**Adoption of Lung Protective ventilation IN patients undergoing Emergency laparotomy surgery: the ALPINE study.**

**A prospective multi-centre observational study**

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**Abstract**

The primary aim was to determine whether patients undergoing emergency laparotomy surgery are ventilated using a lung protective ventilation (LPV) strategy comprising of tidal volume ≤8ml/kg/IBW, PEEP >5 cm H2O and recruitment manoeuvres. The secondary aim was to investigate the association between ventilation factors (LPV strategy, intraoperative FiO2 and peak inspiratory pressure) and the occurrence of post-operative pulmonary complications (PPCs).

Data were collected prospectively in twenty-eight hospitals across London as part of routine National Emergency Laparotomy Audit. Patients were followed up for seven days. Complications were defined according to the European Perioperative Clinical Outcome (EPCO) definition.

Data were collected from 568 patients. The median (IQR] tidal volume observed was 500 ml (450-540 ml), corresponding to a median tidal volume of 8 ml/kg/ideal body weight (IBW) (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 HR=1.06 p=0.69). A peak inspiratory pressure of less than 30 cmH20 was protective against the development of PPC (HR =0.46 CI 0.30-0.72, p=0.001). The median FiO2 was 0.5 (IQR, 0.44 – 0.53) and an increase in FiO2 by 5% increased the risk of developing a PPC by 8% (2.6% - 14.1% p=0.008).

Both intraoperative peak inspiratory pressure and FiO2 are independent factors significantly associated with the development of a PPC in emergency laparotomy patients. Further studies are required to identify their causality effect and to demonstrate if their manipulation could lead to better clinical outcomes.

Keywords: Emergency laparotomy surgery, Lung protective ventilation, post-operative pulmonary complications

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 ≤ 8ml/kg/ideal body weight, positive end-expiratory pressure (PEEP) of ≥ 5cm H2O, recruitment manoeuvres and maintenance of plateau pressure < 30 cmH20 is a well-established standard of care in ventilated patients with Acute Respiratory Distress Syndrome (ARDS) in the intensive care unit3 . Recently there has been 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 injury4. The ventilator strategies employed in patients undergoing emergency surgery currently remain unknown. Identification of intraoperative strategies which 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 a lung protective ventilation (LPV) strategy comprising of tidal volume ≤8ml/kg/IBW, PEEP ≥ 5 cm H2O and use of recruitment manoeuvres. The secondary aim was to investigate the association between ventilation factors (LPV strategy, intraoperative FiO2 and peak inspiratory pressure) and the occurrence of post-operative pulmonary complications (PPCs). We hypothesise that the majority of patients are not ventilated using a LPV strategy but that implementation of the bundle may lead to a reduced occurrence of PPCs.

**Methods**

Adoption of Lung Protective ventilation IN patients undergoing Emergency laparotomy surgery (ALPINE) was a prospective multi-centre observational study undertaken in collaboration with the National Emergency Laparotomy Audit (NELA) and delivered by the Pan-London Peri-operative Audit and Research Network (PLAN). The study was undertaken between the 31st October 2016 and the 31st March 2017 with twenty-eight 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 was 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 (NRES) decision tool (<http://www.hra-decisiontools.org.uk/research/)>. 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 eighteen who underwent expedited, urgent or emergency laparotomy surgery as per NELA guidelines were included5. This comprised any open, laparoscopic or laparoscopically assisted procedures on the gastrointestinal tract. Any elective or diagnostic procedures were excluded.

Intraoperative data collected included demographics, height and weight in order to calculate ideal body weight (IBW). 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. Duration of anaesthesia and grade of most senior anaesthetist was also recorded as either consultant (most senior) or trainee anaesthetist. The mode of ventilation, tidal volume delivered, positive end expiratory pressure (PEEP), peak inspiratory pressure (PIP), use of recruitment manoeuvres and intraoperative FiO2 were recorded. Data for each ventilation parameter were recorded manually by the anaesthetist onto a proforma by recording the modal documented value from the anaesthetic chart for each whole procedure. The development of PPCs were recorded on a daily basis until day 7 post-operatively by reviewing the patient’s notes, routine biochemical results and radiographs if undertaken. PPCs were defined according to the European Perioperative Clinical Outcome (EPCO) definition and included respiratory failure, respiratory infection, atelectasis, bronchospasm, pneumothorax and aspiration pneumonia7 Admission and mode of ventilation in ITU 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 ARISCAT score, a well-validated risk assessment tool for the peri-operative development of PPCs and data were adjusted in the multivariable regression model for these variables8

LPV was defined as low tidal volume ventilation (less or equal to 8ml/kg/ideal body weight), application of PEEP of equal to or more than 5 cmH2O and use of recruitment manoeuvres. A recruitment manoeuvre was defined as 30 seconds of 30 cmH2O continuous positive airway pressure (CPAP) every 30 minutes. The definition of LPV for this study was as per the randomized controlled study conducted by Foutier et al9

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 summarized 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 differences between the two groups: chi-squared 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 (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 variable (see supplementary information). Two multivariable models were fitted; one which included the bundle and one which 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 less than or equal to 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 the 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*. College Station, TX: StataCorp LP).

