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Adoption of *L*ung *P*rotective ventilation *IN* patients undergoing *E*mergency laparotomy: the ALPINE study. A prospective multicentre observational study

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Background: Emergency abdominal surgery is associated with a high risk of postoperative pulmonary complications (PPCs). The primary aim of this study was to determine whether patients undergoing emergency laparotomy are ventilated using a lung-protective ventilation strategy employing tidal volume ≤8 ml kg^{-1} ideal body $weight^{-1}$, PEEP >5 cm H_2O, and recruitment manoeuvres. The secondary aim was to investigate the association between ventilation factors (lung-protective ventilation strategy, intraoperative FiO_2, and peak inspiratory pressure) and the occurrence of PPCs.
Methods: Data were collected prospectively in 28 hospitals across London as part of routine National Emergency Laparotomy Audit (NELA). Patients were followed for 7 days. Complications were defined according to the European Perioperative Clinical Outcome definition.
Results: Data were collected from 568 patients. The median [inter-quartile range (IQR)] tidal volume observed was 500 ml (450–540 ml), corresponding to a median tidal volume of 8 ml kg^{-1} ideal body $weight^{-1}$ (IQR: 7.2–9.1 ml). A lung-protective ventilation strategy was employed in 4.9% (28/568) of patients, and was not protective against the occurrence of PPCs in the multivariable analysis (hazard ratio=1.06; P=0.69). Peak inspiratory pressure of <30 cm H_2O was protective against development of PPCs (hazard ratio=0.46; confidence interval: 0.30–0.72; P=0.001). Median FiO_2 was 0.5 (IQR: 0.44–0.53), and an increase in FiO_2 by 5% increased the risk of developing a PPC by 8% (2.6–14.1%; P=0.008).
Conclusions: Both intraoperative peak inspiratory pressure and FiO_2 are independent factors significantly associated with development of a postoperative pulmonary complication in emergency laparotomy patients. Further studies are required to identify causality and to demonstrate if their manipulation could lead to better clinical outcomes.

Keywords: anesthesia, general; lung-protective ventilation; ventilation, mechanical; postoperative pulmonary complications

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Editor's key points

- Emergency abdominal surgery is associated with a high risk of postoperative pulmonary complications (PPCs), but the benefits of 'protective' ventilation in these patients is uncertain.
- In this prospective observational study, 48% of patients developed a PPC after emergency laparotomy.
- PPCs were associated with increased age, use of high fractional inspired oxygen concentration, and high peak inspiratory airway pressures.
- Lung-protective ventilation was used in <5% of patients, and had no association with the incidence of PPCs.

Emergency laparotomy surgery is associated with a high risk of morbidity and mortality. Postoperative pulmonary complications (PPCs) are the second most common surgical complication and are a significant cause of adverse perioperative outcome.[1] The proportion of patients who develop a PPC following major surgery is variable, but has been estimated to occur in up to 40% of patients undergoing abdominal surgery.[2]

Lung-protective ventilation (LPV), defined as the use of tidal volumes ≤8 ml kg^{-1} ideal body weight $(IBW)^{-1}$, PEEP of ≥5 cm H_2O, recruitment manoeuvres, and maintenance of plateau pressure <30 cm H_2O, is a well-established standard of care in ventilated patients with acute respiratory distress syndrome (ARDS) in the ICU.[3] Recently, there has been an emerging interest in its application in the perioperative setting to reduce the occurrence of PPCs in patients undergoing general anaesthesia for elective surgery. Clinically significant ventilator-induced lung injury occurs from a combination of volutrauma, barotrauma, atelectrauma, biotrauma, and shear strain. It is thought to most likely occur in patients with concurrent physiological insults, such as sepsis, trauma, or major surgery, which preconditions the immune system for an inflammatory response to mechanical lung injury.[4] The ventilator strategies employed in patients undergoing emergency surgery currently remain unknown. Identification of intraoperative strategies that could potentially reduce the development of PPCs in this high-risk group is therefore of considerable clinical importance.

The primary aim of the study was to determine whether patients undergoing emergency laparotomy surgery are ventilated using an LPV strategy comprising of tidal volume ≤8 ml kg^{-1} IBW^{-1}, PEEP ≥5 cm H_2O, and use of recruitment manoeuvres. The secondary aim was to investigate the association between ventilation factors [LPV strategy, intraoperative FiO_2, and peak inspiratory pressure (PIP)] and the occurrence of PPCs. We hypothesise that the majority of patients are not ventilated using an LPV strategy, but that implementation of the bundle may lead to a reduced occurrence of PPCs.

Methods

The Adoption of Lung Protective Ventilation in Patients Undergoing Emergency Laparotomy (ALPINE) was a prospective multicentre observational study undertaken in collaboration with the National Emergency Laparotomy Audit (NELA) and delivered by the Pan-London Perioperative Audit and Research Network. The study was undertaken between October 31, 2016 and March 31, 2017 with 28 hospitals across London participating.

