Expiratory Flow Limitation as a Risk Factor for Pulmonary Complications After Major Abdominal Surgery

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BACKGROUND: Postoperative pulmonary complications are major causes of postoperative morbidity and mortality. Although several risk factors have been associated with postoperative pulmonary complications, they are not consistent between studies and, even in those studies in which these factors were identified, the predictive power is low. We hypothesized that postoperative pulmonary complications would correlate with the presence of intraoperative expiratory flow limitation.

METHODS: Candidates for this prospective observational study were patients undergoing general anesthesia for major abdominal surgery. Preoperative data collection included age, body mass index, American Society of Anesthesiologists class, smoking and dyspnea history, and room air Po_2. Expiratory flow limitation was assessed intraoperatively using the positive end-expiratory pressure test. Postoperative data collection included the incidence of postoperative pulmonary complications.

RESULTS: Of the 330 patients we enrolled, 31% exhibited expiratory flow limitation. On univariate analysis, patients with expiratory flow limitation were more likely to have postoperative pneumonia (5% vs 0%, $P < .001$) and acute respiratory failure (11% vs 1%, $P < .001$) and a longer length of hospital stay (7 vs 9 days, $P < .01$). Multivariate analysis identified that expiratory flow limitation increased the risk of developing postoperative pulmonary complications by >50% (risk ratio, 2.7; 95% confidence interval, 1.7–4.2). Age and Medical Research Council dyspnea score were also significant multivariate risk factors for pulmonary complications.

CONCLUSIONS: Our results show that intraoperative expiratory flow limitation correlates with that of postoperative pulmonary complication after major abdominal surgery. Further work is needed to better understand the relevance of expiratory flow limitation on postoperative pulmonary outcomes. (Anesth Analg 2016;XXX:00–00)

Postoperative pulmonary complications (PPCs) are a major cause of postoperative morbidity, mortality, and increased length of hospital stay.[1] Traditionally, several risk factors have been associated with PPCs, including age, chronic obstructive pulmonary disease (COPD), cigarette use, congestive heath failure, functional dependence, obesity, and obstructive sleep apnea.[1–4] In a 2010 multicenter trial, Canet et al[5] used multivariable logistic regression to identify 7 independent predictors of PPCs including preoperative peripheral capillary oxygen saturation (Spo_2), respiratory infection in the last month, surgical incision, and duration of surgery. The strongest predictor was a preoperative Spo_2 <90%. Although clinically useful because Spo_2 is very easy to determine, patients undergoing major abdominal surgery seldom present with such low Spo_2 values.[6,7] In addition, risk factors for PPCs are not consistent across studies. For example, Smetana et al[2] found that smoking history, the American Society of Anesthesiologists physical status classification, and the presence of both COPD and heart failure were predictive of PPCs, whereas the same parameters did not predict PPCs in a subsequent study by Canet et al.[5] Moreover, even in those studies in which risk factors for PPCs were identified, the odds ratio was relatively low, suggesting a weak predictive ability. Although the reason why risk factors for PPCs are inconsistent between studies is unclear, differences in patient population, underlying disease, drugs used, and new surgical and anesthesiological techniques may all play a role. In addition, the type of surgery might be relevant because predictors appropriate for thoracic surgery such as spirometry or carbon dioxide lung diffusion capacity (DLCO) may not be applicable to patients undergoing major abdominal surgery. For example, spirometry is recommended for the diagnosis of obstructive lung disease but has not translated into effective risk prediction for individual patients.[3,8]

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We hypothesized that expiratory flow limitation (EFL) would be an important risk factor for PPCs. EFL occurs when at a given lung volume the expiratory flow is independent of the patient's expiratory effort or on an increase of elastic recoil pressure. EFL has been described as occurring immediately after peak expiratory flow is reached during the forced vital capacity maneuver.[9] However, patients with acute and/or chronic lung disease can experience EFL even during tidal ventilation, suggesting that expiratory flow is markedly reduced and dynamic hyperinflation may be present.[10] It is not surprising that EFL may help identify patients with greater impairment of lung function and disability. Clinically, EFL is associated with the severity of diseases such as COPD,[10] acute and chronic heart failure,[11,12] cystic fibrosis,[13] acute respiratory distress syndrome,[14] cardiac surgery,[15] spinal cord injury,[16] obesity,[17] sleep apnea,[18] and bronchiectasis.

