 (0.5)	12 (1.6)	0.146
Pre-operative medical history												
ASA physical status, n (%)	214 (27.4)	96 (25.5)	118 (29.1)	0.007	208 (26.8)	14 (17.5)	194 (27.9)	0.000	165 (30.1)	29 (14.6)	194 (26.0)	0.000
ASA I	395 (50.5)	178 (47.3)	217 (53.4)		395 (51.0)	33 (41.3)	362 (52.1)		292 (53.3)	90 (45.2)	382 (51.1)	
ASA II	395 (50.5)	178 (47.3)	217 (53.4)		153 (19.7)	28 (35.0)	125 (18.0)		85 (15.5)	68 (34.2)	153 (20.5)	
ASA III	154 (19.7)	87 (23.1)	67 (16.5)		18 (2.3)	5 (6.3)	13 (1.9)		6 (1.1)	11 (5.5)	17 (2.3)	
ASA IV	18 (2.3)	14 (3.7)	4 (1.0)		1 (0.1)	0 (0.0)	1 (0.1)		0 (0.0)	1 (0.5)	1 (0.1)	
ASA V	1 (0.1)	1 (0.3)	0 (0.0)		208 (26.8)	14 (17.5)	194 (27.9)		165 (30.1)	29 (14.6)	194 (26.0)	
Functional status, n (%)				0.004				0.000				0.006
Independent	708 (90.3)	327 (87.0)	381 (93.4)		702 (90.3)	67 (82.7)	635 (91.2)		506 (92.3)	168 (84.0)	674 (90.1)	
Partially dependent	62 (7.9)	38 (10.1)	24 (5.9)		62 (8.0)	12 (14.8)	50 (7.2)		33 (6.0)	27 (13.5)	60 (8.0)	
Totally dependent	13 (1.7)	11 (2.9)	2 (0.5)		12 (1.5)	2 (2.5)	10 (1.4)		8 (1.5)	5 (2.5)	13 (1.7)	
ARISCAT score, median (IQR)	215 (27.4)	102 (27.1)	113 (27.7)	0.000	16 (3; 26)	23 (11; 32)	16 (3; 24)	0.002	8 (3; 18)	31 (26; 37)	16 (3; 26)	0.000
Smoking, n (%)	40 (5.1)	23 (6.1)	17 (4.2)	0.859	214 (27.5)	22 (27.2)	192 (27.6)	0.442	165 (30.1)	44 (22.0)	209 (27.9)	0.029
Transfusion (< 24 h), n (%)	5 (0.6)	3 (0.8)	2 (0.5)	0.215	39 (5.0)	6 (7.4)	33 (4.7)	0.000	16 (2.9)	22 (11.0)	38 (5.1)	0.000

Table 1 Pre-Operative Characteristics of the Patients According to Subgroups (Continued)

	All Patients	Brain	Spine	<i>p</i> value	All patients	PPC	No PPC	<i>p</i> value	All patients	ARISCAT < 26	ARISCAT ≥ 26	<i>p</i> value
RBC transfusion (< 24 h)	28 (3.6)	16 (4.3)	12 (2.9)	0.589	5 (0.6)	1 (1.2)	4 (0.6)	0.722	1 (0.2)	4 (2.0)	5 (0.7)	0.007
Respiratory infection (< 30d), n (%)	1 (0.1)	0 (0.0)	1 (0.2)	0.322	28 (3.6)	3 (3.7)	25 (3.6)	0.002	7 (1.3)	19 (9.5)	26 (3.5)	0.000
Laboratory tests and vital signs												
Pre-operative values												
SpO ₂ , %, median (IQR)	97 (96; 99)	97 (96; 98)	97 (96; 99)	0.230	97 (96; 99)	97 (95; 98)	98 (96; 99)	0.002	98 (96; 99)	96 (94; 98)	97 (96; 99)	0.000
Hb, (g/dL), mean (SD)	13.8 (1.8)	13.8 (1.8)	13.9 (1.8)	0.540	13.8 (1.8)	13.7 (2.0)	13.8 (1.8)	0.442	14.0 (1.6)	13.3 (2.1)	13.8 (1.8)	0.000
WBC, (cell/mm ³), mean (SD)	7879 (3497)	8199 (3097)	7568 (3825)	0.019	7891 (3503)	9261 (6168)	7721 (2978)	0.000	7696 (3362)	8438 (3845)	7905 (3518)	0.015
Creatinine, (mg/dL), mean (SD)	0.89 (0.69)	0.90 (0.86)	0.88 (0.49)	0.758	0.89 (0.69)	0.87 (0.28)	0.90 (0.73)	0.722	0.87 (0.59)	0.95 (0.91)	0.89 (0.70)	0.192
Surgical characteristics												
Condition, n (%)				0.318				0.140				0.000
Elective	717 (91.5)	338 (89.9)	379 (92.9)		712 (91.6)	73 (90.1)	639 (91.8)		513 (93.6)	172 (86.0)	685 (91.6)	
Urgency	50 (6.4)	28 (7.4)	22 (5.4)		49 (6.3)	4 (4.9)	45 (6.5)		31 (5.7)	16 (8.0)	47 (6.3)	
Emergency	17 (2.2)	10 (2.7)	7 (1.7)		16 (2.1)	4 (4.9)	12 (1.7)		4 (0.7)	12 (6.0)	16 (2.1)	
Planned duration, hours, n (%)				0.000				0.000				0.000
0	1 (0.1)	1 (0.3)	0 (0.0)		1 (0.1)	0 (0.0)	1 (0.1)					
≤ 2	432 (55.1)	186 (49.5)	246 (60.3)		426 (54.8)	36 (44.4)	390 (56.0)		378 (69.0)	25 (12.5)	403 (53.9)	
2–3	201 (25.6)	90 (23.9)	111 (27.2)		201 (25.9)	15 (18.5)	186 (26.7)		124 (22.6)	73 (36.5)	197 (26.3)	
> 3	150 (19.1)	99 (26.3)	51 (12.5)		149 (19.2)	30 (37.0)	119 (17.1)		46 (8.4)	102 (51.0)	148 (19.8)	
Antibiotic prophylaxis, n (%)	711 (90.9)	338 (90.1)	373 (91.6)	0.462	705 (91.0)	74 (91.4)	631 (90.9)	0.897	500 (91.4)	184 (92.0)	684 (91.6)	0.796

P value refers to the between-groups with Fisher-Freeman-Halton Exact test, Mann Whitney u-test, or Kruskal Wallis test, as appropriate. *N* Number, *IQR* Interquartile range, *SD* Standard deviation, *h* Hours, *d* Days, *PPC* Postoperative pulmonary complications, *COPD* Chronic obstructive pulmonary disease, *ASA* American society of anesthesiologists, *RBC* Blood red cells, *SpO₂* Blood oxygen saturation, *Hb* Hemoglobin, *WBC* White blood cells

respectively) (Table 3). The incidence of desaturation was less frequent than hypotension or need of vasoactive drugs. No differences were found in terms of mortality or hospital length of stay in patients who developed and did not develop PPCs or the type of surgery. Patients with ARISCAT ≥ 26 compared to those with ARISCAT < 26, had longer LOS and higher hospital mortality (Table 3).