The study was approved by the Joint Research and Enterprise Office at St George's University Hospitals NHS Foundation Trust, UK. Research registration and patient consent were not required, as data collection was limited only to data used for routine clinical care. This was confirmed by the online National Research Ethics Service decision tool. All data collection was independent of patient management, and no additional tests or investigations were performed. All patients undergoing an emergency laparotomy during the specified period were identified. Intraoperative data were collected as an extension of routine NELA data collection. All data were completely anonymised prior to entering into the electronic database. Institutional approval was obtained for each participating site, which had the study registered as a service evaluation in their department.

All patients over the age of 18 who underwent expedited, urgent, or emergency laparotomy surgery as per NELA guidelines were included.[5] This comprised any open, laparoscopic, or laparoscopically assisted procedures on the gastrointestinal tract. Any elective or diagnostic procedures were excluded.

Intraoperative data collected included patient characteristics, height, and weight in order to calculate the IBW. The IBW was calculated as per the formula used in the ARDSNet trial {♂=50+2.3 [height (in.)]−60)/(♀=45.5+2.3 [height (in.)]−60}.[6] Other variables recorded included the duration of anaesthesia in minutes and the grade of the most senior anaesthetist present (consultant *vs* trainee). The mode of ventilation, tidal volume delivered, PEEP, PIP, use of recruitment manoeuvres, and intraoperative FiO_2 were recorded. Data for each ventilation parameter were recorded manually by the anaesthetist onto a *pro forma* by recording the most documented value from the anaesthetic chart for each whole procedure. The development of PPCs was recorded on a daily basis until Day 7 postoperatively by reviewing the patient's notes, routine biochemical results, and radiographs if undertaken. PPCs were defined according to the European Perioperative Clinical Outcome definition, and included respiratory failure, respiratory infection, atelectasis, bronchospasm, pneumothorax, and aspiration pneumonia.[7] Admission and mode of ventilation in the Intensive Care Unit (ICU) were also recorded. We were unable to collect data on co-morbidities, but data were collected for five out of the seven variables used in Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score, a well-validated risk assessment tool for the perioperative development of PPCs, and data were adjusted in the multivariable regression model for these variables.[8]

LPV was defined as low tidal-volume ventilation (≤8 ml kg^{-1} IBW^{-1}), application of PEEP of ≥5 cm H_2O, and use of recruitment manoeuvres. A recruitment manoeuvre was defined as 30 s of 30 cm H_2O CPAP every 30 min. The definition of LPV for this study was as per the randomised controlled study conducted by Futier and colleagues.[9]

The collected variables were explored both graphically and by summary statistics. Descriptive statistics as per the main binary outcome (defined as experiencing at least one PPC or not within 7 days after surgery) are presented in Table 1. Variables are summarised as means, standard deviations, percentiles for continuous variables, and proportions for categorical/binary data. Additional simple statistical tests have been added as appropriate for a quick assessment of

Table 1 Descriptive statistics for all variables by the outcome defined by the presence of any failure and no failure during the first 7 days after surgery. The *P*-values test the null hypothesis of no difference in the variables across these two groups, and are the result of χ^2 tests for categorical data and appropriate tests for continuous data (*t*-test or Kruskal–Wallis upon normality assumption held). IBW, ideal body weight; IQR, inter-quartile range; PCV, pressure control ventilation; PCV–VG, pressure control ventilation–volume guaranteed; PPC, postoperative pulmonary complication; SD, standard deviation; VCV, volume control ventilation