In spontaneously breathing patients, the negative expiratory pressure (NEP) test is considered the criterion standard for detecting EFL.[9] The NEP test, however, is difficult to apply in ventilated patients during anesthesia because it requires a closed circuit and involves other technical difficulties (connection between the NEP system and the expiratory port of the ventilator). Recently, a new bedside method to detect the presence of EFL has been developed.[19] This method, based on subtracting 3 cm H_2O of positive end-expiratory pressure (PEEP test) at the beginning of expiration, has produced results comparable with those obtained with the NEP test.[19]

Patients may develop EFL during general anesthesia because of the reduction of functional residual capacity that occurs with anesthetic induction[20] and age- and disease-dependent reduction of maximal expiratory flow.[21] We hypothesized that patients who develop EFL during general anesthesia would have a more compromised maximal expiratory flow than patients without EFL. EFL, which is associated with several different clinical conditions, would then represent an important limitation in lung function and correlate with postoperative respiratory complications. To test our hypothesis, we studied whether EFL during anesthesia was a risk factor for PPCs in patients undergoing major abdominal surgery.

METHODS

Study Design and Patients

Candidates for this prospective observational study were patients undergoing major abdominal surgery from January 2013 to January 2014 at the S. Anna University Hospital of Ferrara. This study was approved by the ethics committee of our institution, and written informed consent was obtained from each subject. The study was registered on Clinicaltrial.gov (registration number: 02229591; principal investigator: Dr. S.S.; registration date: August 28, 2014).

The exclusion criteria were as follows: patients younger than age 18 years, surgical intervention lasting <2 hours, and patients' participation refusal.

The severity of chronic dyspnea was rated according to the dyspnea scale proposed by the Medical Research Council.[22] Anesthesia was induced with propofol (1.5 mg/kg), fentanyl (3 μg/kg), and vecuronium bromide/rocuronium (0.1 mg/kg) and maintained with sevoflurane and air–oxygen mixture 50%/50%. Muscle paralysis was monitored by ulnar nerve stimulation. All patients were intubated via a 7.5- or 8.0-mm internal diameter low pressure-cuffed endotracheal tube and ventilated in volume-controlled mode with the tidal volume and respiratory rate titrated to maintain normocapnia (Table 1). The level of PEEP was set at 5 cm H_2O for the duration of surgery.[19]

Procedures

The determination of EFL during general anesthesia and paralysis was performed using the PEEP test. This test is based on a sudden decrease of expiratory resistance obtained by a subtraction of 3 cm H_2O of PEEP during expiration.[19] A patient was considered to have EFL when reducing PEEP by 3 cm H_2O did not increase expiratory flow when compared with the previous breath. If expiratory flow increased with PEEP reduction, the patient was considered not flow limited (Fig. 1). We performed the PEEP test at the beginning and at the end of surgery.

Outcomes

The incidence and type of pulmonary complications within the first 7 postoperative days were recorded by a physician who reviewed the clinical records everyday and was blinded to study group (ie, whether patients were flow limited or not). The details of the definitions of PPCs are reported in the Supplemental Digital Content (Supplemental Appendix 1, http://links.lww.com/AA/B444).[23–28]

Statistical Analysis

The sample size was calculated according to the primary endpoint: the incidence of PPCs in patients with EFL undergoing major abdominal surgery. We estimated from our previous study[19] that the prevalence of EFL in elderly patients undergoing general anesthesia for major abdominal surgery was 42%. Assuming that this proportion is significantly different from the null hypothesis value of 0.5, we calculated that at least 305 patients would be needed to observe differences in the main outcome (type I error rate of 0.05 and a type II error rate of 0.20 [80% power]). After estimating a 10% dropout rate (refusal to participate, interruption of intervention, and lost to follow-up), we chose a sample size of 330 patients. Sample size analysis was performed using MedCalc software (MedCalc software 9.3.6.0, Mariakerke, Belgium).

