Critical Care

CRITICAL CARE

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Critical Care 2009, **13**:R41 doi:10.1186/cc7762

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ISSN 1364-8535

Article type Research

Submission date 22 January 2009

Acceptance date 24 March 2009

Publication date 24 March 2009

Article URL http://ccforum.com/content/13/2/R41

Impact of intraoperative lung protective interventions in patients undergoing lung cancer surgery

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ABSTRACT

Introduction: In lung cancer surgery, large tidal volume and elevated inspiratory pressure are known risk factors of acute lung (ALI). Mechanical ventilation with low tidal volume has been shown to attenuate lung injuries in critically-ill patients. In the current study, we assessed the impact of a protective lung ventilation (PLV) protocol in patients undergoing lung cancer resection.

Methods: We performed a secondary analysis of an observational cohort. Demographic, surgical, clinical and outcome data were prospectively collected over a ten-year period. The PLV protocol consisted in small tidal volume, limiting maximal pressure ventilation and adding end-expiratory positive pressure along with recruitment manoeuvres. Multivariate analysis with logistic regression was performed and data were compared before and after implementation of the PLV protocol: from 1998 to 2003 (historical group, n = 533) and 2003 to 2008 (protocol group, n = 558).

Results: Baseline patient characteristics were similar in the two cohorts, except for a higher cardiovascular risk profile in the intervention group. During one-lung ventilation, protocol-managed patients had lower tidal volume (5.3 ± 1.1 vs. 7.1 ± 1.2 ml/kg in historical controls, $P = 0.013$) and higher dynamic compliance (45 ± 8 vs 32 ± 7 ml/cmH_2O, $P = 0.011$). After implementing PLV, there was a decreased incidence of acute lung injury (from 3.7% to 0.9%, $P < 0.01$) and atelectasis (from 8.8 to 5.0, $P = 0.018$), fewer admissions in ICU (from 9.4% vs 2.5%, $P < 0.001$) and shorter hospital stay (from 14.5 ± 3.3 vs. 11.8 ± 4.1, $P < 0.01$). When adjusted for baseline characteristics, implementation of the open-lung protocol was associated with a reduced risk of acute lung injury (adjusted odds ratio of 0.34 with 95% confidence interval of 0.23 to 0.75; $P = 0.002$).

Conclusions: Implementing an intraoperative PLV protocol in patients undergoing lung cancer resection was associated with improved postoperative respiratory outcomes as evidence by significantly reduced incidences of acute lung injury and atelectasis along with reduced utilization of ICU resources.

Introduction

Compared with other surgical procedures, thoracotomy is associated with the highest 30-days mortality rates, ranging from less than 1% for minor resections to up to 12% for pneumonectomies [1-3]. Postoperative onset of acute hypoxemia, - unrelated to cardiac failure, pulmonary embolism, atelectasis, sepsis or bronchoaspiration -, has attracted much interest as it has become the leading cause of death in patients undergoing lung resection [4, 5]. The guidelines set forth by the American-European Consensus Conference (AECC) on the acute respiratory distress syndrome (ARDS) have been widely adopted to describe this form of Acute Lung Injury (ALI), previously coined postpneumonectomy pulmonary edema, low pressure or permeability pulmonary edema [6]. Contrasting with other adverse cardiopulmonary events, the incidence of post-thoracotomy ALI has not shown any noticeable decrease although various treatment modalities such as non-invasive ventilation and nitric oxide inhalation have reduced the case-fatality rate [7, 8]. Interestingly, large tidal volumes (V_T) or elevated inspiratory pressure during one-lung ventilation have been identified as strong predictors of ALI in two retrospective observational studies [9, 10]. The hypothesis of ventilator-induced lung injury (VILI) during OLV has been further supported by the association between tidal volume exceeding 7-8 ml/kg of predicted body weight (PBW) and the release of systemic and pulmonary inflammatory mediators [11]. Presently, the clinical benefits of lung protective strategies using lower tidal volume (V_T) combined with positive end-expiratory pressure (PEEP) have been clearly demonstrated in randomized controlled trials including only critically-ill patients with ALI/ARDS [12].