Risk factors for PPCs

Multivariable logistic regression was used to identify the predictors of PPCs. Duration of anaesthesia was independently associated for the development of PPCs. Analysing the predictors for type of neurosurgery, for age we found a significantly effect in the brain group (the omnibus *p*-value for the neurosurgery-age interaction was *p* = 0.031), but not in the spine group. (Table ESM S7, ESM Figure S5, Fig. 3). The effect of age on PPC in the

brain group was significant at age above 62 (ESM Figure S5).

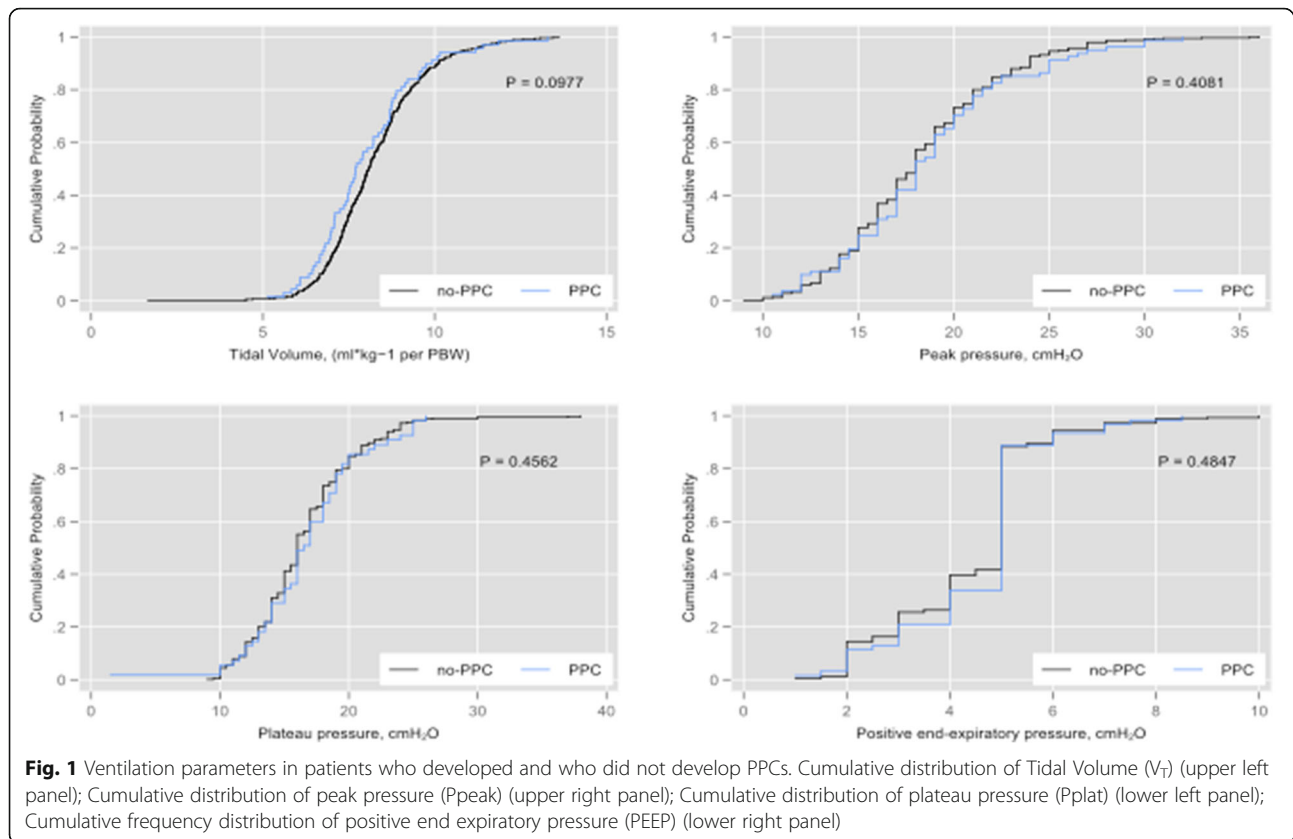
Discussion

Our results show that: 1) Neurosurgical patients are ventilated with low V_T and low PEEP levels, while recruitment manoeuvres are seldom applied. No clinically significant differences exist between the intraoperative ventilator settings and the incidence of PPCs between the subgroups analysed, and in patients undergoing brain and spine surgery. ETCO₂ levels are generally medium-low, especially in the brain surgery group; 2) PPCs are common, with similar incidence in the spine- and the brain surgical groups; 3) Intraoperative complications occur in a large number of patients (44% of the total population); of these, hypotension and the need for vasopressors are common; 4) Increasing age (for the brain group) and long surgical procedures are independently associated with development of PPCs.

