Epidural Analgesia Is Associated with Improved Health Outcomes of Surgical Patients with Chronic Obstructive Pulmonary Disease

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ABSTRACT

Background: Patients with chronic obstructive pulmonary disease (COPD) have increased postoperative morbidity and mortality. Epidural analgesia (EDA) improves postoperative outcome but may worsen postoperative lung function. It is unknown whether patients with COPD benefit from EDA. The objective of this study was to determine whether patients with COPD undergoing major abdominal surgery benefit from EDA in addition to general anesthesia.

Methods: This cohort study included 541 consecutive patients with COPD who underwent major abdominal surgery between 1995 and 2007 at a university medical center. Propensity scores estimating the probability of receiving EDA were used in multivariate correction. The primary outcome was postoperative pneumonia and 30-day mortality.

Results: There were 324 patients (60%) who received EDA in addition to general anesthesia. The incidence of postoperative pneumonia (16% *vs.* 11%; $P = 0.08$) and 30-day mortality (9% *vs.* 5%; $P = 0.03$) was lower in patients who received EDA. After correction EDA was associated with improved outcome for postoperative pneumonia (OR 0.5; 95% CI: 0.3–0.9; $P = 0.03$). The strongest preventive effect was seen in patients with the most severe type of COPD.

Conclusion: This study provides evidence that in patients with COPD who are scheduled for major abdominal surgery, epidural analgesia decreases postoperative pulmonary complications.

What We Already Know about This Topic

- Whether epidural anesthesia and analgesia reduces pulmonary complications in patients with chronic obstructive pulmonary disease (COPD) undergoing major surgery is not known

What This Article Tells Us That Is New

- In a propensity-controlled analysis of more than 500 patients with COPD undergoing major abdominal surgery, epidural anesthesia and analgesia were associated with a 50% reduction in the risk of postoperative pneumonia

PERIOPERATIVE pulmonary complications are common, especially in elderly patients with comorbidities. Approximately 5% of all patients undergoing noncardiac surgery experience significant pulmonary complications.[1,2] Postoperative pulmonary complications include respiratory failure, pneumonia, and atelectasis. Patients with chronic obstructive pulmonary disease (COPD) are particularly vulnerable to postoperative pulmonary complications with risk that is on average 300–700% higher than that of those without COPD.[3] Major abdominal surgery, especially operations near the diaphragm, further increases this risk by causing respiratory muscle weakness and abdominal pain, which together lead to reduced lung volumes, a blunted cough reflex, and atelectasis.[4] One anesthetic method of mitigating abdominal pain is by using epidural analgesia (EDA). Studies have shown that EDA offers superior postoperative pain control with fewer adverse effects compared with intravenous opioids.[5,6] A recent study suggests that the use of EDA is associated with small improvement in survival after elective intermediate to high-risk noncardiac surgical procedures.[7] EDA might also be associated with improved respiratory outcome after surgery.[8–10] However, some studies suggest that EDA can cause a transient impairment in lung function.[11] There are no studies available regarding the effect on patients

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who are at a high risk for postoperative pulmonary complications. The effect of EDA on COPD patients is thus unknown. The aim of the current study was to determine the relationship of the use of postoperative EDA to health outcomes in a large cohort of patients with COPD presenting for major abdominal surgery.

Materials and Methods

The study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, the Netherlands. Because the data were recorded retrospectively and without any specific intervention, the Medical Ethics Committee agreed to waive informed consent.

Study Population

The patient population for this study has been described previously.[12] This observational retrospective study included 556 consecutive patients with COPD who underwent elective major abdominal surgery between 1995 and 2007 at the Erasmus Medical Center, Rotterdam, The Netherlands. Major abdominal surgery was defined as any procedure under general anesthesia involving a midline laparotomic incision that was expected to take more than 60 min and required at least 6 days hospitalization for acute recovery. Patients who had surgery for a ruptured abdominal aortic aneurysm or emergent abdominal surgery for other indications including trauma were excluded from the current study. These patients were excluded because no pulmonary function testing was available. In addition, patients presenting for emergent operations often do not receive EDA before surgery because of hemodynamic and/or respiratory instability or because of pain. Patients who underwent liver transplantation surgery were also excluded because EDA is generally not used in these patients. In the remaining patients, we abstracted the following information from their medical records: demographics (age and sex) and salient risk factors for postoperative pulmonary complications and 30-day mortality including obesity (body mass index [BMI] $\geq$30 kg/m^2), a history of coronary heart disease, congestive heart failure, diabetes mellitus, renal dysfunction (serum creatinine level greater than 160 μM), stroke, or transient ischemic attack. Coronary heart disease was defined as angina pectoris or previous myocardial infarction on the basis of history or a finding of pathologic Q waves on electrocardiography. The revised cardiac risk index (Lee risk index, LRI) was calculated for all patients.[13] The use of cardiovascular medication was also noted. These included β-blockers, statins, clopidogrel, and aspirin. Information on the type, duration, and indications for surgery was retrieved from the anesthesia reports.