Considering the potential injurious effects of large tidal volume in patients with healthy lungs undergoing short-term one-lung ventilation, we hypothesized that adopting a protective lung ventilation (PLV) protocol as part of a collaborative quality improvement initiative would lead to further reduction in the incidence of post-thoracotomy ALI. In our institutional surgical database, we examined if protocol-driven changes in ventilatory strategy initiated in 2003 were associated with better clinical outcomes compared with historical controls.

Materials and Methods

Study design and settings

This retrospective cohort study was approved by the Institutional Research Board and included all consecutive cases of lung cancer resection performed in two affiliated medical institutions: an academic center (Hôpitaux Universitaires de Genève) and one tertiary

reference hospital (Centre Valaisan de Pneumologie in Sion). As it concerned retrospective analysis of data obtained during usual clinical practice, local regulation do not require written informed consent. All patients were operated on by one of two board certified thoracic surgeons and were managed by the same team of cardiothoracic anesthesiologists.

Since March 1st 2003, the PLV strategy was routinely implemented as a best practice model for intraoperative management (PLV cohort, from March 2003 to March 2008). This PLV group entailed the application of low V_T (less than 8 ml/kg of predicted body weight [PBW]), pressure-controlled ventilation, limitation of the inspiratory plateau pressure ($P_{plateau}$) to 35 cmH_2O, the addition of external PEEP (4 and 10 cmH_2O) and performance of vital capacity manoeuvres (raising the inspiratory pressure up to 35 cmH_2O for 7-10 sec) at 30 min intervals.

In our database, we abstracted a comparison group of non-protocolized consecutive patients operated during the preceding 5 years (1998-2003), these patients being referred as the historical control cohort. In this group, conventional volume-targeted ventilation was aimed to achieve V_T of 9-12 ml/kg of PBW during two-lung ventilation and 8-10 ml/kg of PBW during one-lung ventilation while avoiding inspiratory pressure exceeding 35 cmH_2O; no recruitment manoeuvre was performed and PEEP was applied at the discretion of the attending anesthesiologist. In both groups, the same anesthetic workstations were used (Dräger Primus or Zeus, Lübeck, Germany) with respiratory rates and oxygen inspiratory fraction adjusted to keep the end-tidal carbon dioxide between 4 and 6 kPa (30 and 45 mmHg) and the arterial pulsed oxygen saturation above 90%.

The main outcome of interest was the development of ALI, defined according to the AECC criteria as follows: 1) sudden onset of respiratory distress, 2) infiltrates on the chest radiograph consistent with pulmonary edema, 3) impaired oxygenation with an arterial oxygen pressure - to- inspired oxygen fraction ratio (PaO_2/FIO_2 or P/F ratio) less than 300 mm of Hg for ALI, 4) absence of cardiac insufficiency or fluid overload, based on pulmonary arterial catheterization, echocardiogram and/or clinical evaluation ([6]). Additional criteria for post-thoracotomy ALI included the onset respiratory distress within the first 48 hours after surgery. Patients presenting with aspiration of gastric content, pneumonia, bronchopleural fistula or pulmonary embolism who later developed noncardiogenic pulmonary edema were considered as secondary ALI if they fulfilled the AECC criteria.

Secondary outcome variables were in-hospital mortality, ICU admissions, duration of hospital stay as well as respiratory, cardiovascular and surgical complications (see Additional data file 1).

In a previous study, we reported a 4.2% incidence of post-thoracotomy ALI [10]. A sample size of 1'000 operated patients provided the power (80%) to detect a 50% relative risk reduction in post-thoracotomy ALI. Therefore the sample size resulted from *a priori* decision to limit the analysis to two consecutive periods, before and after implementing the PLV strategy, including at least 500 patients per group.

Patients and perioperative management

Besides clinical evaluation, ECG and laboratory screening, routine preoperative work up included pulmonary function tests (Sensor Medics; Yorba Linda, CA) with lung diffusion capacity to carbon monoxide, lung biopsy, CT-scan and/or positron emission tomography of the chest and abdomen. Patients with borderline spirometric results (forced expiratory volume in 1 sec lower than 60-80%% of predicted value), impaired exercise tolerance or cardiac risk factors underwent complementary investigations (peak oxygen consumption, differential lung perfusion/ventilation scan, echocardiography, thallium myocardial scintigraphy and/or coronary angiogram).