Data are presented as frequencies with percentages and mean ± standard deviation or medians with 25th to 75th percentiles range (interquartile range, 25–75), depending on the type of data and their distribution. The Shapiro-Wilk test was used to assess the assumption of normality. Categorical data were compared using the χ^2 test. Unpaired Student *t* tests or Mann-Whitney *U* tests for data with normal or nonnormal distribution, respectively, were used to compare continuous variables.

The association between preoperative baseline patient characteristics and PPCs was modeled using binary logistic regression analysis and is reported as estimated odds ratio and relative 95% confidence interval (CI). A multivariate logistic regression model was used to estimate the

Table 1. Clinical and Demographic Characteristics of the Patients Enrolled

	Without EFL (n = 229)	With EFL (n = 101)	*P*
Age (y)	65 ± 15	70 ± 12	.005
Male sex, n (%)	120 (52)	32 (32)	.0008
BMI (kg/m^2)	26 ± 4	29 ± 5	<.0001
ASA, n (%)			.172
I	14 (6)	4 (4)	.427
II	95 (42)	41 (41)	.880
III	115 (50)	49 (48)	.775
IV	5 (2)	7 (7)	.034
Preoperative comorbidities			
Lung diseases, n (%)	25 (11)	33 (33)	<.0001
COPD	15	18	.002
Emphysema	7	10	.010
Bronchial asthma	3	5	.048
Heart diseases, n (%)	44 (19)	46 (45)	<.0001
Chronic cardiac ischemia	17	20	.001
Cardiac arrhythmia	12	11	.063
Valvular diseases	5	3	.668
Chronic heart failure	10	12	.012
Smoking history, n (%)	96 (42)	42 (42)	.954
Current smokers, n (%) (quit by at least 1 y)	69 (30)	33 (33)	.645
Pack-years	31 ± 9	33 ± 10	.073
Preoperative Spo_2 (room air)	98 [97–100]	97 [96–98]	.0002
MRC	1.7 ± 0.9	2.4 ± 1.1	<.0001
Length of surgery (min)	190 ± 76	208 ± 85	.052
Vascular surgery, n (%)	18 (8)	10 (10)	.690
Major intestinal surgery, n (%)			
Laparotomic	113 (49)	55 (55)	.461
Laparoscopic	98 (43)	36 (35)	.272
Tube caliper 8.0, n (%)	113 (49)	41 (40)	.177
V_T, mL/kg	6.9 ± 1.3	6.7 ± 0.9	.161
RR, breaths/min	14 ± 0.9	13 ± 1	.051
Crystalloids (mL/kg/h)	3.0 [2.3–3.5]	6.0 [5.0–9.0]	<.0001
Urinary output (mL)	200 [0–400]	150 [0–300]	.139
Transfused patients, n (%)	27 (12)	13 (13)	.782
PPCs, n (%)	29 (13)	42 (42)	<.0001
ICU admission, n (%)	11 (5)	17 (17)	.0003
LOS	7 ± 4	9 ± 4	.004

Normally distributed data are expressed as mean ± standard deviation. Not normally distributed data are expressed as median [interquartile range].

Abbreviations: ASA, American Society of Anesthesiologists physical status classification; BMI, body mass index; COPD, chronic obstructive pulmonary disease; MRC, Medical Research Council scale for dyspnea; ICU, intensive care unit; LOS, length of hospital stay; PPCs, postoperative pulmonary complications; RR, respiratory rate; Spo_2, peripheral capillary oxygen saturation; V_T, tidal volume.