Pulmonary Function Testing

A diagnosis of COPD was based on postbronchodilator spirometric values in conjunction with a history of cough, sputum production, and/or dyspnea. COPD was defined according to the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) forced expiratory volume in 1 s (FEV_1) to forced expiratory volume (FEV) ratio less than 70%.[14] Disease severity was classified into three groups: I = mild COPD ($FEV_1/FVC < 0.70$ and $FEV_1 \geq 80\%$ of the predicted FEV_1); II = moderate COPD ($FEV_1/FVC < 0.70$ and $50\% < FEV_1 < 80\%$ of the predicted FEV_1); and III = severe COPD ($FEV_1/FVC < 0.70$ and $30\% < FEV_1 < 50\%$ of the predicted FEV_1).[14] We used the equation of Quanjer *et al.*,[15] adjusted for age, sex, and height, to calculate the predicted FEV_1 value, which has been demonstrated to make an accurate prediction. The equation for males is 4.30 $\times$ height (m) – age $\times$ 0.029–2.49 and for women is 3.95 $\times$ height (m) – age $\times$ 0.025–2.60.[16] Patients in whom spirometry was not performed were excluded from the study population. As per hospital protocol, all patients with mild COPD continued their own medication during the perioperative period. Patients with moderate and severe COPD continued their own medication and received a perioperative stress dose of steroids (20 mg prednisone the day before surgery, 20 mg on the day of surgery, and 20 mg on the first postoperative day).

Perioperative Pain Management

All operations were performed under general anesthesia with neuromuscular block and inhalation agents as per hospital protocol. Epidural analgesia was offered to all patients at the outpatient clinic if no contraindications existed. There were no documented cases where there were any contraindications for epidural analgesia present. As per hospital protocol, all anticoagulant drugs are stopped 10 days before surgery. Low-molecular-weight heparins are not started before surgery. The evening before surgery plasmatic coagulation tests were performed if the patient had been taking coumarin derivatives. If the international normalized ratio is more than 1.6, vitamin K is provided to the patient. Overall no coagulation abnormalities were present that limited the choice between EDA and non-EDA. Before induction of anesthesia, an epidural catheter was placed at the level T7–10 using a midline or paramedian approach for those who received EDA. The quality of the EDA was tested before the start of the surgery using cold and warm discrimination. There was one documented case where no block was obtainable after initial placement. A second attempt led to successful placement. Epidural infusions were standardized using a combination of bupivacaine 0.1% with sufentanil 0.5 mcg/ml to achieve an epidural infusion rate of 5–10 ml/h. During surgery continuous infusion is started at the discretion of the anesthesiologist. If epidural placement was not possible or if patients refused, patients were given patient-controlled intravenous analgesia (PCA). PCA consisted of morphine 1 mg/ml with a 6-min lockout and was left in place as long as necessary. Of the total population of 541 patients, 5 were placed in the PCA group because of their refusal of EDA. Another 10 patients were placed in the PCA group after EDA placement was considered unsuccessful. To make sure that those pa-

tients placed in the EDA group had a working EDA, patients were placed in the EDA or PCA group based on how they were discharged from the recovery ward. In the postoperative phase all patients were visited by a nurse experienced in treating postoperative pain once daily. Numeric analog scale scores are obtained and the pain management is adjusted if needed (numeric analog scale more than 6). All patients received 1,000 mg acetaminophen four times daily. The epidural catheter was removed on the fourth postoperative day, and patients were instructed to take tramadol if needed. Information about how long the epidural was actually left in place was found in 25% of the patients. In all of these patients the EDA was removed on the fourth postoperative day.