After anesthesia induction, a left-sided double-lumen tube was inserted and its correct position was confirmed by fiberoptic bronchoscopy. Lung resection with systematic lymph node dissection was performed through an anterolateral muscle-sparing thoracotomy. Thoracic epidural anesthesia (TEA) was initiated intraoperatively and continued postoperatively until chest drain removal.

Intraoperatively, intravenous crystalloids were infused at a rate of 2-4 ml/kg/h and blood losses were compensated with colloids and with red blood cell concentrates if the hemoglobin levels decreased below 80-90 g/L. All patients were extubated in the operating theater and admitted in an intermediate care unit for at least 12 hours before being transferred to the surgical ward. During the first 48 hours after surgery, aerosolized salbutamol and ipratropium were routinely prescribed and fluid balance of maximum 500 ml per day was targeted, by limiting oral and intravenous fluid intakes. A restrictive transfusion policy was adopted throughout both study periods, with transfusion triggers ranging 80 and 95 g/L. Antimicrobial prophylaxis with cefazoline was administered for 24 hours.

Data Collection

Demographic, clinical, surgical and anesthetic data as well as perioperative complications were abstracted from a prospective registry including all patients who underwent thoracic surgery. These data were collected by study nurses, entered in the surgical database in the same manner during both study periods and crossed checked for accuracy. Before surgical incision and 30 min after the start of one-lung ventilation, the following ventilatory data were recorded: V_T (in ml/kg PBW), $P_{plateau}$, PEEP and FIO_2 ; the effective dynamic compliance was obtained by dividing the ventilator-delivered V_T by the peak P_{aw} minus PEEP. Intra— and postoperatively, the use of vasopressor drugs was recorded as well as the urine output and the amount of fluid intake (colloids, crystalloids and blood products). On the first day after surgery, arterial oxygen pressure (PaO_2 in kPa) was measured using a blood gas analyzer (ABL-5 10 analyzer, Radiometer, Copenhagen, Denmark) and the P/F ratio was calculated as the $Pa0_2/FIO_2$ ratio. Postoperative complications were defined according to standard criteria (see additional data file 1).

Statistical analysis

For comparisons between the two cohorts, unpaired Student *t* test was used for normally distributed data and the Mann-Whitney *U* test for non-normally distributed data. The Kolmogorov-Smirnov test was applied to decide if the cohorts were normally distributed. Prevalence of risk factors and incidence of complications in the two groups were compared by Fisher exact test. Multivariate logistic regression analysis using backward selection was performed to assess whether demographic, clinical, laboratory and surgical factors, fluid and ventilatory management were associated with the occurrence of primary ALI. We choose an inclusive cut-off for the empiric level of significance ($p<0.2$) at which we retained variables. The final model was assessed for goodness of fit using the Hosmer-Lesmeshow test and for omitted covariates and model misspecification using the link test [13]. All analysis were performed using SPSS software (version 14.0 for Microsoft Windows; SPSS, Chicago, IL) and statistical significance was specified to a two-tailed type I error (p value) set below the 0.05 level.

Results

Over a 10-year period, 1'091 patients underwent pulmonary resection for malignancy and complete data were available in 533 from March, 1st 1997 to February 28th, 2003 and in 558 from March, 1st 2003 to February 28th, 2008.

As detailed in Table 1, baseline characteristics of patients were similar between the two cohorts, except for a higher cardiovascular risk profile in the PLV cohort as evidence by a greater prevalence of hypertension and diabetes mellitus along with more frequent prescription of cardiovascular drugs.

The type of surgery, distribution of pathological cancer stages, need for chemo-radiotherapy as well as the duration of one-lung ventilation and surgery did not differ between the groups (Table 2). Fluid and vasopressor therapies were also similar, however, a higher proportion of patients received continuous TEA in the PLV cohort compared with the historical controls (98.2% vs. 92.3%, $p< 0.05$).