Variables	Type	No PPC (280)		At least one PPC (275)		All (568) Missing outcome (13/2.3%)		Test
		No (proportion)	Mean/SD Median/(IQR)	No (proportion)	Mean/SD Median/(IQR)	No (proportion)	Mean/SD Median/(IQR)	
Age (yr)	Continuous	280	57.41/19.07 59 (43, 72)	275	66.95/17.25 71 (56, 81)	568	62.17/18.67 66 (18, 96)	P<0.001
	Missing	0		0		0		
Gender	Male	122		133		307 (54.05%)		P=0.24
	Female	158		141		260 (45.77%)		
	Missing	0		1		1 (0.17%)		
Height (cm)	Continuous	280	72.93/20.40 68 (60, 83)	275	75.15/17.20 75 (65, 85)	568	167.73/9.67 168 (160, 175)	P=0.39
	Missing	0		0		0		
Weight (kg)	Continuous	280	168.12/10.11 169.5 (160, 176)	275	167.41/9.01 168 (161, 174)	568	74.14/18.91 70 (62, 85)	P=0.012
	Missing	0		0		0		
Ideal body weight (kg)	Male	122	71.08 72.39 (66.93, 75.12)	133	68.98/6.54 69.66 (65.1, 73.3)	307 (54.05%)	70.1/6.6 70.6/(66, 75.1)	P=0.011
	Female	158	54.57 54.24 (49.69, 59.70)	141	54.11/6.21	260 (45.77%)	54.3/6.9 54.2/(49.7, 58.8)	P=0.83
	Missing	0		1		1 (0.17%)		
Preoperative oxygen saturation/SpO_2	Continuous	270	96.91/2.29 97 (96, 99)	258	95.82/3.18 96 (94, 98)	540	96.4/2.8 97/(95, 98)	P<0.001
	Missing	10		17		27 (4.7%)		
Intraoperative FiO_2 (%)	Continuous	275	48.25/9.30 50 (45, 50)	272	52.24/12.57 50 (45, 55.5)	559	50.3/11.2 50/(44, 53)	P<0.001
	Missing	5		3		9 (1.5%)		
Duration anaesthesia (min)	Continuous	261	171.55/83.46 151 (120, 205)	252	180.74/90.91 176 (120, 220)	522	177.1/88.96 165/(120, 210)	P=0.22
	Missing	19		23		46 (8%)		
Ventilation mode	PCV	45		53		100 (17.61%)		P=0.87
	PCV-VG	93		88		185 (32.57%)		
	VCV	82		82		169 (29.75%)		
	Other	21		21		42 (7.39%)		
	Missing	39		31		72 (12.3%)		
Grade anaesthetist	Consultant	238		225		474 (83.5%)		P=0.26
	Lower grade	38		47		87 (15.3%)		
	Missing	4		3		7 (1.2%)		
Tidal volume (ml)	Continuous	272	494.72/62.21 500 (450, 540)	271	495.03/63.53 500 (450, 550)	555	494.4/62.9 500 (450, 540)	P=0.88
	Missing	8		4		13 (2.2%)		
Tidal volume <8 ml kg^{-1} IBW^{-1}	Yes	132		128		267 (50.5%)		P=0.79
	No	140		142		287 (47%)		
	Missing	8		5		14 (2.5%)		
Tidal volume (ml kg^{-1})	Continuous	272	8.19/1.30 8.09 (7.23, 9.09)	270	8.23/1.37	554	8.2/1.3 8.09/(7.2, 9.1)	
	Missing	8		3		14 (2.5%)		
Use of PEEP	Yes	254		257		523 (92.1%)		P=0.72
	No	18		16		34 (6%)		
	Missing	8		2		11 (1.9%)		
Most frequent PEEP	Continuous	271	5.05/1.9 5 (5, 6)	270	5.6/2.3 5 (5, 7)	552	5.35/2.1 5 (5, 6)	P=0.001
PEEP >5 cm H_2O	Yes	214		218		438 (77.1%)		P=0.61
	No	57		52		114 (20.1%)		
	Missing	9		5		16 (2.8%)		
Peak inspiratory pressure	Continuous	263	19.61/4.44 19 (16, 22)	266	21.91/5.34 21 (18, 24)	540	20.7/5.04 20/(17, 23.5	P=0.001
Peak inspiratory pressure (<30 cm H_2O)	Yes	259		246		516 (90.9%)		P=0.001
	No	4		20		24 (4.2%)		
	Missing	17		9		28 (4.9%)		
Use of recruitment manoeuvre	No	226		228		465 (81.9%)		P=0.63
	Yes	25		29		54 (9.5%)		
	Missing	29		18		49 (8.6%)		
Bundle	Yes	13		15		28 (4.9%)		P=0.73
	No	232		234		477 (83.4%)		
	Missing	35		26		63 (11.1%)		

differences between the two groups: χ^2 tests for categorical data and/or *t*-tests or Kruskal–Wallis for continuous data (upon normality assumptions). Parametric Weibull settings for interval censored data, accounting for the inherent hierarchical structure, have been applied for both univariate associations and to build a final parsimonious model (Supplementary information).

Categorical data are displayed as proportion of total number (%), and cross-sectional continuous data are displayed as median [inter-quartile range (IQR) (range)]. A series of survival settings were explored to understand the risk of developing PPCs in association with the bundle and the various demographic and clinical variables (see Supplementary information). Two multivariable models were fitted: one that included the bundle and one that included the components of the bundle individually. Variability between hospitals was accounted for through a cluster-type estimation, and statistical significance was set at a *P*-value of $\leq$0.05. A sample-size calculation was undertaken prior to conducting the study, which estimated the minimum number of patients needed to undertake a logistic regression with approximately 10 explanatory variables (details in Supplementary information). The potential bias introduced by the presence of missing observations was assessed by considering two extreme scenarios, in which all the missing observations were assumed to have had the bundle applied or not. Further analyses, assuming that 2.3% of the missing outcome belonged to the patients who either developed a PPC or not, did not reveal a different qualitative statistical picture.

Data were entered in Access 2013 (Microsoft®), and the analyses have been carried out using STATA (Stata Statistical Software: Release 15; StataCorp, College Station, TX, USA).

Results

A total of 28 hospitals across Greater London participated in the ALPINE study with 568 patients included in the final analysis. There were a similar proportion of patients from each hospital with no single hospital contributing a significantly greater number. The median [IQR (range)] age of patients was 66 yr (48–78 yr) with the majority of patients being male (307 males *vs* 260 females). The patient and ventilation baseline characteristics can be viewed in Table 1. The majority of patients undergoing emergency surgery (*n*=474/568; 84%) were anaesthetised by a consultant anaesthetist. The preferred mode of ventilation was pressure control ventilation–volume guaranteed in 185/568 patients (33%) with volume control accounting for 30% of cases followed by pressure control (18%). The median [IQR (range)] preoperative oxygen saturations were 97% (95–98%).