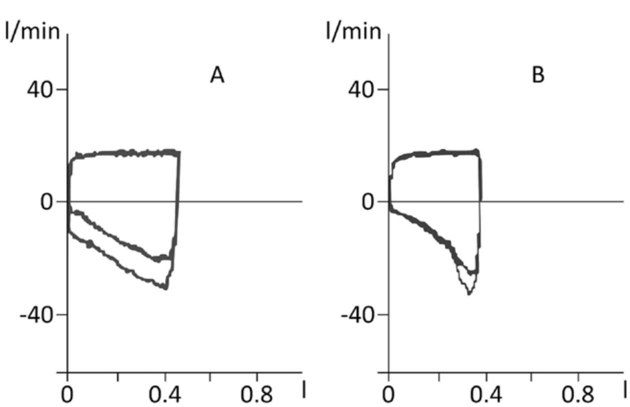

Figure 1. Flow–volume loops of representative patients undergoing positive end-expiratory pressure (PEEP) test. A, Subtraction of 3 cm H_2O of PEEP increased the expiratory flow, and the patients were classified as not flow-limited. B, Subtraction of 3 cm H_2O of PEEP did not increase expiratory flow, except for a brief initial transient, which is mainly the result of a sudden reduction of volume of the upper airways and heralds flow limitation. See text for further explanations.

association between PPCs and EFL adjusting for covariates (age, Medical Research Council [MRC], American Society of Anesthesiologists, and length of surgery). In the same fashion, Poisson regression model with a robust error variance was performed to assess unadjusted and adjusted risk ratios and relative 95% CI. For multivariate regression, we chose a threshold age >65 years based on previous studies of pulmonary complications[5] and surgical duration >240 minutes based on the third quartile for surgical duration for intestinal procedures in our hospital.

Statistical analyses were performed using SPSS 20.0 statistical software (SPSS Inc, Chicago, IL) and STATA (StataCorp. 2011, Stata Statistical Software: Release 12; StataCorp LP, College Station, TX). In all statistical analyses, a 2-tailed test was performed and the *P* value ≤.05 was considered statistically significant.

RESULTS

Three hundred thirty patients were enrolled. Their clinical characteristics are presented in Table 1 and the flowchart of the study in Figure 2. After anesthesia induction, 64 patients (19.3%) had EFL. All patients with EFL at the beginning of the procedure and an additional 37 (11.3%) patients demonstrated EFL at the end of surgery. Hence, by applying the PEEP test, 2 groups of patients were identified: the EFL group (101 patients, 31%) and the no EFL group (229 patients, 69%) (Fig. 1). Patients who developed EFL during anesthesia were older and had a higher body mass index and an MRC score. No differences were detected in terms of duration and the type of surgery (Table 1).

In univariate analysis, patients with EFL had a higher percentage of PPCs ($P = .003$; Table 1). Acute respiratory failure, respiratory infection, and pneumonia were more common in the group with EFL (Table 2). Among the patients with EFL who developed an acute respiratory failure, 73% were reintubated and 27% were managed with noninvasive positive pressure ventilation. The intensive care unit admission rate was higher, and hospital length of stay was longer in patients with EFL (Table 1).

In multivariate analysis (Table 3), factors associated with PPCs included the presence of EFL ($P < .0001$), MRC dyspnea score ≥3 ($P = .002$), and age ≥65 years ($P = .023$). The presence of EFL doubled the possibility of developing PPCs after major abdominal surgery (odds ratio: 4.2; 95% CI, 2.3–7.6). The odds ratios for MRC ≥3 and age ≥65 years were 2.6 and 2.1, respectively (Table 3).

Using Poisson regression analysis (Table 4), we estimated the relative risk of PPCs given the intraoperative presence of EFL ($P < .0001$), MRC dyspnea score ≥3 ($P = .006$), and age ≥65 years ($P = .024$). The presence of EFL increased the risk of developing PPCs after major abdominal surgery by >50% (risk ratio, 2.7; 95% CI, 1.7–4.2). The relative risk factors for MRC ≥3 and age ≥65 years were 1.8 and 1.7, respectively (Table 4).

DISCUSSION

In this study, we found in patients undergoing major abdominal surgery that EFL, as assessed intraoperatively by the PEEP test, was a significant risk factor for PPC.