During one-lung ventilation, $V_T < 8$ ml/kg was achieved in 92% of protocolized-PLV patients (vs. 24% in historical controls) resulting in significantly lower V_T and $P_{plateau}$ while dynamic compliance, PEEP and respiratory rate were significantly higher, compared with the historical control cohort (Table 3).

In PLV cohort, there was a reduction in the frequency of postthoracotomy ALI (from 3.7% to 0.9% in the historical control cohort; $p < 0.01$) along with a lower incidence of atelectasis, fewer admissions in ICU and shorter hospital stay (Table 4). In the control cohort, patients ventilated with $V_T < 8$ ml/kg presented a trend for a lower rate of ALI (0.8% vs. 4.9% in patients ventilated with $V_T > 8$ ml/kg, P=0.08).

The cause of death was primarily attributed to ALI in 1 out of 5 patients in the PLV group (vs. 6/20 in the historical controls), other causes being related to sepsis (2/5 vs. 4/20, respectively), thromboembolism (1/5 and 3/20, respectively) and myocardial infarct (1/5 vs. 1, respectively). In-hospital mortality and the incidence of cardiovascular complications and secondary ALI did not differ between the two groups.

When adjusted for baseline characteristics and perioperative nonrespiratory management, the PLV intervention was associated with a decreased likelihood of ALI occurrence: adjusted Odds Ratio (OR) of 0.34 (95% confidence interval [CI] of 0.23 to 0.75; p=0.002). As detailed in Table 5, multivariate logistic regression analysis identified other independent risk factors for ALI: the extent of lung resection (pneumonectomy, adjusted OR of 2.52 with 95% CI of

1.34 to 7.71]), V_T (adjusted OR of 1.17 per ml/kg increase with 95% CI of 1.02 to 1.26), alcohol consumption (exceeding 60 g per day, adjusted OR of 1.93 with 95% CI of 1.14 to 5.71) and the cumulated amount of perioperative fluid infused (adjusted OR of 1.42 per 1 ml/kg/h increase with 95% CI of 1.09 to 4.32). There was no evidence that additional covariates would improve the model (p=0.21 by the Wald link specification test). The c-index for this model was 0.64 and the Hosmer-Lemeshow test for lack of fit was not significant (p=0.56).

Discussion

This observational study is the first to indicate that implementation of an intraoperative ventilatory strategy aimed to limit lung overdistension while maintaining functional residual capacity with external PEEP and recruitment maneuvers leads to significant reduction in the incidence of post-thoracotomy ALI and atelectasis along with fewer admissions in ICU and shorter hospital stay.

Importantly, lowering the risk of ALI with PLV by more than 50% was independent of age, severity of underlying lung and cardiovascular diseases as well as other perioperative interventions. Although these results were obtained by comparison with a historical control group, they strongly suggest that the PLV strategy may also benefit to patients undergoing lung cancer resection. Alternatively, the improved respiratory outcome in PLV-treated patients supports the hypothesis that ALI and atelectasis may in part be caused by or be related to intraoperative factors: VILI or ventilator-associated injuries and the reduction of functional residual capacity consequent to the effects of surgical insults, anesthesia and muscle paralysis [14, 15]. High shear stress associated with cyclic opening of collapsed areas (atelectotrauma) and deformation of the alveolar epithelium (strain) during OLV are thought to generate a proinflammatory state (biotrauma) leading to pulmonary tissue alterations.

By the late 90s, standard V_T for managing thoracic surgical patients had already been adjusted downwards (from 10-12 ml/kg in the 1980s) to 8-10 ml/kg although no specific guidelines existed for one-lung ventilation. Our historical control data were consistent with these values and, after implementation of the PLV protocol, V_T declined from mean values of 7.1 to 5.3 ml/kg during the one-lung ventilation period. We used predicted, rather actual body weight for calculating V_T per kilogram of body weight to avoid lung overdistension in obese patients and in women who have smaller lung volumes [[16]]. Importantly, the ventilatory endpoints (V_T less than 8 ml/kg and $P_{plateau}$ less than 35 cmH_2O) were achieved in more than 80% of patients. Compliance to the new ventilatory guidelines was facilitated by the relatively short ventilatory time (less than 3 hours), the absence of acute critical illnesses and the commitment of a small number of cardiothoracic anesthesiologists. Interestingly, similar protective ventilatory strategies applied in ICU settings have been associated with a decreased incidence of ALI in high-risk patients, although the target V_T was achieved in only 50 to 60% of cases [17-19].