Follow-up and Endpoints

Follow-up was completed in 541 of the study patients (94%). Ten patients were excluded because anesthesia reports were missing, and five patients were lost to follow-up. Survival status was obtained from the municipal civil registries and the postoperative clinical characteristics were retrieved from the hospital medical records. The primary endpoints of the study were postoperative pneumonia within 10 days and 30-day mortality regardless of the cause. Postoperative pneumonia was defined as clinical symptoms of pneumonia (*e.g.*, cough, shortness of breath, fever, hypoxemia, or phlegm production) plus new or progressive infiltrates or consolidations on a chest radiograph.

Table 1. Baseline Patient Characteristics of COPD Patients with and without Epidural Analgesia Undergoing Major Abdominal Surgery

	Epidural N (%)	No Epidural N (%)	Unadjusted *P* Value	Adjusted *P* Value*
No. of patients	324	217		
Age (years)	66.2	65.3	0.376	0.983
Male sex	252 (77)	149 (69)	0.018	0.998
BMI > 30	28 (9)	25 (12)	0.271	0.965
COPD classification				
Mild	152 (47)	79 (36)	0.016	0.916
Moderate	129 (40)	66 (30)	0.026	0.999
Severe	43 (13)	72 (33)	<0.001	0.875
Risk factors				
Coronary heart disease	44 (14)	34 (16)	0.498	0.989
Congestive heart failure	7 (2)	17 (8)	0.002	0.974
Cerebrovascular disease	22 (7)	18 (8)	0.513	0.977
Diabetes mellitus	157 (48)	88 (41)	0.071	0.926
Renal dysfunction	6 (2)	10 (5)	0.073	0.996
Leerisk index				
1	142 (44)	98 (45)	0.760	0.897
2	143 (44)	85 (39)	0.252	0.701
≥3	39 (12)	34 (16)	0.227	0.982
Medication use				
Statins	41 (13)	20 (9)	0.217	0.970
β-blockers	99 (31)	53 (24)	0.121	0.962
Aspirin	59 (18)	25 (12)	0.037	0.915
Clopidogrel	2 (1)	2 (1)		
Surgical procedure				
Length of procedure (min)	279	238	<0.001	0.925
Surgery for malignancy	212 (68)	106 (49)	<0.001	0.966
Types of surgery			0.008	
Colon	174 (54)	139 (64)		
Hepatico/pancreatico/biliary	8 (3)	10 (5)		
Esophagogastric	15 (5)	7 (3)		
Other abdominal	17 (5)	5 (2)		
Endocrine	1 (0)	0 (0)		
Gynecology	7 (2)	11 (5)		
Urologic	33 (10)	22 (10)		
Aorta elective	63 (19)	20 (9)		
Other	6 (2)	3 (1)		

**P* values after propensity score adjustment. Propensity score was constructed using a multivariate logistic regression model with the following variables: age, sex, obesity, severity of COPD, length of surgery, diabetes mellitus, renal dysfunction, surgery for malignancy, all variables on cardiovascular history, and cardiovascular medications.

BMI = body mass index; COPD = chronic obstructive pulmonary disease.

Table 2. Spirometric Values of the Study Cohort

	Epidural N = 324	No Epidural N = 217	*P* Value
Entire cohort			
FEV_1/VC (%)	59	59	0.37
VC (liters)	3.90	3.27	<0.001
Mild COPD			
FEV_1/VC (%)	64	64	0.41
VC (liters)	4.26	4.11	0.06
Moderate COPD			
FEV_1/VC (%)	54	58	0.04
VC (liters)	3.72	3.39	0.10
Severe COPD			
FEV_1/VC (%)	39	43	0.003
VC (liters)	3.2	2.6	0.009

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 s; VC = vital capacity.