Table 2 Intra-Operative Characteristics of the Patients According to Subgroups

	All Patients	Brain	Spine	<i>p</i> value	All patients	PPC	No PPC	<i>p</i> value	All patients	ARISCAT < 26	ARISCAT ≥ 26	<i>p</i> value
n (%)	784 (100.0)	376 (48.0)	408 (52.0)		777 (100.0)	81 (10.4)	696 (89.6)		748 (100.0)	548 (73.3)	200 (26.7)	
Ventilation and vital signs												
Ventilatory mode, n (%)				0.000				0.376				0.452
Volume controlled	494 (63.8)	259 (70.2)	235 (58.0)		488 (63.5)	50 (64.1)	438 (63.5)		467 (63.2)	341 (62.9)	126 (64.0)	
Pressure controlled	149 (19.3)	42 (11.4)	107 (26.4)		149 (19.4)	20 (25.6)	129 (18.7)		146 (19.8)	112 (20.7)	34 (17.3)	
Pressure support	3 (0.4)	2 (0.5)	1 (0.2)		3 (0.4)	0 (0.0)	3 (0.4)		3 (0.4)	1 (0.2)	2 (1.0)	
Spontaneous	64 (8.3)	21 (5.7)	43 (10.6)		64 (8.3)	4 (5.1)	60 (8.7)		60 (8.1)	42 (7.7)	18 (9.1)	
Other	64 (8.3)	45 (12.2)	19 (4.7)		64 (8.3)	4 (5.1)	60 (8.7)		63 (8.5)	46 (8.5)	17 (8.6)	
V _T , ml, median (IQR)	510 (475; 575)	511 (475; 584)	506 (471; 562)	0.183	510 (475; 575)	500 (458; 560)	513 (475; 575)	0.096	510 (475; 572)	506 (475; 565)	525 (480; 590)	0.142
V _T , (ml/kg PBW), median (IQR)	8.0 (7.3; 9.0)	8.2 (7.3; 9.1)	8.0 (7.2; 8.9)	0.150	8.0 (7.3; 9.0)	7.7 (7.0; 8.8)	8.1 (7.3; 9.0)	0.060	8.0 (7.3; 9.0)	8.0 (7.3; 9.0)	8.0 (7.3; 9.1)	0.420
P _{Peak} , cmH ₂ O, median (IQR)	18 (15; 21)	18 (15; 21)	18 (16; 21)	0.225	18 (15; 21)	18 (16; 21)	18 (15; 21)	0.183	18 (15; 21)	18 (15; 21)	18 (16; 21)	0.061
P _{Plateau} , cmH ₂ O, median (IQR)	16 (14; 19)	16 (14; 19)	16 (14; 18)	0.201	16 (14; 19)	17 (14; 19)	16 (14; 19)	0.150	16 (14; 19)	16 (14; 18)	17 (15; 19)	0.012
PEEP, cmH ₂ O, median (IQR)	5.0 (3.0; 5.0)	5.0 (4.0; 5.0)	5.0 (3.0; 5.0)	0.669	5.0 (3.0; 5.0)	5.0 (4.0; 5.0)	5.0 (3.0; 5.0)	0.225	5.0 (3.0; 5.0)	5.0 (3.0; 5.0)	5.0 (3.3; 5.0)	0.156
DP, cmH ₂ O, median (IQR)	12 (11; 15)	13 (11; 15)	12 (10; 16)	0.585	12 (11; 15)	13 (11; 15)	12 (11; 15)	0.201	12 (11; 15)	12 (11; 15)	14 (11; 17)	0.009
RR, bpm, mean (SD)	12.0 (1.5)	12.1 (1.5)	12.0 (1.4)	0.237	12.0 (1.5)	12.1 (1.7)	12.0 (1.4)	0.669	12.0 (1.4)	12.1 (1.3)	11.9 (1.7)	0.188
FiO ₂ , %, median (IQR)	50 (43; 65)	50 (40; 60)	50 (44; 68)	0.021	50 (43; 64)	50 (46; 65)	50 (42; 63)	0.585	50 (43; 65)	50 (43; 70)	50 (45; 60)	0.143
SpO ₂ , %, median (IQR)	99 (98; 100)	99 (99; 100)	99 (98; 100)	0.169	99 (98; 100)	99 (98; 100)	99 (98; 100)	0.237	99 (98; 100)	99 (99; 100)	99 (98; 100)	0.069
ETCO ₂ , mmHg, mean (SD)	33 (4)	32 (4)	33 (5)	0.001	33 (4)	33 (4)	33 (5)	0.554	33 (4)	33 (4)	33 (5)	0.549
MP, J/min, median (IQR)	6.6 (4.9; 9.2)	6.9 (5.0; 10.3)	6.2 (4.8; 7.8)	0.058	6.6 (4.9; 9.2)	6.1 (4.8; 10.5)	6.6 (4.9; 9.1)	0.856	6.6 (4.9; 9.3)	6.6 (4.9; 8.6)	6.7 (5.1; 10.8)	0.230
MAP, mmHg, mean (SD)	80 (12)	79 (12)	80 (13)	0.083	79 (12)	78 (11)	80 (13)	0.021	79 (12)	79 (12)	80 (13)	0.212
Heart rate, bpm, mean (SD)	71 (12)	69 (12)	72 (12)	0.004	71 (12)	68 (12)	71 (12)	0.169	70 (12)	71 (12)	70 (13)	0.355
RM, n (%)	54 (6.9)	29 (7.8)	25 (6.1)	0.365	54 (6.9)	29 (7.8)	25 (6.1)	0.365	51 (6.8)	36 (6.6)	15 (7.5)	0.664
Anesthesia characteristics												
Opioids, n (%)												
No	2 (0.3)	0 (0.0)	2 (0.5)		2 (0.3)	0 (0.0)	2 (0.5)		90 (12.0)	65 (11.9)	25 (12.5)	
Yes	782 (99.7)	376 (100.0)	406 (99.5)	0.174	782 (99.7)	376 (100.0)	406 (99.5)	0.629	746 (99.7)	546 (99.6)	200 (100.0)	0.392
Opioids type, n (%)				0.000				0.055				0.836
Short acting	221 (28.2)	137 (36.4)	84 (20.6)		220 (28.3)	20 (24.7)	200 (28.7)		2 (0.3)	2 (0.4)	0 (0.0)	
Long acting	466 (59.4)	189 (50.3)	277 (67.9)		460 (59.2)	43 (53.1)	417 (59.9)		212 (28.3)	154 (28.1)	58 (29.0)	
Total fluids, ml, median (IQR)	1500 (1000; 2000)	1500 (1000; 2000)	1500 (1000; 2000)	0.022	1500 (1000; 2000)	1800 (1200; 2125)	1500 (1000; 2000)	0.001	1500 (1000; 2000)	1300 (1000; 2000)	2000 (1100; 3000)	0.000
Cristalloids	1175 (1000; 2000)	1200 (1000; 2000)	1000 (1000; 1500)	0.012	1200 (1000; 2000)	1500 (1000; 2050)	1000 (1000; 2000)	0.000	1200 (1000; 2000)	1000 (1000; 1500)	1725 (1000; 2475)	0.000
Colloids	0.0 (0.0; 500.0)	0.0 (0.0; 500.0)	0.0 (0.0; 500.0)	0.649	0.0 (0.0; 500.0)	0.0 (0.0; 500.0)	0.0 (0.0; 500.0)	0.719	0.0 (0.0; 500.0)	0.0 (0.0; 125.0)	0.0 (0.0; 500.0)	0.649

P-value refers to the between-groups difference with Fisher-Freeman-Halton Exact test, Mann Whitney u-test, or Kruskal Wallis test, as appropriate. *N* Number; *IQR* Interquartile range, *SD* Standard deviation, *PPC* Postoperative pulmonary complications, *PBW* Predicted body weight, *V_T* Tidal volume, *P_{Peak}* Peak pressure, *P_{Plateau}* Plateau pressure, *PEEP* Positive end-expiratory pressure, *DP* Driving pressure, *RR* Respiratory rate, *FiO₂* Fraction of inspired oxygen, *SpO₂* Blood oxygen saturation, *ETCO₂* End-tidal carbon dioxide, *MP* Mechanical power, *MAP* Mean arterial pressure, *HR* Heart rate, *RM* Recruitment maneuvers



To our knowledge, this is the first prospective observational study in neurosurgical patients specifically focusing on the prevalence of PPCs and the effects of intraoperative mechanical ventilation settings on PPCs development. Our study is a sub-analysis of the LAS VEGAS study [10], a large international observational study describing the ventilator settings and PPCs occurrence in the perioperative period across different countries, and can therefore be considered representative for the current clinical practice in this population.