The median (IQR) weight was 70 kg (62–85 kg), and the median IBW corresponded to 70.6 kg in males (66–75.1 kg) and 54.2 kg in females (49.7–58.8 kg). The median (IQR) tidal volume received was 500 ml (450–540 ml). This corresponded to a median tidal volume of 8 ml kg^{-1} IBW^{-1} (IQR: 7.1–9 ml) with the highest tidal volume documented as 14 ml kg^{-1} IBW^{-1}. A total of 265 patients (50.5%) received a tidal volume of $\leq$8 ml kg^{-1} IBW^{-1}. The vast majority of patients (*n*=523; 92%) were ventilated with PEEP with a median value of 5 cm H_2O (IQR: 5–6 cm H_2O). The median PIP was 20 cm H_2O (IQR: 17–23.5 cm H_2O) with the highest documented PIP of 40 cm H_2O. The distribution of PIP according to the development of PPCs can be viewed in Fig. 1. The majority of patients (*n*=516; 91%) had a PIP of $\leq$30 cm H_2O. The median intraoperative FiO_2 administered was 0.5 (IQR: 0.44–0.53) with 1.0 being the highest FiO_2 administered. Only 10% of patients (54/568) received an

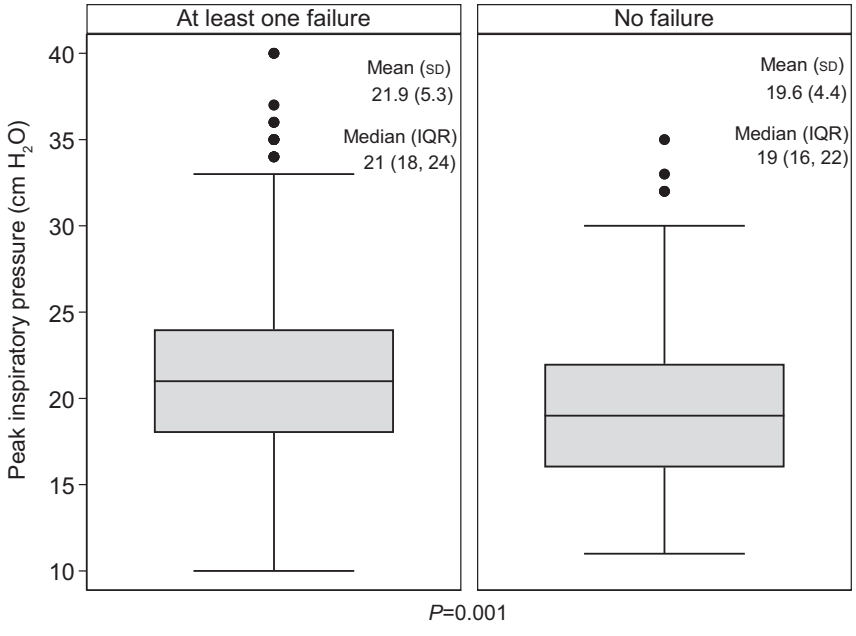

Fig 1. Box plot of the distribution of peak inspiratory pressure according to the development of postoperative pulmonary complications ("failure"). The *P*-value evaluates the strength of its univariate association with the outcome (Table 2). IQR, inter-quartile range; SD, standard deviation.

intraoperative recruitment manoeuvre defined as 30 s of 30 cm H_2O CPAP. In total, 28/568 patients (4.9%) met the criteria for LPV as defined previously.

Out of a total of 568 patients, 275 (48%) patients developed a PPC within 7 days. Out of these 275 patients, 55% (n=175) developed at least two PPCs within 7 days. Postoperative respiratory failure was the most common PPC (n=197; 35%) followed by atelectasis (n=182; 32%). The distribution of PPCs is presented in Table 2. The median time to develop a PPC was 1 day (IQR: 1–1), and the median duration of the PPC was 4 days (IQR: 1–17). Most patients developed the first PPC within 1 day after operative intervention (213/275; 77.5%).

Univariable analyses (Table 3) revealed that age, PIP, and FiO_2 were positively associated with the development of a PPC (P<0.004). Both higher preoperative oxygen saturations and use of PEEP >5 cm H_2O intraoperatively were associated with a reduced occurrence of PPCs (P=0.001).

In the multivariable survival analysis, the implementation of the LPV bundle was not associated with a reduction in the development of PPCs. However, increasing age, PIP, and FiO_2 remain strong predictors for the risk of development of one or more PPCs (P<0.008) (Table 4). A PIP of <30 cm H_2O reduces the risk by half [hazard ratio=0.47; 95% confidence interval (CI) (0.30, 0.72; P=0.001)]. More precisely, an increase in age of 5 yr was associated with an increase of a PPC by 6% (4–8%; P<0.001). An increase in FiO_2 by 5% increased the risk of PPC by 8% (2.6–14.1%; P=0.008). The distribution of PPCs according to intraoperative FiO_2 is presented in Fig. 2, and the effects of intraoperative FiO_2 and PIP on the survival curves associated to PPC are shown in Fig. 3.