Thoracic surgical candidates represent a particular group of non-critically ill patients in whom ventilation-induced cytokine upregulation produces a proinflammatory state that render the host more vulnerable to subsequent "hit(s)" such as ischemia-reperfusion, hypoxia-reoxygenation and direct tissue trauma [20-22]. Depletion of pulmonary glutathione stores observed in alcoholic patients is expected to further exacerbate oxidative lung injuries [23].

To date, three randomized controlled trials including patients undergoing thoracotomy have compared the application of traditional high V_T with the "open lung strategy" combining low V_T and PEEP. Although Wrigge et al failed to document any difference in systemic inflammatory markers [24], Schilling et al. found reduced alveolar concentrations of TNF-α and soluble intercellular adhesion molecules in patients ventilated with small V_T (5 vs 10 ml/kg) [25]. Confirming these positive results, Michelet et al. reported an attenuated systemic proinflammatory response, lower interstitial pulmonary edema and improved oxygenation index allowing earlier extubation in the protective ventilation group among patients undergoing oesophagectomy [26].

In this study, we adopted a PLV including pressure controlled ventilation, external PEEP and recruitment manoeuvres. Actually, delivery of a decelerating gas flow has been reported to achieve more homogeneous flow distribution and lower peak airway pressure [27]. Different lung recruitment strategies have been shown to re-expand the collapsed dependent lung areas that develop in almost all anesthetized patients. During thoracic surgery, application of recruitment manoeuvres with moderate PEEP levels to the dependent lung has been shown to improve oxygenation and to reduce both intrinsic PEEP levels and static elastance of the respiratory system without causing significant cardiovascular deterioration [28]. Our data confirm the good hemodynamic tolerance to the PLV protocol since fluid and vasopressor requirements were similar in the two cohorts. Given the difficulties in constructing static P-V curves, we did not titrate PEEP but we set a fixed "moderate" level of PEEP that could potentially cause alveolar hyperinflation in healthy or emphysematous areas [29]. This possibility seems unlikely since we observed higher compliance in patients managed with the PLV protocol that supports the stabilizing effects of PEEP along with effective re-expansion of previously collapsed areas following recruitment manoeuvres [30,31].

We acknowledged several limitations in the current study. Although data were collected by clinicians and validated by scientific investigators, we assume variability in initial ventilator settings with the possibility that higher inspiratory pressures and tidal volume were deliberately chosen to correct transient hypoxemia and hypercapnia. The observational design

limits the ability to infer causality between the lung protective protocol and lowering the incidence of ALI. Although statistics were helpful to adjust for some confounding variables, unmeasured factors and other changes in practice or patient case mix may have decreased the confidence in observed effects. For instance, potentially beneficial therapies such as preoperative statin and angiotensin-converting enzyme treatment, continuous TEA, goal-directed fluid therapy using transoesophageal Doppler monitoring, inhalation of beta-2 agonists in high-risk patients, and early postoperative mobilization were popularized during the postintervention period, and thereby could have contributed to the overall reduction in respiratory complications and in hospital length of stay [32]. On the other hand, despite higher prevalence of hypertension in the protocol-treated cohort, mortality and cardiovascular adverse events were unchanged compared with the control cohort. Finally, major limitations also stem from the definition of ALI that may cover different clinical patterns and histological findings, that may explain significant interobserver diagnostic disagreement particularly in postoperative patients [33]. In this study, we excluded patients with delayed onset of ALI triggered by infection, bronchial aspiration of gastric content and allogenic transfusion. Accordingly, post-thoracotomy ALI likely identified a more homogenous group of patients predisposed to the injurious effects of mechanical ventilation. The reliability of ALI diagnostic criteria could have been improved by additional measurements of plasma brain natriuretic factor and lung water content with the transpulmonary thermodilution technique [34, 35].