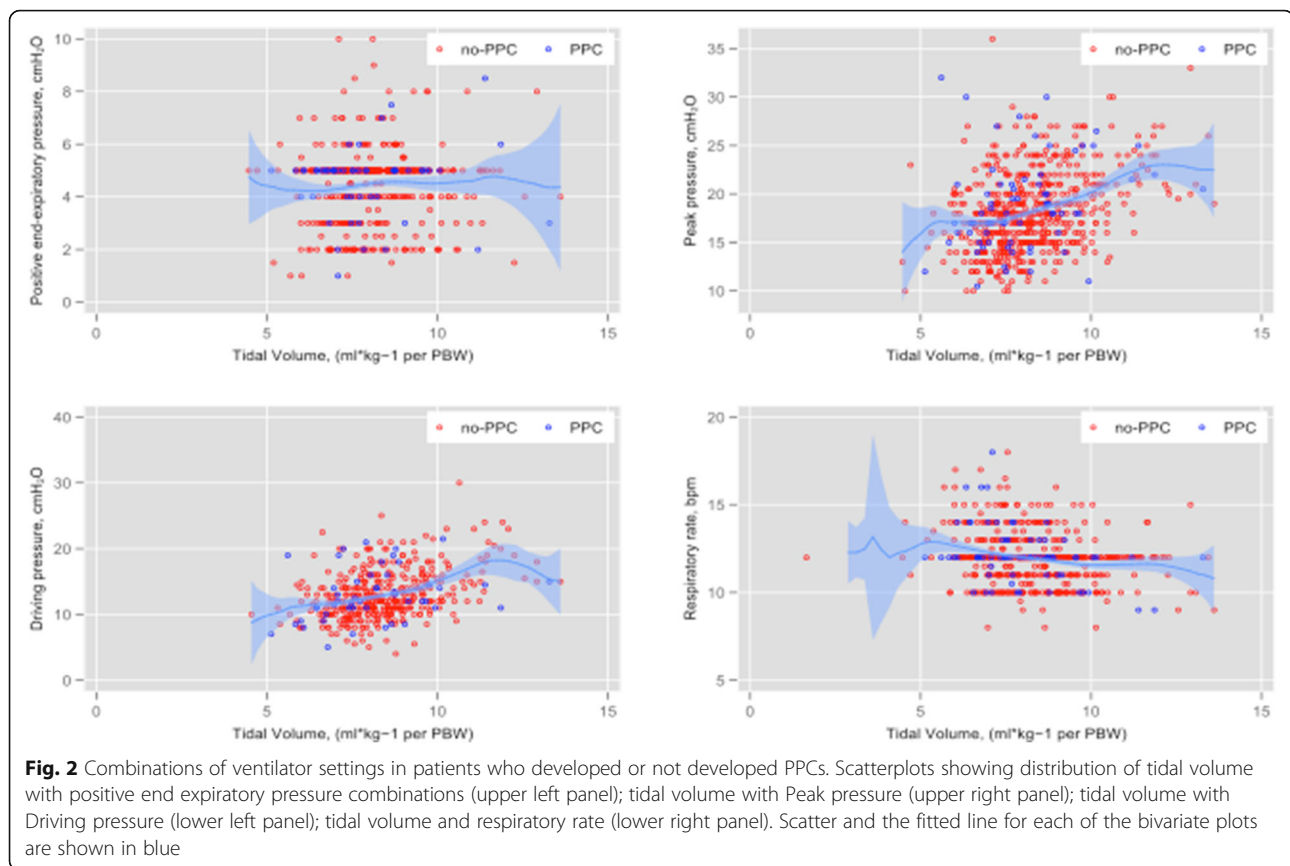
Ventilator strategies in patients undergoing neurosurgical interventions

Currently applied lung-protective ventilation strategies have shown to reduce PPCs [13, 14]. In patients undergoing spine surgery, the prone position has various effects on pulmonary function, including a decreased dynamic lung compliance and increased peak inspiratory pressure [13]; however, no large observational studies or randomized controlled trials are available regarding protective ventilator settings and their effect on PPCs in the prone position in non-ARDS patients.

In brain injured patients, lung-protective ventilation could be deleterious [7]; in particular, possible high intra-thoracic pressures when using high PEEP levels and permissive hypercapnia can have detrimental effects

on cerebral perfusion pressure (CPP) and intracranial pressure (ICP). Therefore, brain injury patients are traditionally ventilated with tidal volumes approximating 9 ml/kg of PBW [5]. However, recent studies suggest that high V_T is a risk factor for acute lung injury even in patients with neurological disorders [4]. Indeed, our results suggest that the use of low V_T is increasingly applied also in neurosurgical patients. Similarly, the application of PEEP in brain injured patients has been traditionally considered detrimental for ICP, by reducing venous outflow [15]. However, recent evidence demonstrates that PEEP application might not compromise ICP, provided that arterial blood pressure is preserved [16, 17].

In our cohort, neurosurgical patients were ventilated with low PEEP levels and no differences in PEEP levels were detected between the brain and spine groups. No data is available on the effects of RM in neurosurgical patients and their role within the intraoperative protective ventilation bundle remains unclear. In brain injured patients, RMs can have a dangerous effect on ICP by impairment of jugular blood outflow, and increase of intra-thoracic pressure with impediment of cerebral venous return to the right atrium [8]. Although pressure-control recruitment manoeuvres improve oxygenation without impairing ICP or CPP, there is still concern regarding their application in neurosurgical patients, and therefore



are rarely performed [8]. Indeed, our results show that recruitment manoeuvres are seldom applied in neurosurgical patients.

To date, no clinical studies comparing pressure-controlled ventilation (PCV) and VCV in brain injured patients are published. In obese [18], ARDS [19], and thoracic patients [20], research suggests no difference in outcome between the modes of ventilation (PCV and VCV). In a trial [21] including patients undergoing spinal surgery, PCV decreased intraoperative surgical bleeding compared with the VCV group ($p < 0.001$), possibly by lowering peak inspiratory pressures. A recent randomized controlled trial during lumbar spine surgery demonstrated that hemodynamic variables and arterial blood gas results did not differ significantly between the VCV and PCV with volume guaranteed (PCV-VG) mode groups [13]. Also, a recent large observational study suggested that PCV is associated with increase of PPC compared to VCV [22]. This association is not confirmed by our results. In our cohort, patients undergoing spinal surgery were more frequently ventilated with VCV than the brain injured group. However, despite the pathophysiological differences of prone vs supine ventilation, we did not find any other differences in the ventilator settings between the two groups.