Table 3 Univariable analysis. Crude associations between the occurrence of postoperative pulmonary complications and the collected clinical and demographic variables. CI, confidence interval; LPV, lung-protective ventilation

Variables	Hazard ratio	95% CI low	95% CI high	P-value
Age (5 yr effect)	1.05	1.03	1.07	<0.001
Tidal volume (ml)	0.99	0.99	1.00	0.820
Use of PEEP	1.03	0.81	1.31	0.778
PEEP >5 cm H_2O	1.06	1.02	1.10	0.001
Peak inspiratory pressure	1.04	1.02	1.05	<0.001
Intraoperative FiO_2 % (5% effect)	1.07	1.02	1.13	0.004
Peak inspiratory pressure (<30 cm H_2O)	0.45	0.28	0.72	0.001
Tidal volume <8 ml kg^{-1} IBW^{-1}	0.97	0.87	1.09	0.651
PEEP >5	1.04	0.88	1.23	0.616
Recruitment manoeuvre	1.02	0.82	1.26	0.824
Use of LPV strategy	0.97	0.70	1.34	0.874

Discussion

This prospective multicentre observational study of patients in London, UK revealed that 48% of patients undergoing emergency laparotomy surgery developed a PPC, and that age, intraoperative FiO_2, and PIP were associated with its development. It also showed that only 4.9% of patients received a LPV strategy. To our knowledge, this is the first study to explore the ventilator strategies employed in emergency abdominal surgery, and also to show a much higher proportion of PPCs than previously reported. Previous trials have reported a proportion between 20% and 40%, although much lower proportions have also been reported depending on the definition of PPC used and population examined.[2] Postoperative respiratory failure has consistently been reported as

Table 2 Distribution and duration of postoperative pulmonary complications within 7 days. Continuous data are summarised by their median, IQR, and ranges, whilst categorical variables are summarised by group numbers and percentages. IQR, inter-quartile range

Variable	Category	Number	Median	IQR	Range
Respiratory failure	Yes (duration)	197	4	(2, 7)	1, 7
	Yes (time to first failure)		1	(1, 1)	1, 6
	No	361			
Respiratory infection	Yes (duration)	97	5	(3, 7)	1, 7
	Yes (time to first failure)		2	(1, 4)	1, 6
	No	461			
Atelectasis	Yes (duration)	182	3	(2, 6)	1, 7
	Yes (time to first failure)		1	(1, 3)	1, 7
	No	373			
Pneumothorax	Yes (duration)	2	2.5	2, 3	2, 3
	Yes (time to first failure)		1.5	1, 2	1, 2
	No	553			
Bronchospasm	Yes (duration)	21	1	(1, 4)	1, 6
	Yes (time to first failure)		2	(1, 4)	1, 6
	No	534			
Aspiration pneumonia	Yes (duration)	16	3	(2, 4.5)	2, 7
	Yes (time to first failure)		2	(1, 5)	1, 6
	No	539			
Any postoperative pulmonary complication	Yes (duration)	275	4	2, 7	1, 7
	Yes (time to first failure)		1	1, 1	1, 7
	No	280			

Table 4 Multivariable analysis. The estimates derived from an interval-censored survival setting modelling the time since surgery to the first postoperative pulmonary complication. CI, confidence interval

	Hazard ratio	P-value	95% CI low	95% CI high
Model 1: using the bundle only				
Age (5 yr effect)	1.05	<0.01	1.03	1.08
Intraoperative FiO_2 % (5% increase)	1.08	0.008	1.02	1.15
Peak inspiratory pressure (≤30 *vs* >30)	0.47	0.001	0.30	0.73
Bundle (yes *vs* no)	1.06	0.693	0.77	1.47
Constant	0.60	0.028	0.39	0.94
Model 2: using the bundle components				
Age (5 yr effect)	1.05	0.000	1.03	1.08
Intraoperative FiO_2 % (5% increase)	1.08	0.009	1.02	1.15
Peak inspiratory pressure (≤30 *vs* >30)	0.47	0.001	0.30	0.74
Ideal tidal volume (≤8 *vs* >8)	1.01	0.854	0.89	1.13
Most frequent use (≥5 *vs* <5)	0.98	0.885	0.78	1.23
Use manoeuvre (yes *vs* no)	1.05	0.637	0.84	1.32