Our data are consistent with the existing literature. The presence of EFL has been reported in patients with a wide variety of lung diseases and has recently been demonstrated

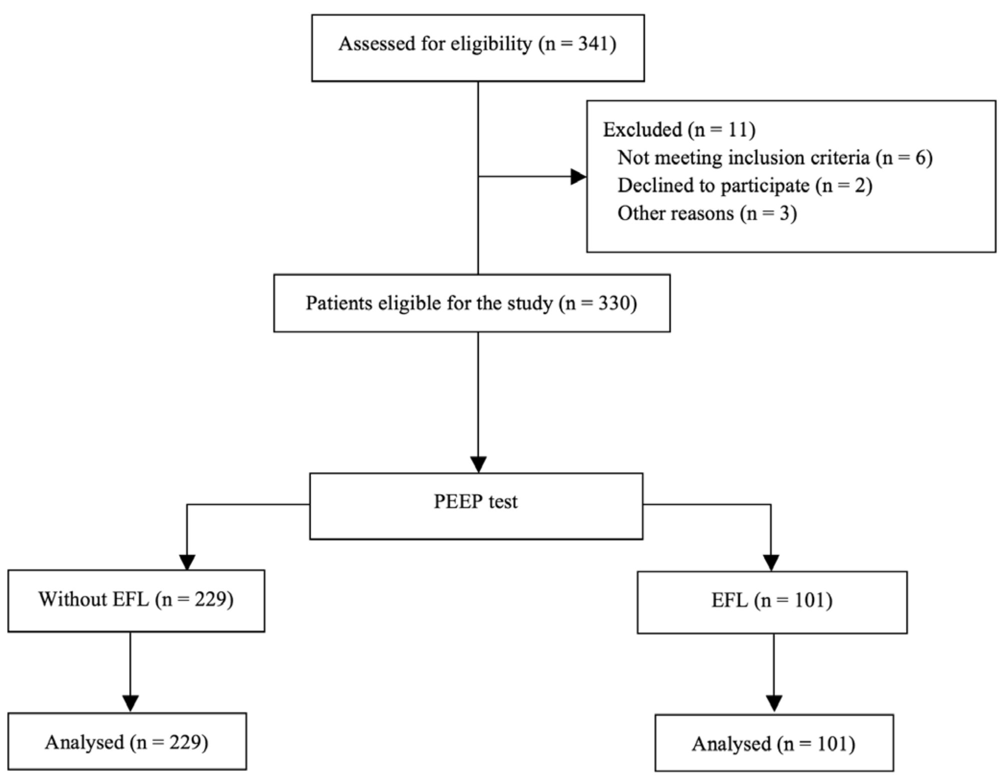

Figure 2. Flowchart of the study.

Table 2. Different Categories of PPCs in Patients With and Without Expiratory Flow Limitation

	Without EFL (n = 229)	With EFL (n = 101)	*P*
Hypoxemia, n (%)	18 (8)	14 (14)	.89
Acute respiratory failure, n (%)	2 (1)	11 (11)	<.001
Invasive mechanical ventilation, n	2	8	
Noninvasive mechanical ventilation, n	0	3	
Bronchospasm, n (%)	2 (1)	2 (2)	.72
Respiratory infection, n (%)	7 (3)	10 (10)	.01
Pneumonia, n (%)	0	5 (5)	.001

Abbreviations: EFL, expiratory flow limitation; PPCs, postoperative pulmonary complications.