**Results**

A total of 28 hospitals across Greater London participated in the ALPINE study with 568 patients included in the final analysis. There was 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 years (48-78 years) with the majority of patients being male (307 Male *vs* 260 Female). The patient and ventilation baseline characteristics and 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 (PCV-VG) in 185/568 patients (33%) with volume control accounting for 30% of cases followed by pressure control (18%). The median (IQR [range] pre-operative oxygen saturations were 97% (95-98%).

The median (IQR) weight was 70 kg (62-85 kg) and the median ideal body weight 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/IBW (IQR, 7.1 – 9 ml) with the highest tidal volume documented as 14ml/kg/IBW. A total of 265 patients (50.5 %) received a tidal volume of less than or equal to 8ml/kg/IBW. The vast majority of patients (n = 523, 92%) were ventilated with PEEP with a median value of 5 cm H2O (IQR, 5 -6 cm H2O). The median peak inspiratory pressure (PIP) was 20 cm H2O (IQR, 17 – 23.5 cm H2O) with the highest documented PIP of 40 cm H2O. The distribution of PIP according to the development of PPCs can be viewed in Figure 1. The majority of patients (n = 516, 91%) had a PIP of less than or equal to 30 cm H2O. The median intraoperative FiO2 administered was 0.5 (IQR, 0.44-0.53) with 1.0 being the highest FiO2 administered. Only 10% of patients (54/568) received an intraoperative recruitment manoeuvre defined as 30 seconds of 30 cm H2O CPAP. In total, 28/568 patients (4.9%) met the criteria for LPV as previously defined above.

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. Post-operative respiratory failure was the most common PPC (n= 197, 35%) followed by atelectasis (n= 182, 32%). The distribution of PPCs can be viewed in Table 2. The median time to develop a PPC was one day (IQR, 1-1) and the median duration of the PPC was 4 days (IQR, I-17). Most patients developed the first PPC within one day after operative intervention (213/275, 77.5%).

Univariable analyses (Table 3) reveal that age, PIP and FiO2 are positively associated with development of a PPC (p<0.004). Both higher pre-operative oxygen saturations and use of PEEP > 5 cm H2O intraoperatively are associated with a reduced occurrence of PPCs (p=0.001).

In the multivariable survival analysis, implementation of the LPV bundle was not associated with a reduction in the development of PPCs. However, increasing age, PIP and FiO2 remain strong predictors for the risk of development of one or more PPCs (p<0.008) (Table 4). A PIP of less than 30 cmH2O reduces the risk by half (HR=0.47, 95%CI (0.30, 0.72, p=0.001). More precisely, an increase in age of 5 years is associated with an increase of a PPC increases by 6% (4% - 8%, p<0.001). An increase in FiO2 by 5% increases the risk of PPC by 8% (2.6% – 14.1%, p=0.008). The distribution of PPCs according to intraoperative FiO2 can be viewed in Figure 2 and the effects of intraoperative FiO2 and PIP on the survival curves associated to PPC are shown in Figure 3.

**Discussion**

This prospective multi-centre observational study revealed that 48% of patients undergoing emergency laparotomy surgery developed a PPC and that age, intraoperative FiO2 and peak inspiratory pressure are 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 examined2. Postoperative respiratory failure has consistently been reported as the most common PPC and this was also confirmed in the ALPINE study10.

The impact of developing a PPC is significant. Mortality is increased with between 14% to 30% of patients who sustain a PPC dying within 30 days of major surgery compared to 0.2% to 3% of those without10. Length of stay is also significantly increased by up to 17 days thus PPCs represent 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 surgery11.

Recently there has been increasing evidence that a 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 period9,10,12. The definition of LPV in this study was adopted from Foutier et al who conducted to date the largest randomised controlled trial of LPV in abdominal surgery9. This comprised a TV of 6-8ml/kg/IBW, a PEEP of 6-8 cm H20, and recruitment manoeuvres every 30 minutes. In our study, only 4.9 % of patients undergoing emergency surgery were ventilated with a LPV strategy thus highlighting that uptake of a lung protective approach is not widespread. This is likely attributed to the fact that less than 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 500ml which equated to a median tidal volume of 8ml/kg/IBW. This was much lower than the standard ventilation group in the RCT by Foutier et al 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 less than 8ml/kg/IBW irrespective of the amount of PEEP used9. However, tidal volume was not found to be a predictor for the development of a PPC in our analysis, a finding which has also been corroborated by the LAS VEGAS study which looked at the ventilation practice of over 9000 patients14. We also found that PEEP was used in 92% of patients with 82% of patients receiving a PEEP of ≥ 5cm H20. 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 which have advocated higher levels of PEEP to prevent PPCs14-16. It should be noted however that these studies compared high levels of PEEP (>6 cm H20) against zero PEEP. Interestingly, a hospital based registry study of over 69 000 patients suggested that a PEEP level of 5 cm H2O is most beneficial, with higher or lower levels associated with increased risk17. In fact, high levels of PEEP (>10 cm H2O) have been proposed to actually cause harm with increase haemodynamic compromise and no reduction in the occurrence of PPCs15. Our findings are similar to a retrospective study conducted by Levin et al which found that the median tidal volume employed by anaesthetists was 525 ml (median tidal volume 8ml/kg/IBW) with a median level of 4 cm H20 of PEEP18. 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 VILI.