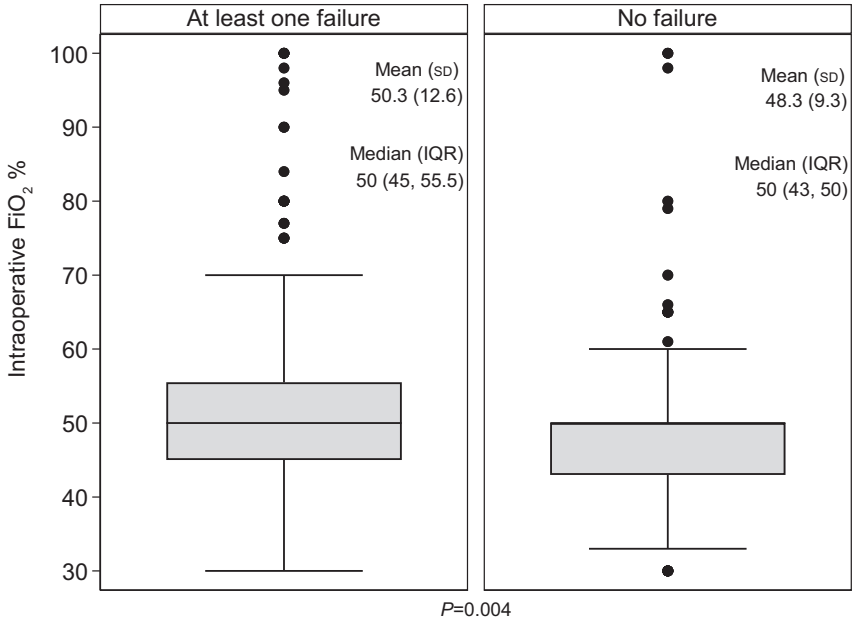

Fig 2. Box plot of the distribution of intraoperative FiO_2 according to the development of postoperative pulmonary complications ("failure"). The *P*-value evaluates the strength of its univariate association with the outcome (Table 2). IQR, inter-quartile range; SD, standard deviation.

the most common PPC, and this was also confirmed in the ALPINE study.[15]

The impact of developing a PPC is significant. Mortality is increased with between 14% and 30% of patients who sustain a PPC dying within 30 days of major surgery compared to 0.2–3% of those without.[15] The length of stay is also significantly increased by up to 17 days; thus, PPCs represent a substantial financial burden in an era where cost effectiveness is paramount. The aetiology of PPCs is multifactorial and includes ventilation–perfusion mismatch and hypoxaemia as a result of general anaesthesia and postoperative pain. Both emergency surgery and abdominal surgery are established risk factors for their development, with emergency surgery conferring a two-to six-fold increase in the risk of PPCs compared to elective surgery.[10]

Recently, there has been increasing evidence that an LPV strategy is associated with a reduced occurrence of PPCs. Much of the high-quality evidence generated from these studies has focused on abdominal surgery in the elective period.[9,11,12,15] The definition of LPV in this study was adopted from Futier and colleagues[9] who conducted to date the largest randomised controlled trial (RCT) of LPV in abdominal surgery. This comprised a tidal volume (TV) of 6–8 ml kg^{-1} IBW^{-1}, a PEEP of 6–8 cm H_2O, and recruitment manoeuvres every 30 min. In our study, only 4.9% of patients undergoing emergency surgery were ventilated with an LPV strategy, and thus, highlighting