Conclusions

In this observational study, we demonstrated the effectiveness of combining low V_T, PEEP and recruitment manoeuvres. This intraoperative "open-lung" approach was easily implemented in clinical practice and resulted in a reduced incidence of postoperative ALI and atelectasis. Implementation of a bundle of scientifically-based perioperative interventions represents an integral component of clinical quality management. Future clinical trials will determine whether optimization of other ventilator settings (e.g., oxygen inspiratory fraction, PEEP level, periodicity of recruitment manoeuvre) may improve respiratory outcome in specific groups of surgical patients requiring mechanical ventilation.

Key messages

- Intraoperative application of small tidal volume, PEEP and recruitment manoeuvres was successfully achieved in 92% patients undergoing lung cancer resection over a five-year period.
- Adoption of this lung ventilatory strategy was associated with a reduced incidence of acute lung injury (0.9% vs. 3.7%) and atelectasis (5% vs. 8.8%) and with fewer admissions in ICU (2.5% vs. 9.4%) and shorter length of hospital stay.
- Traditional intraoperative ventilatory settings can be harmful, therefore new guidelines should be proposed.

Abbreviations:

AECC = American-European Consensus Conference; ALI = acute lung injury; ARDS = acute respiratory distress syndrome; OLV = one lung ventilation; PaO_2/FIO_2 = oxygenation index, ratio of arterial oxygen pressure to inspired oxygen fraction; PBW = predicted body weight; PLV = protective lung ventilation; TEA = thoracic epidural anesthesia; TLV = two lung ventilation; V_T = tidal volume; VILI = ventilator-induced lung injury.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

ML and JMT participated in the study design, data analysis and interpretation of the data as well as the writing of the manuscript. JD, VL and ML participated in data collection and statistical analysis. JD, YV and JR participated in the literature search and interpretation of the study. AS and JR participated in revising the bibliography, correcting and editing the manuscript. All authors have read and approved the final manuscript.

Acknowledgements

The Lancardis Fundation from Sion in Switzerland granted support for this study. Neither source influenced the study design, data collection, analysis, reporting, or decision to submit the manuscript for publication.

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Table 1 Preoperative characteristics of the two cohorts of thoracic surgical patients

	Historical Control N=533	PLV N=558	P
Age	**62 (12)**	**63 (12)**	0.956
> 70 yrs (%)	**29**	**30**	0.568
Gender, Female (%)	**35.6**	**36.9***	0.709
BMI (kg/m^2)	**25.1 (4.6)**	**25.3 (5.1)**	0.567
Smoking (%)			
Current	**66.2**	**63.8**	0.724
Ex-smoker (> 6 months)	**10.1**	**11.3**	0.884
Alcohol (> 60g/day)	**13.1**	**14.2**	0.686
ASA classes 3 & 4 (%)	**42.2**	**48.4***	0.047
Co-morbidities (%)			
Hypertension	**24.4**	**35.1***	<0.01
Coronary Artery Disease	**8.4**	**9.7***	0.546
Heart Failure	**5.8**	**8.7***	0.066
Hypercholesterolemia	**16.7**	**22.9***	0.013
Peripheral artery disease	**7.5**	**7.6**	0.951
Diabetes mellitus	**9.6**	**10.7**	0.045
Arrythmia	**2.1**	**2.7**	0.633
Conduction blockade	**8.4**	**7.3**	0.576
Stroke	**2.4**	**2.8**	0.602
Prior PTCA/CABGS (%)	**2.6**	**4.3**	0.179
Preop medications (%)			
Beta-blockers	**5.6**	**10.4***	0.006
ACE Inhibitors / AII Antagonists	**11.1**	**16.5***	0.012
Statins	**8.1**	**9.7**	0.534
Corticoids	**3.9**	**4.1**	0.999
Anti-platelets	**4.1**	**7.4***	0.032
Calcium channel blockers	**3.7**	**4.1**	0.874
Lung function			
FVC, L/min	**3.51 (1.07)**	**3.49 (0.96)**	0.885
FVC, % predicted value	**95 (21)**	**92 (22)**	0.798
FEV1, L/min	**2.5 (1.1)**	**2.4 (0.9)**	0.825
FEV1, % predicted value	**82 (18)**	**81 (19)**	0.912
TLC, L/min	**6.2 (1.4)**	**6.3 (1.8)**	0.892
TLC, % predicted value	**102 (18)**	**101 (17)**	0.921
CO Diffusion Capacity, % predicted value	**54 (14)**	**53 (13)**	0.896
Laboratory data			
Hematocrit (%)	**41.0 (5.1)**	**40.8 (4.9)**	0.885
Creatinine clearance (ml/min)	**83 (23)**	**85 (28)**	0.387