Statistical Analysis

Continuous data are presented as means and were compared using a Student's *t* test. Categoric variables are expressed as percentages and were compared using a chi-square test. Univariate and multivariate logistic regression analyses were used to determine the relationship of EDA use to postoperative morbidity and mortality. Regression analyses were adjusted for relevant covariates, including age, sex, obesity, LRI, surgery for malignancy, and severity of COPD. Because patients were not randomized for EDA we developed a propensity score, using a multivariate logistic regression model, to adjust for the likelihood of receiving EDA. The variables in this model included age, sex, obesity, severity of COPD, length of surgery, diabetes mellitus, renal dysfunction, surgery for malignancy, all variables on cardiovascular history, and cardiovascular medications. The model fit and predictive power of the propensity score model were validated with the Hosmer-Lemeshow goodness-of-fit test ($P = 0.797$) and c-statistic (0.70), respectively. Assessing validity should be checked to determine whether it allows sufficient overlapping of the propensity score. The graphic method of examination by histograms and box plots within quintiles showed a balance of the estimated propensity score between patients who received EDA and those who did not.[17] The EDA propensity score was included, in addition to the original variables of age, sex, obesity, LRI, surgery for malignancy, and severity of COPD, as an additional covariate in our regression models to adjust the effect of treatment method in evaluating outcome endpoints. Odds ratios (ORs) were calculated from these models together with their 95% CIs. For all tests, a two-sided *P* value of less than 0.05 was considered significant. All statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL).

Results

Baseline Characteristics

The baseline characteristics of the study patients are presented in table 1. Overall most of the patients (74%) were men. Of the 541 patients, 231 (43%) were classified with mild COPD, 195 (36%) with moderate COPD, and 115 (21%) with severe COPD. The spirometric values are presented in table 2. An epidural procedure in 60% of the patients was performed more frequently in those with mild or moderate COPD than in those with severe disease. Adjustments for propensity score yielded two treatment groups with no significant differences in baseline characteristics. No procedural-related complications were noted in the EDA group, except for one patient who described a paresthesia sensation in the legs for several hours after surgery. After EDA removal the patient left the hospital 1 week later without complaints.

Association Between Epidural Analgesia and Postoperative Pneumonia

The primary and secondary endpoints are presented in table 3. Postoperative pneumonia was diagnosed in 68 patients (13%). The incidence of pneumonia was slightly higher in patients who did not receive EDA than in those who did (16% *vs.* 11%; $P = 0.08$). Severity of COPD did not significantly modify the risk of pneumonia (mild COPD, 10%; moderate COPD, 17%; severe COPD, 13%; $P = 0.07$). Multivariate analysis was performed using a propensity score to adjust for various factors including severity of disease. The results of this analysis are presented in table 4. In this analysis, the use of EDA was associated with reduced risk of postoperative pneumonia (OR 0.5; 95% CI: 0.3–0.9; $P = 0.03$). Subgroup analysis by COPD severity demonstrated reduced risk, but no significant difference was observed due to inadequate sample size (Mild: OR 0.6; 95% CI: 0.2–1.5; $P = 0.25$, Moderate: OR 0.6; 95% CI: 0.3–1.5; $P = 0.27$, Severe: OR 0.2; 95% CI 0.04–1.3; $P = 0.21$). The c-index of the model predicting pneumonia was 0.67.

Epidural Analgesia and 30-Day Mortality

Within 30 days after surgery, 35 patients (6.5%) died. The risk of mortality also increased along the LRI gradient (2% with LRI of 1, 7.0% with LRI of 2, and 21% with LRI of 3 or more; $P < 0.001$). In the crude analysis, death occurred more often in patients who did not receive EDA than in those who did (9% *vs.* 5%; $P = 0.03$). However, with inclusion of potential confounders into a multivariate model, the

Table 3. Primary Endpoints among the Study Cohort

	Epidural N (%) 324	No Epidural N (%) 217	*P* Value
Postoperative pneumonia*	33 (11)	35 (16)	0.08
30-day mortality	15 (5)	20 (9)	0.03

* Postoperative pneumonia was defined as clinical symptoms of pneumonia (*e.g.*,. cough, shortness of breath, fever, hypoxemia, or phlegm production) plus a new or progressive infiltrates or consolidations on a chest radiograph.