Table 3. Association Between Baseline Characteristics of Patients and Development of PPCs According to Logistic Regression Analysis Adjusted for Potential Confounders

	Univariate Analysis			Multivariate Analysis		
	Crude Odds Ratio	95% CI	*P*	Adjusted Odds Ratio	95% CI	*P*
EFL (reference: absence)						
Presence	5.1	2.9–8.9	<.0001	4.2	2.3–7.6	<.0001
Age (years; reference: <65 y)						
≥65	2.5	1.4–4.5	.001	2.1	1.1–4.1	.023
ASA (reference: <3)						
≥3	2.4	1.4–4.3	.002	1.9	1.0–3.6	.059
MRC (reference: <3)						
≥3	3.5	2.0–6.0	<.0001	2.6	1.4–4.8	.002
Length of surgery (reference: <240 min)						
≥240 min	2.2	1.2–4.0	.010	1.9	1.0–3.7	.059
Sex (reference: male)						
Female	1.2	0.7–2.0	.545			
Smoking history (reference: absence)						
Presence	0.8	0.5–1.3	.372			
Preoperative Spo_2 (reference: Spo_2 >96%)						
≤96%	1.8	1.0–3.3	.055			
Lung disease (reference: absence)						
Presence	1.2	0.6–2.4	.549			

A series of exploratory analyses were performed to assess for potential 2-way interaction between EFL and the other categorical explanatory variables, and no significant 2-way interactions were detected (all *P* ≥.27).

Abbreviations: ASA, American Society of Anesthesiologists physical status classification; CI, confidence interval; EFL, expiratory flow limitation; MRC, Medical Research Council scale for dyspnea; PPCs, postoperative pulmonary complications; Spo_2, peripheral capillary oxygen saturation.

Table 4. Association Between Baseline Characteristics of Patients and Development of PPCs According to Poisson Logistic Regression Analysis Adjusted for Potential Confounders

	Univariate Analysis			Multivariate Analysis		
	Crude Relative Risk	95% CI	*P*	Adjusted Relative Risk	95% CI	*P*
EFL (reference: absence)						
Presence	3.4	2.2–5.2	<.0001	2.7	1.7–4.2	<.0001
Age (years; reference: <65 y)						
≥65	2.1	1.3–3.4	.002	1.7	1.1–2.7	.024
ASA (reference: <3)						
≥3	2.0	1.3–3.2	.003	1.6	1.0–2.5	.058
MRC (reference: <3)						
≥3	2.5	1.7–3.8	<.0001	1.8	1.2–2.9	.006
Length of surgery (reference: <240 min)						
≥240 min	1.8	1.2–2.8	.007	1.5	1.0–2.3	.079
Sex (reference: male)						
Female	1.1	0.7–1.7	.546			
Smoking history (reference: absence)						
Presence	0.8	0.5–1.3	.376			
Preoperative Spo_2 (reference: Spo_2 >96%)						
≤96%	1.6	1.0–2.4	.047			
Lung disease (reference: absence)						
Presence	1.2	0.7–2.0	.544			

A series of exploratory analyses were performed to assess for potential 2-way interaction between EFL and the other categorical explanatory variables, and no significant 2-way interactions were detected (all *P* ≥.19).

Abbreviations: ASA, American Society of Anesthesiologists physical status classification; EFL, expiratory flow limitation; MRC, Medical Research Council scale for dyspnea; PPCs, postoperative pulmonary complications; Spo_2, peripheral capillary oxygen saturation.

in patients undergoing general anesthesia.[19] The supine position (among others) together with pulmonary effects of anesthesia causes a decrease in functional residual capacity.[20] This decrease promotes either cyclic airway closure at end-expiration or continuous closure during the entire breath. Such intermittent airways closure can cause ventilation–perfusion mismatch that impede oxygenation. Moreover, the repetitive closing and opening of airways during tidal ventilation promotes an inflammatory reaction that can predispose to pulmonary infection.[29] Continuous airway closure may cause atelectasis because of absorption of trapped gas behind the occluded airway,[20] which can lead to shunt and postobstructive infection.[30] However, because not all patients undergoing general anesthesia develop EFL, factors related to patients themselves likely act in promoting this phenomenon. The age-related increase of closing capacity is patient-specific and reflects both loss of lung recoil and decreased resistance of the peripheral airways to collapse.[31,32] Moreover, with advancing age, maximal expiratory flow decreases at low lung volume, making older patients more susceptible to tidal EFL. These alterations of respiratory function can be further enhanced in patients with a smoking history.[32] All in all, when patients become flow-limited during general anesthesia, it is likely that their respiratory function is more compromised compared with patients without EFL.