In our cohort, ETCO_2 levels were generally medium-low, with significantly lower values in the brain surgery group compared to the spinal surgery group. This result suggests that patients undergoing brain surgery are more likely to be hyperventilated. This is most likely out of concern for potential increased intracranial pressure.

Although the subgroup with $\text{ARISCAT} \geq 26$ shows higher values of driving pressure and plateau pressure (plateau pressure (17 vs 16 cmH_2O , $p = 0.012$), and higher driving pressure (14 vs 12 cmH_2O ; $p = 0.009$), these values still remain within the recommended ranges for protective ventilation [22, 23]. In general, in the whole population, a low total energy was applied to the respiratory system [23] (median mechanical power (6.2 J/min)), with values which remain far from the threshold of 12 J/min suggested as increased risk of lung injury [23].

Post-operative pulmonary complications

Clinical studies suggest that the application of protective ventilation can reduce PPCs [24, 25], with high V_T identified as an independent predictor of PPCs development [26, 27]. Trials in obese [27] and non-obese [28] patients undergoing abdominal surgery demonstrated that the intraoperative application of high level of PEEP and RMs

Table 3 Outcomes According to Subgroups

	All Patients	Brain	Spine	<i>p</i> value	All patients	PPC	No PPC	<i>p</i> value	All patients	ARISCAT < 26	ARISCAT ≥ 26	<i>p</i> value
<i>n</i> (%)	784 (100.0)	376 (48.0)	408 (52.0)		777 (100.0)	81 (10.4)	696 (89.6)		748 (100.0)	548 (73.3)	200 (26.7)	
PPCs, <i>n</i> (%)												
PPCs	81 (10.4)	46 (12.4)	35 (8.6)	0.085	777 (100.0)	81 (10.4)	696 (89.6)	0.000	80 (10.8)	43 (7.9)	37 (18.6)	0.000
Need of oxygen	69 (8.9)	38 (10.2)	31 (7.6)	0.202	81 (10.4)	81 (100.0)	0 (0.0)	0.000	68 (9.2)	39 (7.2)	29 (14.6)	0.002
Respiratory failure	14 (1.8)	8 (2.2)	6 (1.5)	0.478	69 (8.9)	69 (85.2)	0 (0.0)	0.000	14 (1.9)	6 (1.1)	8 (4.0)	0.010
NIV	9 (1.2)	4 (1.2)	5 (1.2)	0.963	14 (1.8)	14 (17.3)	0 (0.0)	0.000	9 (1.3)	7 (1.3)	2 (1.1)	0.801
ARDS	1 (0.1)	1 (0.3)	0 (0.0)	0.295	9 (1.2)	5 (6.3)	4 (0.6)	0.003	1 (0.1)	0 (0.0)	1 (0.5)	0.098
Pneumothorax	1 (0.1)	1 (0.3)	0 (0.0)	0.295	1 (0.1)	1 (1.2)	0 (0.0)	0.003	1 (0.1)	0 (0.0)	1 (0.5)	0.098
Secondary outcomes, <i>n</i> (%)												
Severe PPCs	19 (2.4)	13 (3.5)	6 (1.5)	0.068	19 (2.4)	19 (23.5)	0 (0.0)	0.000	19 (2.6)	6 (1.1)	13 (6.5)	0.000
Intra-operative complications	344 (43.9)	154 (41.1)	190 (46.6)	0.121	342 (44.1)	46 (56.8)	296 (42.6)	0.015	336 (44.9)	237 (43.2)	99 (49.5)	0.128
Desaturation	38 (4.9)	23 (6.1)	15 (3.7)	0.110	37 (4.8)	11 (13.6)	26 (3.7)	0.000	36 (4.8)	21 (3.8)	15 (7.5)	0.038
Unplanned RMs	25 (3.2)	15 (4.0)	10 (2.5)	0.220	24 (3.1)	5 (6.2)	19 (2.7)	0.091	22 (2.9)	12 (2.2)	10 (5.0)	0.043
Pressure reduction	25 (3.2)	11 (2.9)	14 (3.4)	0.692	25 (3.2)	3 (3.7)	22 (3.2)	0.795	22 (2.9)	17 (3.1)	5 (2.5)	0.666
Flow limitation	5 (0.6)	3 (0.8)	2 (0.5)	0.590	4 (0.5)	1 (1.3)	3 (0.4)	0.322	4 (0.5)	2 (0.4)	2 (1.0)	0.289
Hypotension	275 (35.1)	117 (31.2)	158 (38.7)	0.028	274 (35.3)	34 (42.0)	240 (34.5)	0.185	270 (36.1)	197 (35.9)	73 (36.5)	0.890
Vasopressors	245 (31.3)	104 (27.7)	141 (34.6)	0.040	244 (31.4)	37 (45.7)	207 (29.8)	0.004	242 (32.4)	168 (30.7)	74 (37.0)	0.101
New arrhythmias	9 (1.1)	6 (1.6)	3 (0.7)	0.257	9 (1.2)	0 (0.0)	9 (1.3)	0.303	9 (1.2)	5 (0.9)	4 (2.0)	0.227
Hospital LOS, days, median (IQR)	2 (1; 5)	2 (1; 5)	2 (1; 5)	0.993	2 (1; 5)	3 (1; 5)	2 (1; 5)	0.447	2 (1; 5)	2 (1; 5)	3 (1; 5)	0.033
Hospital mortality	5 (0.7)	4 (1.2)	1 (0.3)	0.145	5 (0.7)	1 (1.3)	4 (0.6)	0.500	5 (0.7)	1 (0.2)	4 (2.2)	0.006

n Number, *IQR* Interquartile range, *PPCs* Postoperative pulmonary complications, *NIV* Non-invasive ventilation, *ARDS* Acute respiratory distress syndrome, *LOS* Length of hospital stay, *RMs* Recruitment maneuvers, *ARISCAT* Assess respiratory risk in surgical patients in Catalonia

did not reduce PPCs, when compared with lower PEEP level without RMs.