Table 4. Adjusted Odds Ratios for Outcome Parameters Using Multivariable Analysis* and Additional Propensity Score Adjustment†

	Pneumonia		30-Day Mortality	
	Multivariate OR [95% CI]	Propensity Adjusted OR [95% CI]	Multivariate OR [95% CI]	Propensity Adjusted OR [95% CI]
Age (per year increase)	1.02 (0.997–1.05)	1.02 (0.99–1.05)	1.06 (1.02–1.11)	1.06 (1.02–1.11)
Male sex	1.7 (0.9–3.3)	1.6 (0.8–3.3)	1.0 (0.4–2.3)	1.0 (0.4–2.4)
BMI ≥ 30	0.9 (0.3–2.2)	0.9 (0.4–2.3)	0.8 (0.2–3.0)	0.8 (0.2–3,0)
COPD classification				
Mild	1	1	1	1
Moderate	2.0 (1.1–3.6)	2.0 (1.1–3.6)	1.0 (0.4–2.8)	1.1 (0.4–2.8)
Severe	1.0 (0.4–2.1)	1.1 (0.4–3.1)	3.0 (1.3–7.4)	3.0 (1.2–7.4)
Lee risk index				
1	1	1	1	1
2	1.3 (0.7–2.3)	1.2 (0.7–2.3)	4.4 (1.4–13)	4.4 (1.4–14)
≥3	1.8 (0.9–3.9)	1.9 (0.9–3.9)	15 (4.6–49)	15 (4.6–49)
Surgery for malignancy	0.8 (0.5–1.4)	0.7 (0.4–1.4)	1.4 (0.6–3.0)	1.4 (0.6–3.0)
Epidural analgesia	0.6 (0.3–0.9)	0.5 (0.3–0.9)	0.6 (0.3–1.2)	0.6 (0.3–1.2)

* Variables included in multivariate analysis included EDA, age, sex, obesity, LRI, surgery for malignancy and severity of COPD. † The following variables were used for constructing the a propensity score for the prediction of receiving epidural analgesia: age, sex, obesity, severity of COPD, length of surgery, diabetes mellitus, renal dysfunction, surgery for malignancy, all variables on cardiovascular history and cardiovascular medications. The propensity adjusted analysis were all the variables entered in the multivariate analysis + the propensity score predicting EDA.

BMI = body mass index; COPD = chronic obstructive pulmonary disease; EDA = epidural analgesia; LRI = Lee risk index.

use of EDA was no longer significant with 30-day mortality (OR 0.6; 95% CI: 0.3–1.2; $P = 0.25$).

Discussion

In a large group of patients with COPD who underwent abdominal surgery, we showed that the use of EDA, in concert with general anesthesia, was associated with reduced incidence of postoperative pneumonia. COPD is a well-known risk factor for postoperative pulmonary complications.[1,10,18] A recent study by Canet *et al.*[2] identified seven independent risk factors for postoperative pulmonary complications: low preoperative arterial oxygen saturation, acute respiratory infection during the previous month, age, preoperative anemia, upper abdominal or intrathoracic surgery, surgery duration of at least 2 h, and emergency surgery. Although the number of patients with COPD with postoperative pulmonary complications was almost five times higher in comparison with patients without COPD (16.4% *vs.* 3.5%; $P < 0.001$), COPD was not identified as an independent risk factor in this study. Potential interventions to reduce postoperative pulmonary complications include smoking cessation, preoperative exercise training, early mobilization, postoperative total parenteral nutrition, and optimal treatment of postoperative pain.[4] Although postoperative pain management is enhanced by the use of EDA, its use in patients with COPD has been controversial because of ongoing fears that it may acutely reduce lung function. For example, the use of high-thoracic epidurals has been associated with decreased spirometric values by possibly blocking intercostal muscle innervation.[19] However, other studies have failed to show any deleterious respiratory effects from EDA.[20] Whether EDAs cause material changes in lung function in patients with COPD is uncertain. EDA appears to provide superior pain control over systemic opioids in patients undergoing major abdominal surgery.[6,21] EDA may also reduce postoperative pulmonary complications.[8–10] In a meta-analysis by Ballantyne *et al.*[22] there was a nonsignificant trend toward a lower incidence of pulmonary infections postoperatively in favor of epidural opioids over the use of systemic opioids (relative risk 0.53; 95% CI 0.18–1.53). The same study also showed that the use of epidural local anesthetics significantly decreased the incidence of pulmonary infections (relative risk 0.36; 95% CI 021–0.65). In a more recent review, which included more heterogeneous surgical procedures, neuraxial blockade was associated with decreased incidence of postoperative pneumonia (OR 0.61; 95% CI 0.48–0.76).[23] However, other studies have failed to demonstrate a beneficial effect of EDA on postoperative pneumonia.[24,25] In a randomized controlled trial by Norris *et al.*,[26] 168 patients undergoing surgery of the abdominal aorta were randomly assigned to receive either thoracic epidural analgesia combined with a light general anesthesia, general anesthesia alone intraoperatively, or either intravenous or epidural patient-controlled analgesia postoperatively.[26] Although length of stay was considered the primary outcome variable, postoperative outcomes were similar among the four treatment groups with respect to death, myocardial infarction, myocardial ischemia, reoperation, pneumonia, and renal failure. It should be noted that the treatment groups were relatively small and only two patients with postoperative pneumonia were identified. By studying a large group of patients and by focusing on the highest risk group (*i.e.*, those with COPD) for post-