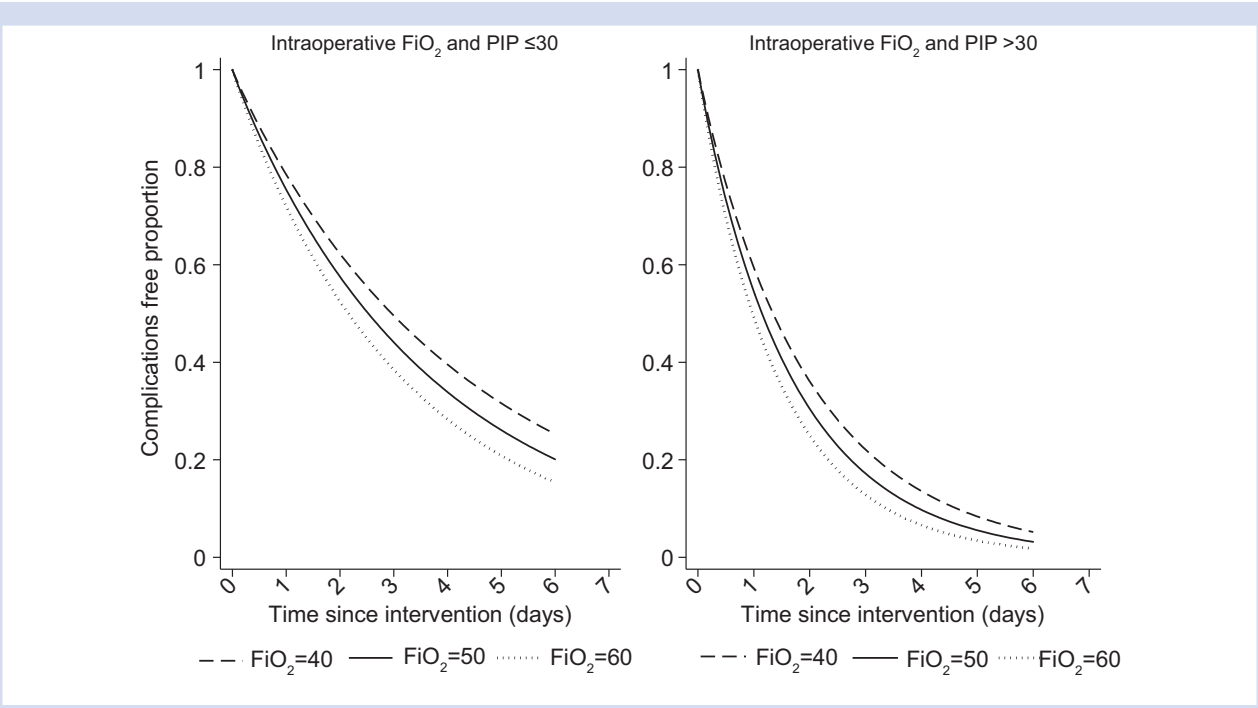

Fig 3. Association of FiO_2 and peak inspiratory pressure (PIP) with occurrence of postoperative pulmonary complications within 7 days (estimated stratified survival curves). Age is set at the average of 62 yr.

that uptake of a lung-protective approach is not widespread. This is likely attributed to the fact that <10% of patients actually received a recruitment manoeuvre. In addition, we noted that adherence to the bundle was not protective against the development of PPCs, which may be explained by the fact that we may have had a smaller population sample in comparison to other studies, or by the fact that our population comprised a higher risk cohort.

Our results show that the most frequently chosen tidal volume was 500 ml, which equated to a median tidal volume of 8 ml kg^{-1} IBW^{-1}. This was much lower than the standard ventilation group in the RCT by Futier and colleagues,[9] suggesting that lower tidal volumes are now more frequently employed. A meta-analysis published in 2015 concluded that the risk of PPCs was significantly lower in patients ventilated with a tidal volume of <8 ml kg^{-1} IBW^{-1} irrespective of the amount of PEEP used.[9] However, tidal volume was not found to be a predictor for the development of a PPC in our analysis, a finding that has also been corroborated by the Local Assessment of Ventilatory Management During General Anesthesia for Surgery (LAS VEGAS) study, which looked at the ventilation practice of over 9000 patients.[13] We also found that PEEP was used in 92% of patients, with 82% of patients receiving a PEEP of ≥5 cm H_2O. No association was found between the use of PEEP and the occurrence of PPCs. Again, this was also confirmed in the LAS VEGAS study, but is in contrast to other studies that have advocated higher levels of PEEP to prevent PPCs.[13–15] It should be noted, however, that these studies compared high levels of PEEP (>6 cm H_2O) against zero PEEP. Interestingly, a hospital-based registry study of over 69 000 patients suggested that a PEEP level of 5 cm H_2O is most beneficial, with higher or lower levels associated with increased risk.[16] In fact, high levels of PEEP (>10 cm H_2O) have been proposed to actually cause harm with increase haemodynamic compromise and no reduction in the occurrence of PPCs.[14] Our findings are similar to a retrospective study conducted by Levin and colleagues,[17] which found that the median tidal volume employed by anaesthetists was 525 ml (median tidal volume 8 ml kg^{-1} IBW^{-1}) with a median level of 4 cm H_2O of PEEP. They concluded that low tidal volumes with low levels of PEEP were significantly associated with an increase in 30 day mortality ($P<0.0002$), which suggests that tidal volume and PEEP may not be the driving forces behind the development of ventilator induced lung injury (VILI).

Our analysis suggests that there is a significant association between PIP and the development of PPCs, and that maintaining the PIP at <30 cm H_2O reduces the risk of developing a PPC by almost half. A logistic regression fitted to the data highlights the effect of high PIPs on the occurrence of PPCs. For example, a 30-yr-old patient ventilated with an FiO_2 of 0.5, PEEP of 5 cm H_2O, but a PIP of >30 cm H_2O has a 66% chance of developing a PPC compared to 27% if the PIP is <30 cm H_2O. This finding is consistent with the results from the LAS VEGAS report, which found that patients who were ventilated with higher peak pressures and higher driving pressures were more likely to develop a PPC.[9] Their results indicate that, for every increase in peak pressure of 1 cm H_2O, there was a 3% increase in the odds ratio for the development of PPCs. Similar findings were also reported by Levin and colleagues,[19] which concluded that higher plateau pressures were associated with respiratory complications with an observed reduction in PPCs with a reduction in plateau pressure to a median of 16 cm H_2O. The authors inferred that it was the interplay between tidal volume and compliance that determines the effects of the high plateau and driving pressures on the development of PPCs, and that the tidal volume to compliance ratio is of greater significance on clinical outcome than tidal volume alone. As stated by the authors, both these factors are modifiable, with

ventilator settings contributing to plateau pressures, and both recruitment manoeuvres and PEEP improving lung compliance. A recent trial published by Amato and colleagues,[18] which examined the ventilator parameters of over 3000 patients with ARDS, found that driving pressure (plateau pressure − PEEP) was most strongly associated with increased survival with an increase of 7 cm H_2O of driving pressure resulting in an increase in mortality (relative risk: 1.41; 95% CI: 1.31–1.51; $P<0.001$). Neto and colleagues[19] also corroborated this finding in a meta-analysis, which concluded that intraoperative high driving pressure is associated with an increased risk of PPCs. Similar to above, changes in tidal volume or PEEP were not independently associated with increased survival, only if the changes themselves led to a reduction in driving pressure.