Several mechanisms may link the presence of EFL to PPCs in patients undergoing major surgery. The marked reduction of expiratory flow, which is independent of expiratory muscle activity, can impair cough and hence secretion removal.[16] Retention of secretions in the respiratory tract is associated with the development of atelectasis, bronchitis, bronchopneumonia, and peripheral airway obstruction.[33] Taken together, these mechanisms support the link between PPCs and postoperative infection/pneumonia we observed.

Our findings also have clinical relevance. Because their risk of PPCs is higher, patients who exhibit EFL during surgery should be managed more cautiously. Great effort should be made to prevent postoperative hypoxia, retention of secretions, and respiratory infections (Table 2). Additional pulmonary therapy such as aggressive pulmonary toilet and/or greater monitoring may also have benefit. Further work is needed to determine whether preventive strategies based on the detection of EFL during surgery can improve outcomes.

In the current literature, PPCs have been associated with generic risk factors such as a smoking history,[34] exacerbation of asthma, chronic heart failure, and COPD.[2,5] However, these factors have a limited ability to predict which patients are more prone to develop PPCs,[5] possibly because, as has been previously demonstrated for patients with COPD, the disease is often based on clinical criteria rather than a confirmed spirometric diagnosis.[35] In addition, preoperative pulmonary function tests do not always identify patients who develop PPCs[36] nor do they capture severity of airway obstruction in patients with COPD.[10] Although DLCO has correlated with postoperative mortality in patients undergoing surgical resection for lung cancer,[37] the DLCO test requires special equipment, is time-consuming for patients, and is costly. In contrast, the PEEP test we used to determine the presence of EFL is very easy to perform both in the operating room and intensive care unit and does not require the use of expensive devices. Moreover, the PEEP test allows detection of EFL for the entire duration of the surgical procedure because patients can become flow-limited at any point during surgery.[19]

The strength of EFL as a risk factor for PPCs is that it does not pertain only to a specific disease state such as COPD, but can be found in patients with different disease processes. Our data support the argument that EFL identifies patients who are overall more ill by finding an increased rate of complications, both respiratory and cardiovascular, and by an increased length of stay of approximately 2 days (7 vs 9 days; Table 1).

Our multivariate analysis also identified the MRC dyspnea scale[22] as a risk factor for PPCs (Table 1). This observation was not surprising because the MRC scale has previously correlated with EFL in patients with COPD.[10] The determination of MRC scale before surgery may then identify those patients in whom the presence of EFL should be determined.

One previously described risk factor for PPCs was the preoperative Spo_2. However, we did not find this parameter significant during logistic regression analysis, even in absence of EFL. This lack of significance may have been because few of our patients experienced Spo_2 values <90% (Table 1).

Our study has several limitations. Because the PEEP test allows determination of EFL only after anesthesia induction, it cannot be used for preoperative risk stratification. However, our results suggest that an MRC scale >3 correlates well with PPCs (Table 3) and may also help to identify those patients who are at greater risk of developing EFL. The PEEP test will give the definitive answer to this clinical question. Of note, in patients with COPD, EFL is the respiratory variable that better correlates with the MRC scale.[10]

Furthermore, we have previously demonstrated that the use of PEEP can partially prevent the development of EFL.[19] Because the patients enrolled in this study were ventilated with 5 cm H_2O of PEEP, our results may not be applicable to patients ventilated at zero-PEEP level, in which the incidence of PPCs may have been even higher.

In conclusion, we found in a prospective observational trial that the intraoperative presence of EFL is a risk factor for PPC in patients undergoing major abdominal surgery. Further work is needed to better understand the relevance of EFL on postoperative pulmonary outcomes.

DISCLOSURES

Name: Savino Spadaro, MD.
Contribution: This author designed the study. He helped conduct the study, collect the data, analyze the data, and write the manuscript.
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Contribution: This author helped design the study, analyze the data, and write the manuscript.
This manuscript was handled by: Avery Tung, MD, FCCM.

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