operative pneumonia, our study does affirm the benefits of EDA in mitigating the risk of postoperative pneumonia. As with postoperative pneumonia, the effects of EDA on postoperative mortality have also shown conflicting results.[7,9,23,27] A recent retrospective cohort study of 259,037 patients showed a small improvement in 30-day postoperative survival (relative risk 0.89; 95% CI 0.81–0.98) with 477 being the number needed to treat.[7] In their systematic review, Rodgers *et al.*[23] report that overall mortality was reduced by a third in patients who were allocated to neuraxial blockade (OR 0.7; 95% CI: 0.54–0.90). Our study results are in general agreement with these findings because a nonsignificant beneficial effect of EDA was found on 30-day mortality.

Several limitations should be taken into account when interpreting our results. First, this was an observational study. Causality therefore cannot be assumed. To minimize the possibility of confounding we carefully collected salient clinical and demographic information and performed adjustments for these covariates in the regression analysis. In addition, EDA was not randomly assigned and therefore subject to confounding by indication. To address this limitation, propensity score analysis was used as a *post hoc* statistical method that estimates treatment effect when subjects are not randomly assigned to a specific treatment group.[28] Three propensity score-based methods are commonly used in medical literature: matching, covariate adjustment, and stratification. Recognizing that there is no universally accepted "gold standard" technique, and because of our restrictive pool of control subjects and our relatively small sample size, we decided to use covariate adjustment. However, the most important limitation of propensity methods is, like other adjustment methods, that it can only adjust for observed and known confounders and does not protect against bias from unknown or imperfectly measured confounders.[29] Residual bias therefore cannot be excluded. Second, we could not fully rule out the possibility that some individuals with COPD also had asthma. However, although bronchial hyperresponsiveness is more common (and more severe) in asthma than in COPD, more than 70% of patients with COPD (who smoke) also demonstrate bronchial hyperresponsiveness. Third, because we did not have lung function or biochemical measurements following surgery, the mechanism by which EDA reduces postoperative pneumonia and mortality remains unknown. In addition, there are many other unmeasured covariates that might have contributed to the development of a postoperative pneumonia that were not included in our model. The c-index of the model predicting pneumonia was 0.67; if other covariates were included in our analyses EDA might lose its beneficial effect. Fourth, as per hospital protocol, all patients with moderate and severe COPD received a perioperative stress dose of steroids. A stress dose of steroids remains a point of discussion because some hospitals treat COPD patients with their own dose of steroids in the perioperative phase. Studies and COPD guidelines still advocate the use of systemic glucocorticosteroid treatment in the perioperative phase to prevent exacerbations.[10,30–32] However, the use of steroids is also associated with increased wound infections in the postoperative period. Finally, it should be emphasized that performing EDA is not a procedure free of risk. Although only one complication was noted in our population, epidural abscess and bleeding are rare but serious complications that should be brought to the attention of all surgeons and anesthesiologists because of the major effect on the patient. A risk-benefit analysis should be made for each individual patient.

In summary, the results of the current study suggest that epidural analgesia reduces postoperative pneumonia in patients with COPD undergoing major abdominal surgery. Although the exact mechanisms by which this occurs are unknown, our data suggest that the use of epidural analgesia should be encouraged in patients with COPD undergoing major abdominal surgery.

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