BMI, body mass index; PTCA, percutaneous coronary angioplasty; CABGS, coronary artery bypass graft surgery; ACE, Angiotensin-Converting Enzyme; AII, angiotensin II; FVC, forced vital capacity; FEV1, forced expiratory volume in the first second; TLC, total lung capacity; *P < 0.05 between the two groups

Table 2 Perioperative surgical and medical characteristics, mean (SD) or number (%)

	Historical Control N=533	PLV N=558	P
Preoperative chemotherapy	10.8	14.4	0.080
Type of surgery, % cases			
Pneumonectomy or bi-lobectomy	21.4	17.6	0.129
Lobectomy	54.2	56.1	0.575
Lesser resection	18.7	20.5	0.542
Explorative thoracotomy	5.4	3.2	0.099
Pathologic Stages, % patients			
Ia and Ib	42	44	0.531
IIa and IIb	22	23	0.750
IIIa	18	19	0.733
IIIb and IV	11	8	0.389
Other	7	6	0.833
Thoracic Epidural Analgesia,% patients	83.7	95.0*	<0.001
Intraoperative period			
Duration of anesthesia, min	166 (62)	176 (74)	0.228
Duration of surgery, min	114 (47)	121 (56)	0.354
Duration of One-Lung-Ventilation, min	71 (18)	74 (20)	0.421
Total intraop fluid intake, ml.kg^{-1}.h^{-1}	5.6 (2.8)	5.8 (2.9)	0.587
IV crystalloids, ml.kg^{-1}.h^{-1}	3.6 (1.4)	3.5 (1.6)	0.652
IV colloids, ml.kg-1.h-1	2.0 (1.5)	2.3 (1.8)	0.187
RBC Transfusion, % patients	1.50	1.61	0.991
Urine ouput, ml.kg-1.h-1	1.8 (1.2)	1.5 (1.4)	0.287
Phenylephrine, mg	528 (443)	588 (487)	0.338
Ephedrine, mg	15 (13)	16 (14)	0.542
Cumulative fluid intake (24h), ml.kg^{-1}.h^{-1}	6.4 (3.2)	6.6 (3.1)	0.385
Postoperative period			
Total fluid intake, ml/24h	1657 (573)	1496 (608)	0.182
RBC Transfusion, % patients	2.25	1.79	0.890
Urine ouput, ml/24h	868 (334)	781 (234)	0.254
Chest drainage, ml/24h	378 (172)	342 (125)	0.774
PaO2/FIO2, kPa	45.1 (6.2)	44.7 (5.9)	0.513
Blood hemoglobin at POD1, g/L	119 (13)	121 (20)	0.834
Serum creatinine at POD1, mg/L	93 (30)	84 (31)	0.303

PaO_2/FIO_2, ratio of arterial oxygen pressure to inspiratory fraction of oxygen; POD1, first postoperative day