In our univariable analysis, lower preoperative oxygen saturations (SpO_2) were associated with an increased risk of PPCs ($P<0.001$). This is consistent with other research, which has indicated that patients with preoperative SpO_2 of 91–95% were twice as more likely to develop a PPC compared to those with SpO_2 of >96%.[20] Our analysis also suggested that intraoperative FiO_2 was significantly associated with an increased risk of PPCs, and that an increase in FiO_2 by 5% increases the risk of PPC by 8% (2.6–14.1%; $P=0.008$). We found that 60% of patients undergoing emergency laparotomy surgery were ventilated with an $FiO_2 \geq 0.5$. Again, logistic regression fitted to the data highlights the significance of FiO_2; an FiO_2 of 0.7 in a 30-yr-old patient with PIP <30 cm H_2O suggests a 40% chance of acquiring a PPC. Our data do not allow us to discriminate between the clinical need for a high FiO_2 to maintain a minimum SpO_2, or a clinical choice to use a higher FiO_2 independently of SpO_2. Although a higher FiO_2 has been recommended to reduce the risk of surgical site infections, high FiO_2 has also deleterious effects; for instance, it can lead to an increase in absorption atelectasis and oxidative stress to the lungs.[21] A recently published hospital-based registry study found that a high median FiO_2 was associated with an increased risk of respiratory complications in a dose-dependent manner (adjusted odds ratio for high *vs* low FiO_2: 1.99; 95% CI: 1.72–2.31; $P<0.001$) and an increase in 30 day mortality (odds ratio for high *vs* low FiO_2: 1.97; 95% CI: 1.30–2.99; $P<0.001$).[22] Although several hypotheses exist to explain the underlying mechanism behind hyperoxia and pulmonary complications, the exact cause remains unknown. It is thought that the atelectasis resulting from a high FiO_2 leads to intrapulmonary shunt and reduced oxygenation, and predisposes to infection.[22] Hyperoxia can also lead to oxidative stress leading to increased inflammation, which is thought to be more pertinent in patients with underlying respiratory co-morbidities. At present, there is no consensus regarding the optimum FiO_2 or intraoperative SpO_2, and further research into this area is warranted.

The findings of ALPINE were associated with limitations. The most significant limitation of the study was that we were unable to adjust the results of the multivariable analysis for the likelihood of developing a PPC using the ARISCAT score, the most well-known and externally validated risk assessment tool for the development of PPCs. Out of the seven variables included in the ARISCAT tool, we were unable to collect data on previous respiratory infections in the last month and on the presence of preoperative anaemia. The results were, however, adjusted for the five remaining variables (age, preoperative oxygen saturations, duration of procedure, surgical incision, and emergency procedure). Secondly, whilst it was observational in nature, the fact that it was both voluntary and prospective may have had an impact on the delivery of the ventilation by the anaesthetist and influenced the ventilator strategies employed. Thirdly, the ventilator parameters were recorded as the 'most frequently documented', and so, although they are more than likely to be reflective of true practice, it is possible that the peak pressures and tidal volumes used varied throughout the procedure, and thus, they may not be wholly representative. Lastly, as the data were only collected as part of routine standard care, we were limited to collecting data on PPCs on the patients who had the information readily available, as we were unable to order any additional investigations to confirm the diagnosis.

In conclusion, we have shown that the majority of patients undergoing emergency laparotomy surgery received a median tidal volume of 8 ml kg^{-1} IBW^{-1}, a PEEP of 5 cm H_2O, and a median PIP of 20 cm H_2O, and that <5% were ventilated using LPV. We also found that age, increased FiO_2, and PIP were significantly associated with development of PPCs. As both PIP and FiO_2 are potentially modifiable factors, an RCT in the near future to determine their effect further would be of clinical benefit. Our analysis suggests that future research should revolve less around low tidal volumes and PEEP, and focus more on determining optimal PIP and FiO_2.

Authors' contributions

Study conception and design: X.W., M.C.H., P.M.O., M.C.
Advice on data-collection strategy: I.C.S.
Data collection: PLAN.
Acquisition and interpretation of data: I.C.S., X.W., M.C.
Data analysis: I.C.S., X.W., P.M.O.
Statistical aspects, including design, data analysis, and crude interpretation: I.C.S.
Writing of manuscript: X.W.
Revising manuscript: X.W., M.C.H., P.M.O., M.C.
Accountability for all aspects of the study: M.C.
All authors have read and approved the final manuscript.

Declaration of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.bja.2018.04.048.

Appendix

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