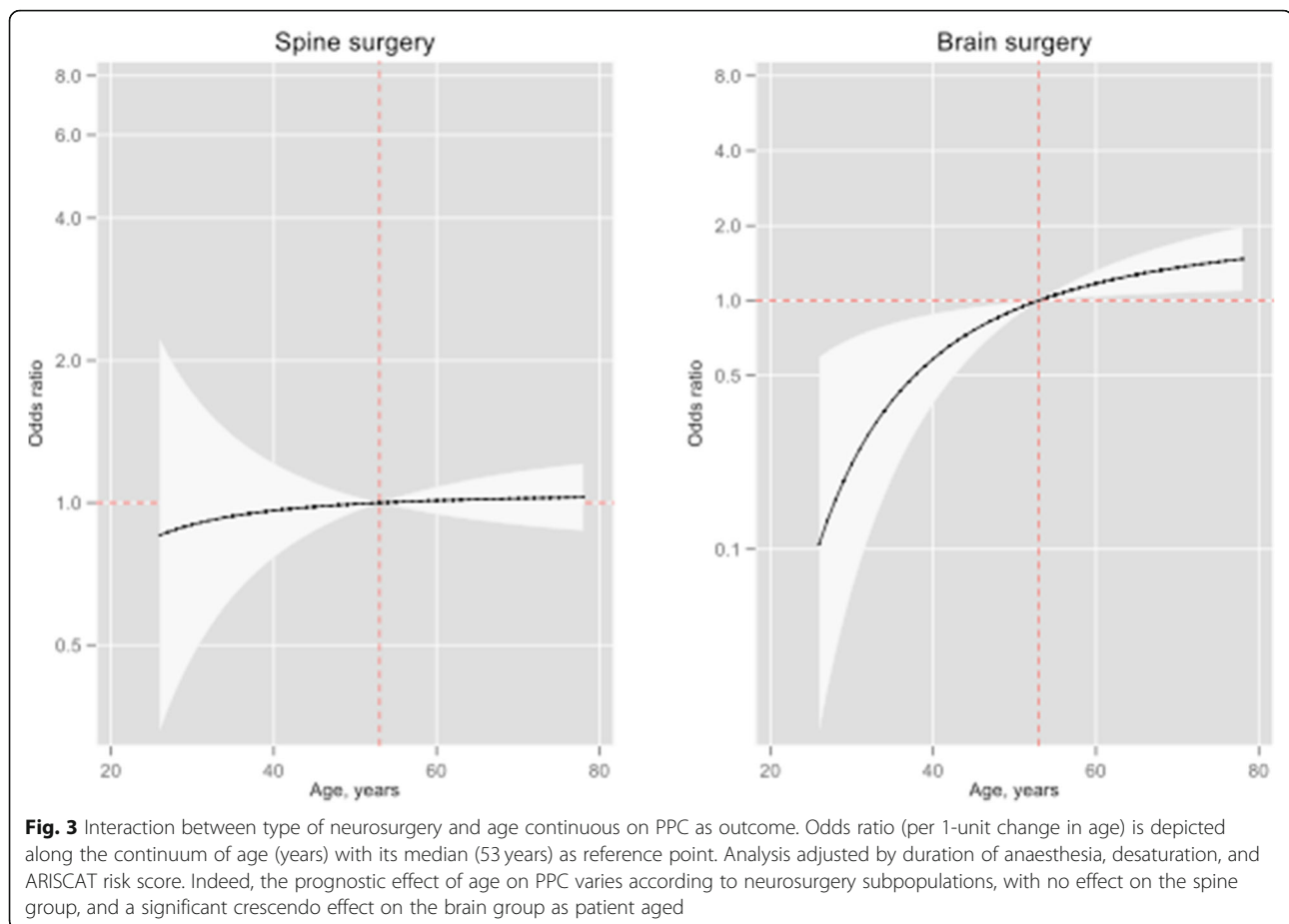
In our neurosurgical population, 10.3% of patients developed PPCs, similar to the results from the whole population of the LAS VEGAS [8]. No clinically significant differences exist in the incidence of PPCs when comparing the different intraoperative ventilator settings in the subgroups analysed.

Patients who developed PPCs had worse preoperative conditions (age, ARISCAT score, ASA status), longer duration of anaesthesia (thus suggesting a more complicated surgical procedure), intraoperative complications (in particular hypotension) and the administration of higher volumes of fluid. This latter point is of extreme importance as cerebral and spinal perfusion pressures are generally maintained by the administration of vasopressors and a large

amount of fluids; however, a positive fluid balance can increase the risk for pulmonary damage and complications [28]. Finally, increasing age in the brain surgical group was associated with PPCs occurrence, thus making preoperative assessment extremely important in the management of this group of patients in order to optimize hospital resources and empathetically begin discussions with patients and their carers.

Intraoperative complications and outcomes

In our cohort, intraoperative complications occurred in a large number of patients (44% of our total population). Moreover, we found an increased prevalence of intraoperative hemodynamic deterioration as compared to respiratory impairment in the intraoperative settings. According to our results, patients undergoing



spine surgery have commonly episodes of intraoperative hypotension requiring the use of vasoactive drugs, probably related to the effects of prone position on cardiac function, including a decreased cardiac index [13].

Our results suggest that in neurosurgical patients, the most common intraoperative complications are related to hemodynamic rather than respiratory function. The fact that hypotension and hemodynamic impairment are common might suggest that limited levels of PEEP could be beneficial in this type of patients by having less negative impact on hemodynamic. These results are in accordance with recently published literature [24, 29], suggesting that the use of high PEEP can negatively impact the hemodynamic system, thus challenging the traditional concept of “open lung approach”, and avoiding repeated alveolar collapse and expansion and keeping the lung partially at rest [30].

Limitations

Several limitations need to be mentioned. First, the manuscript derives from a secondary analysis from the LAS VEGAS study. Thus, the results represent

an observation of associations and do not allow to draw causality conclusions, considering that there exist unaccounted confounding factors.

Second, this is an unplanned secondary analysis from the main study, and even though we built a meticulous statistical model, there could still be confounding factors affecting our results.

Third, as the design of the original study focused on intraoperative settings and variables in the general population, limited information was available regarding specific perioperative data in neurosurgical patients, in particular on the use neuro-monitoring and type of brain and spine surgery.

Conclusions

The main findings of this study are that MV settings in neurosurgical patients are characterized by low V_T and low PEEP with seldom use of RMs. PPCs are frequent in this population and not associated with intraoperative ventilator setting. Further studies are warranted to assess the effect of ventilation strategies on the outcome of this cohort of patients.

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s12871-020-00988-x>.

Additional file 1.