Table 3 Intraoperative Ventilatory management

	Historical Control N=533	PLV N=558
Two Lung Ventilation		
Tidal Volume, ml/kg PBW	9.2 (2.8)	6.5 (2.0)*
% Patients with VT < 8 ml/kg	24	92 *
Inspiratory Plateau Pressure, cmH2O	16 (5)	12 (4)*
Positive End-Expiratory Pressure, cmH_2O	3 (2)	3 (3)
Dynamic Compliance, ml/cmH2O	52.4 (9.1)	53.5 (8.7)
Inspiratory Oxygen fraction, %	40 (4)	38 (13)
Respiratory Rate, cycle/min	11 (1)	14 (2)*
One Lung Ventilation		
Tidal Volume, ml/kg PBW	7.1 (1.2)	5.3 (1.1)*
Inspiratory Plateau Pressure, cmH2O	20 (7)	15 (6)*
Positive End-Expiratory Pressure, cmH2O	3.3 (2.1)	6.2 (2.4)*
Dynamic Compliance, ml/cmH2O	32.2 (7.5)	44.6 (6.9)*
Inspiratory Oxygen fraction, %	64 (9)	67 (8)
Respiratory Rate, cycle/min	13 (2)	15 (2)*

PBW, predicted body weight; *P<0.05 between the two groups

Table 4 Postoperative outcomes of patients undergoing lung cancer resection

	Historical Control N=533	PLV Group N=558	P
Length of Hospital Stay, day	14.5 (3.3)	11.8 (4.1)*	< 0.001
Admission in ICU, %	9.4	2.5*	< 0.001
Mortality, %	2.8	2.3	0.753
Re-operation, %	1.0	1.6	0.687
Respiratory complications, %	14.4	10.8	0.080
Atelectasis	8.8	5.0*	0.018
Pneumonia	5.6	4.1	0.309
Bronchopleural fistula	1.5	1.3	0.873
Acute Lung Injury	3.8	0.9*	0.032
Pneumonectomy	10.7	3.1	0.094
Lobectomy, bi-lobectomy	1.7	0.2	0.174
Lesser resection	3.8	0.7	0.282
Mechanichal ventilation > 24h	4.1	3.5	0.379
Cardiovascular Complications, %	12.0	11.3	0.723
Myocardial Infarct	1.3	0.9	0.711
Heart Failure	0.9	1.4	0.635
Stroke	0.8	0.7	0.951
Arrhythmia's	11.8	10.4	0.514
Renal dysfunction	5.1	3.0	0.123

*$P<0.05$ between the two groups; Chi^2 with Yates correction or unpaired Student-t test

Table 5 Variables associated with post-thoracotomy ALI

Characteristics	Unadjusted Analysis Odds Ratio (95% CI)	P-value	Adjusted Analysis Odds Ratio (95% CI)	P-value
Age, per 10-year increase	1.09 (0.80 - 1.89)	0.382	-	-
Chronic alcohol consumption	1.76 (1.11 - 5.2)	0.013	1.93 (1.14 - 5.71)	0.001
FEV1 < 60%	1.12 (0.78 - 2.05)	0.254	-	-
ASA class 3/4	1.21 (0.72 - 2.21)	0.214	-	-
ACE Inhibitor therapy	0.85 (0.55 - 2.12)	0.315	-	-
Statin therapy	0.81 (0.45 - 2.97)	0.198	-	-
Chemo-radiotherapy	1.52 (1.09 - 3.83)	0.021	1.40 (0.91 - 2.98)	0.203
Advanced TNM stages (III-IV)	1.63 (1.09 - 3.01)	0.018	1.45 (0.87 - 2.84)	0.234
Thoracic epidural anaesthesia	0.92 0.78 - 1.92)	0.563	-	-
Duration of surgery	1.37 (0.78 - 2.67)	0.312	-	-
Red Blood Cell Transfusion	1.09 (0.23 - 7.24)	0.789	-	-
Pneumonectomy	2.41 (1.29 - 8.12)	0.005	2.52 (1.34 - 7.71)	< 0.001
Fluid infused, per 1 ml.k-1.h-1 increase	1.33 (1.02 - 5.08)	0.032	1.42 (1.09 - 4.32)	0.011

FEV_1, Forced expiratory volume in 1 sec; ACE Inhibitor, Angiotensin-Converting Enzyme Inhibitor

Additional data file 1
The following additional data are available with the online version of this paper. This table lists the major non-fatal complications occurring during the in-hospital postoperative stay. Standard criteria are used to define these adverse events.

Additional files provided with this submission:

Additional file 1: licker adf 1.doc, 20K
http://ccforum.com/imedia/2013010620263929/supp1.doc