Our analysis suggests that there is a significant association between PIP and the development of PPCs and that maintaining the PIP at less than 30cm H2O reduces the risk of a 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-year-old patient ventilated with a Fi02 of 0.5, PEEP of 5 cmH2O but a PIP of more than 30cm H20 has a 66% chance of developing a PPC compared to 27% if the PIP is less than 30cm H2O. 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 PPC9. Their results indicate that for every increase in peak pressure of 1 cm H2O, there was a 3% increase in the odds ratio for the development of PPCs. Similar findings were also reported by Ladha et al 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 H2O18. 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 et al 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 7cm H2O of driving pressure resulting in an increase in mortality (relative risk, 1.41; 95% confidence interval [CI], 1.31 to 1.51; p<0.001) 19.Neto *et al* also corroborated this finding in a meta-analysis which concluded that intraoperative high driving pressure is associated with an increased risk of PPCs20. 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 pre-operative oxygen saturations (SpO2) were associated with an increased risk of PPCs (p<0.001). This is consistent with other research which has indicated that patients with preoperative SpO2 of 91-95% were twice as more likely to develop a PPC compared to those with SpO2 of more than 96%.21 Our analysis also suggested that intraoperative FiO2 was significantly associated with an increased risk of PPCs and that an increase in FiO2 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 FiO2 ≥0.5. Again, logistic regression fitted to the data highlights the significance of FiO2; an FiO2 of 0.7 in a 30-year-old patient with PIP less than 30 cmH2O suggests a 40% chance of acquiring a PPC. Our data does not allow us to discriminate between the clinical need for a high FiO2 to maintain a minimum SpO2 or a clinical choice to use a higher FiO2 independently of SpO2. Although a higher FiO2 has been recommended to reduce the risk of surgical site infections, high FiO2 has also deleterious effects, for instance it can lead to an increase in absorption atelectasis and oxidative stress to the lungs22. A recently published hospital-based registry study found that a high median FiO2 was associated with an increased risk of respiratory complications in a dose dependent manner (adjusted odds ratio for high *vs* low FiO2 1.99, 95% CI 1.72 -2.31, p<0.001) and an increase in 30-day mortality (odds ratio for high *vs* low FiO2 1.97, 95% CI 1.30 – 2.99, p<0.001)23. 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 FiO2 leads to intrapulmonary shunt and reduced oxygenation and predisposes to infection23. Hyperoxia can also lead to oxidative stress leading to increased inflammation which is thought to be more pertinent in patients with underlying respiratory comorbidities. At present there is no consensus regarding the optimum FiO2 or intraoperative SpO2 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 pre-operative anaemia. The results were however adjusted for the five remaining variables (age, pre-operative oxygen saturations, duration of procedure, surgical incision and emergency procedure). Secondly, while 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 was 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 receive a median tidal volume of 8ml/kg/IBW, a PEEP of 5 cm H2O and a median PIP of 20 cm H2O, and that less than 5 % are ventilated using a LPV strategy. We have also shown that age, increased FiO2 and PIP are significantly associated with the development of PPCs. As both PIP and FiO2 are potentially modifiable factors, a RCT in the near future to further determine their effect would be of clinical benefit. Our analysis suggests that future research revolves less around low tidal volumes and PEEP and focuses more on determining the optimum PIP and FiO2.

**Authors contributions and Authorship**

XW: Substantial contribution to conception and design of study, acquisition and interpretation of data. Wrote and revised the manuscript.

MCH: Significant contribution to conception and design of study and revision of article.

PMO: Contribution to conception and design of study. Contribution to data analysis and revision of article

ICS: Substantial contribution: advice on data collection strategy and responsible for all the statistical aspects of the study including design, data analysis and crude interpretation.

MC: Substantial contribution to conception and design, acquisition and interpretation of data. Revision of article. Accountable for all aspects of study

PLAN: Responsible for data collection

All authors have read and approved the final manuscript.

**Collaborators**

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**Illustrations**

**Figure 1.** Boxplot of the distribution of peak inspiratory pressure (PIP) according to the development of PPCs. The p-value evaluates the strength of its univariate association with the outcome (Table 2).

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**Figure 2**. Boxplot of the distribution of intraoperative FiO2 according to the development of PPCs. The p-value evaluates the strength of its univariate association with the outcome (Table 2).



**Figure 3.** The effects of FiO2 values and and PIP on the occurrence of PPCs within 7 days (estimated stratified survival curves). Age is set at the average of 62 years