Abbreviations

V_T: Tidal volume; Pplat: Plateau pressure; PEEP: Positive end-expiratory pressure; RM: Recruitment manoeuvres; PBW: Predicted body weight; PPCs: Post-operative pulmonary complications; ESM: Electronic supplemental material; Ppeak: Peak pressure; RR: Respiratory rate; FiO₂: Fraction of inspired oxygen; ETCO₂: End-tidal carbon dioxide; SpO₂: Peripheral saturation of oxygen; MP: Mechanical power; ASA: American Society of Anaesthesiologists; ARISCAT: Assess Respiratory Risk in Surgical Patients in Catalonia; VCV: Volume-controlled ventilation; IQR: Interquartile range; SD: Standard deviation; PCV: Pressure-controlled ventilation; LOS: Length of stay; CPP: Cerebral perfusion pressure; ICP: Intracranial pressure

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Contributors

Las Vegas Investigators:

Austria

LKH Graz, Graz: Wolfgang Kroell, Helfried Metzler, Gerd Struber, Thomas Wegscheider

AKH Linz, Linz: Hans Gombotz

Medical University Vienna: Michael Hiesmayr, Werner Schmid, Bernhard Urbanek

Belgium

UCL - Cliniques Universitaires Saint Luc Brussels: David Kahn, Mona Momeni, Audrey Pospiech, Fernande Lois, Patrice Forget, Irina Grosu

University Hospital Brussels (UZ Brussel): Jan Poelaert, Veerle van Mossevelde, Marie-Claire van Malderen

Het Ziekenhuis Oost Limburg (ZOL), Genk: Dimitri Dylst, Jeroen van Melkebeek, Maud Beran

Ghent University Hospital, Gent: Stefan de Hert, Luc De Baerdemaeker, Bjorn Heyse, Jurgan Van Limmen, Piet Wyffels, Tom Jacobs, Nathalie Roels, Ann De Bruyne

Maria Middelaers, Gent: Stijn van de Velde

European Society of Anaesthesiology, Brussels: Brigitte Leva, Sandrine Damster, Benoit Plichon

Bosnia and Herzegovina

General Hospital "prim Dr Abdulah Nakas" Sarajevo: Marina Juros-Zovko, Dejana Djonović- Omanović

Croatia

General Hospital Cakovec, Cakovec: Selma Pernar

General Hospital Karlovac, Karlovac: Josip Zunic, Petar Miskovic, Antonio Zilic

University Clinical Hospital Osijek, Osijek: Slavica Kvolik, Dubravka Ivic, Darija Azenic-Venzera, Sonja Skiljic, Hrvoje Vinkovic, Ivana Oputric

University Hospital Rijeka, Rijeka: Kazimir Juricic, Vedran Frkovic

General Hospital Dr J Benčević, SlavonSKI Brod: Jasminka Kopic, Ivan Mirkovic

University Hospital Center Split, Split: Nenad Karanovic, Mladen Carev, Natasa Dropulic

University Hospital Merkur, Zagreb: Jadranka Pavicic Saric, Gorjana Erceg, Matea Bogdanovic Dvorscak

University Hospital Sveti Duh, Zagreb: Branka Mazul-Sunko, Anna Marija Pavicic, Tanja Goranovic

University Hospital, Medical school, "Sestre milosrdnice" (Sister of Charity),

Zagreb: Branka Maldini, Tomislav Radocaj, Zeljka Gavranovic, Inga Mladic-Batinica, Mirna Sehovic

Czech Republic

University Hospital Brno, Brno: Petr Stourac, Hana Harazim, Olga Smekalova, Martina Kosinova, Tomas Kolacek, Kamil Hudacek, Michal Drab

University Hospital Hradec Kralove, Hradec Kralove: Jan Brujevic, Katerina Vitkova, Katerina Jirmanova

University Hospital Ostrava, Ostrava: Ivana Volfova, Paula Dzuraková, Katarina Liskova

Nemocnice Znojmo, Znojmo: Radovan Dudas, Radek Filipisky

Egypt

El Sahel Teaching hospital, Cairo: Samir el Kafrawy

Kasr Al-Ainy Medical School, Cairo University: Hisham Hosny Abdelwahab, Tarek Metwally, Ahmed Abdel-Razek

Beni Sueif University Hospital, Giza: Ahmed Mostafa El-Shaarawy, Wael Fathy Hasan, Ahmed Gouda Ahmed

Fayoum University Hospital, Giza: Hany Yassin, Mohamed Magdy, Mahdy Abdelhady

Suis medical Insurance Hospital, Suis: Mohamed Mahran

Estonia

North Estonia Medical Center, Tallinn: Eiko Herodes, Peeter Kivik, Juri Oganjan, Annika Aun

Tartu University Hospital, Tartu: Alar Sormus, Kaili Sarapuu, Merilin Mall, Juri Karjagin

France

University Hospital of Clermont-Ferrand, Clermont-Ferrand: Emmanuel Futier, Antoine Petit, Adeline Gerard

Institut Hospitalier Franco-Britannique, Levallois-Perret: Emmanuel Marret, Marc Solier

Saint Eloi University Hospital, Montpellier: Samir Jaber, Albert Prades

Germany

Fachkrankenhaus Coswig, Coswig: Jens Krassler, Simone Merzky

University Hospital Carl Gustav Carus, Dresden: Marcel Gama de Abreu, Christopher Uhlig,

Thomas Kiss, Anette Bundy, Thomas Bluth, Andreas Gueldner, Peter Spieth, Martin Scharffenberg, Denny Tran Thiem, Thea Koch

Duesseldorf University Hospital, Heinrich-Heine University: Tanja Treschan, Maximilian Schaefer,

Bea Bastin, Johann Geib, Martin Weiss, Peter Kienbaum, Benedikt Pannen

Diakoniekrankenhaus Friederikenstift, Hannover: Andre Gottschalk, Mirja Konrad, Diana Westerheide, Ben Schwerdtfeger

University of Leipzig, Leipzig: Hermann Wrigge, Philipp Simon, Andreas Reske, Christian Nestler

Greece

"Alexandra" general hospital of Athens, Athens: Dimitrios Valsamidis,

Konstantinos Stroumpoulis

General air force hospital, Athens: Georgios Antholopoulos, Antonis

Andreou, Dimitris Karapanos

Areataieion University Hospital, Athens: Kassiani Theodoraki, Georgios Gkiokas, Marios-Konstantinos Tasoulis

Attikon University Hospital, Athens: Tatiana Sidiropoulou, Foteini Zafeiropoulou, Panagiota Florou, Aggeliki Pandazi

Ahepa University Hospital Thessaloniki, Thessaloniki: Georgia Tsaousi, Christos Nouris, Chryssa Pourzitaki,

Israel

The Lady Davis Carmel Medical Center, Haifa: Dmitri Bystritski, Reuven Pizov, Arieh Eden

Italy

Ospedale San. Paolo Bari, Bari: Caterina Valeria Pesce, Annamaria Campanile, Antonella Marrella

University of Bari "Aldo Moro", Bari: Salvatore Grasso, Michele De Michele

Institute for Cancer Research and treatment, Candiolo, Turin: Francesco Bona, Gianmarco Giacoletto, Elena Sardo

Azienda Ospedaliera per l'emergenza Cannizzaro, Catania: Luigi Giancarlo, Vicari Sottosanti

Ospedale Melegnano, Cernusco, Milano: Maurizio Solca

Azienda Ospedaliera - Universitaria Sant'Anna, Ferrara: Carlo Alberto Volta, Savino Spadaro, Marco Verri, Riccardo Ragazzi, Roberto Zoppellari

Ospedali Riuniti Di Foggia - University of Foggia, Foggia: Gilda Cinnella, Pasquale Raimondo, Daniela La Bella, Lucia Mirabella, Davide D'antini

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- Ukraine
- Institute Of Surgery And Transplantology, Kiev:** Andriy Mazur
- Zaporizhzhia State Medical University, Zaporizhzhia:** Sergiy Vorotyntsev
- United Kingdom
- SWARM Research Collaborative: for full list of SWARM contributors please see www.ukswarm.com
- Northern Devon Healthcare NHS Trust, Barnstaple:** Guy Rousseau, Colin Barrett, Lucia Stancombe

Golden Jubilee National Hospital, Clydebank, Scotland: Ben Shelley, Helen Scholes
Darlington Memorial Hospital, County Durham and Darlington Foundation NHS Trust, Darlington: James Limb, Amir Rafi, Lisa Wayman, Jill Deane
Royal Derby Hospital, Derby: David Rogerson, John Williams, Susan Yates, Elaine Rogers
Dorset County Hospital, Dorchester: Mark Pullett, Sarah Moreton, Stephanie Jones
The Princess Alexandra NHS Hospital Trust, Essex: Suresh Venkatesh, Maudrian Burton, Lucy Brown, Cait Goodall
Royal Devon and Exeter NHS Foundation Trust, Exeter: Matthew Rucklidge, Debbie Fuller, Maria Nadolski, Sandeep Kusre
Hospital James Paget University Hospital NHS Foundation Trust, Great Yarmouth: Michael Lundberg, Lynn Everett, Helen Nutt
Royal Surrey County Hospital NHS Foundation Trust, Guildford: Maka Zuleika, Peter Carvalho, Deborah Clements, Ben Creagh-Brown
Kettering General Hospital NHS Foundation Trust, Kettering: Philip Watt, Parizade Raymode
Barts Health NHS Trust, Royal London Hospital, London: Rupert Pearse, Otto Mohr, Ashok Raj, Thais Creary
Newcastle Upon Tyne Hospitals NHS Trust The Freeman Hospital High Heaton, Newcastle upon Tyne: Ahmed Chishti, Andrea Bell, Charley Higham, Alistair Cain, Sarah Gibb, Stephen Mowat
Derriford Hospital Plymouth Hospitals NHS Trust, Plymouth: Danielle Franklin, Claire West, Gary Minto, Nicholas Boyd
Royal Hallamshire Hospital, Sheffield: Gary Mills, Emily Calton, Rachel Walker, Felicity Mackenzie, Branwen Ellison, Helen Roberts
Mid Staffordshire NHS, Stafford: Moses Chikungwa, Clare Jackson
Musgrove Park Hospital, Taunton: Andrew Donovan, Jayne Foot, Elizabeth Homan
South Devon Healthcare NHS Foundation Trust /Torbay Hospital, Torquay, Torbay: Jane Montgomery, David Portch, Pauline Mercer, Janet Palmer
Royal Cornwall Hospital, Truro: Jonathan Paddle, Anna Fouracres, Amanda Datson, Alyson Andrew, Leanne Welch
Mid Yorkshire Hospitals NHS Trust; Pinderfields Hospital, Wakefield: Alastair Rose, Sandeep Varma, Karen Simeson
Sandwell and West Birmingham NHS Trust, West Bromich: Mrutyunjaya Rambhatla, Jaysimha Susarla, Sudhakar Marri, Krishnan Kodaganallur, Ashok Das, Shivarajan Algarsamy, Julie Colley
York Teaching Hospitals NHS Foundation Trust, York: Simon Davies, Margaret Szewczyk, Thomas Smith
United States
University of Colorado School of Medicine/University of Colorado Hospital, Aurora: Ana Fernandez- Bustamante, Elizabeth Luzier, Angela Almagro
Massachusetts General Hospital, Boston: Marcos Vidal Melo, Luiz Fernando, Demet Sulemanji
Mayo Clinic, Rochester: Juraj Sprung, Toby Weingarten, Daryl Kor, Federica Scavonetto, Yeo Tze

Authors' contributions

CR wrote the first draft of the manuscript, performed the statistical analysis and contributed to conception and design, acquisition of data, or analysis and interpretation of data, to the final drafting the article and revised it critically for important intellectual content; PP wrote the first draft of the manuscript; DB helped CR and PP to write the first draft of the manuscript; SNTH, ASN, TB, JC, MH, MHW, GHM, MFVM, CP, SJ, WS, PS, HW, LB, MGA, MJS, PP, DB contributed to conception and design, acquisition of data, or analysis and interpretation of data, to the final drafting the article and revised it critically for important intellectual content; all authors have read and approved the submitted manuscript; and agreed that the article is accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data and materials

The dataset used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Ethical approval is in accordance with the Declaration of Helsinki and the study was first approved by the ethical committee of the Academic Medical Center, Amsterdam, the Netherlands (W12_190#12.17.0227). Each participating centre obtained the approval from the local ethical review board, and written informed consent was obtained from patients or next of kin, according to ethical requirements.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Anaesthesia and Intensive Care, San Martino Policlinico Hospital, IRCCS for Oncology and Neurosciences, Largo Rosanna Benzi 8, 16131 Genoa, Italy. ²Department of Intensive Care, Amsterdam University Medical Centers, location 'AMC', Amsterdam, The Netherlands. ³Department of Anaesthesiology, Amsterdam University Medical Centers, location 'AMC', Amsterdam, The Netherlands. ⁴Department of Critical Care Medicine, Hospital Israelita Albert Einstein, Sao Paulo, Brazil. ⁵Department of Anaesthesiology and Intensive Care Medicine, Pulmonary engineering group, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany. ⁶Department of Anaesthesiology and Postoperative Care, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain. ⁷Division Cardiac, Thoracic, Vascular Anesthesia and Intensive Care, Medical University Vienna, Vienna, Austria. ⁸Operating Services, Critical Care and Anaesthesia, Sheffield Teaching Hospitals and University of Sheffield, Sheffield, UK. ⁹Department of Anaesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, MA, USA. ¹⁰Department of Anesthesiology and Intensive Care Medicine, University Hospital Bonn, Bonn, Germany. ¹¹Department of Anaesthesia and Intensive Care, Saint Eloi Montpellier University Hospital, and PhyMedExp, University of Montpellier, Montpellier, France. ¹²Department of Biotechnology and Sciences of Life, ASST-Setteleghi Ospedale di circolo e Fondazione Macchi, University of Insubria, Varese, Italy. ¹³Department of Anaesthesiology and Intensive Care Medicine, University of Leipzig, Leipzig, Germany. ¹⁴Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Genoa, Italy. ¹⁵Mahidol-Oxford Tropical Medicine Research Unit (MORU), Mahidol University, Bangkok, Thailand.

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