ORIGINAL ARTICLE

The Beta Agonist Lung Injury Trial Prevention
A Randomized Controlled Trial

Gavin D. Perkins[1,2], Simon Gates[2], Daniel Park[1,2], Fang Gao[1,3], Chris Knox[2], Ben Holloway[4], Daniel F. McAuley[5,6], James Ryan[7], Joseph Marzouk[8], Matthew W. Cooke[1,2], Sarah E. Lamb[2], and David R. Thickett[3,4]; on behalf of the BALTI-Prevention Collaborators*

[1]Heart of England NHS Foundation Trust, Bordesley Green East, Birmingham, United Kingdom; [2]Warwick Clinical Trials Unit, University of Warwick, Coventry, United Kingdom; [3]Centre for Translational Inflammation Research, School of Clinical and Experimental Medicine, University of Birmingham, Birmingham, United Kingdom; [4]University Hospitals Birmingham, Birmingham, United Kingdom; [5]Centre for Infection and Immunity, Queen's University of Belfast, Belfast, Ireland; [6]Regional Intensive Care Unit, Royal Victoria Hospital, Grosvenor Road, Belfast, Ireland; [7]The James Cook University Hospital, South Tees Hospitals NHS Foundation Trust, Middlesbrough, United Kingdom; and [8]University Hospital Coventry and Warwickshire NHS Trust, Coventry, United Kingdom

Abstract

Rationale: Experimental studies suggest that pretreatment with β-agonists might prevent acute lung injury (ALI).

Objectives: To determine if in adult patients undergoing elective esophagectomy, perioperative treatment with inhaled β-agonists effects the development of early ALI.

Methods: We conducted a randomized placebo-controlled trial in 12 UK centers (2008–2011). Adult patients undergoing elective esophagectomy were allocated to prerandomized, sequentially numbered treatment packs containing inhaled salmeterol (100 μg twice daily) or a matching placebo. Patients, clinicians, and researchers were masked to treatment allocation. The primary outcome was development of ALI within 72 hours of surgery. Secondary outcomes were ALI within 28 days, organ failure, adverse events, survival, and health-related quality of life. An exploratory substudy measured biomarkers of alveolar-capillary inflammation and injury.

Measurements and Main Results: A total of 179 patients were randomized to salmeterol and 183 to placebo. Baseline characteristics were similar. Treatment with salmeterol did not prevent early lung injury (32 [19.2%] of 168 vs. 27 [16.0%] of 170; odds ratio [OR], 1.25; 95% confidence interval [CI], 0.71–2.22). There was no difference in organ failure, survival, or health-related quality of life. Adverse events were less frequent in the salmeterol group (55 vs. 70; OR, 0.63; 95% CI, 0.39–0.99), predominantly because of a lower number of pneumonia (7 vs. 17; OR, 0.39; 95% CI, 0.16–0.96). Salmeterol reduced some biomarkers of alveolar inflammation and epithelial injury.

Conclusion: Perioperative treatment with inhaled salmeterol was well tolerated but did not prevent ALI.
Clinical trial registered with International Standard Randomized Controlled Trial Register (ISRCTN47481946) and European Union database of randomized Controlled Trials (EudraCT 2007-004096-19).

Keywords: acute lung injury; adrenergic β_2 receptor agonists; esophagectomy; one-lung ventilation; adult respiratory distress syndrome

(Received in original form August 28, 2013; accepted in final form December 19, 2013)

*A complete list of the BALTI-Prevention Collaborators can be found before the beginning of the References.

Supported by National Institute for Health Research (NIHR), GlaxoSmithKline, and Intensive Care Foundation. G.D.P. was funded by a Clinician Scientist Award from the NIHR and receives support from the Intensive Care Foundation. D.R.T. was funded by the Wellcome Trust. The project received funding from the NIHR Research for Patient Benefit Program and was supported by the NIHR Comprehensive Research Network. GlaxoSmithKline provided an unrestricted educational grant to fund the biomarker assays. Pulsion donated the PiCCO catheters used during this study. This article presents independent research funded by the NIHR. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

Author Contributions: G.D.P., S.G., F.G., D.F.M., C.K., J.M., and S.E.L. designed the main trial. D.R.T., G.D.P., and D.P. designed the translational studies. D.P., D.R.T., G.D.P., J.M., and J.R. contributed to data collection and chest radiograph interpretation (D.R.T., B.H.). C.K. and S.G. analyzed the main trial results. D.P. and G.D.P. analyzed translational study data. All authors contributed to interpretation of the study results. G.D.P., C.K., and D.R.T. produced the first draft of the final report. All authors made a substantial involvement in its revision before submission and approved the final version.

Correspondence and requests for reprints should be addressed to Gavin D. Perkins, M.B. Ch.B., M.D., Warwick Clinical Trials Unit, University of Warwick, Coventry CV4 7AL, UK. E-mail: g.d.perkins@warwick.ac.uk

Am J Respir Crit Care Med Vol 189, Iss 6, pp 674–683, Mar 15, 2014
Copyright © 2014 by the American Thoracic Society
Originally Published in Press as DOI: 10.1164/rccm.201308-1549OC on January 6, 2014
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: Two recent notable studies (BALTI-2 and ALTA) cast doubt on the effectiveness of β-agonists as a treatment for acute lung injury and acute respiratory distress syndrome (ALI/ARDS). The concept of prophylactic treatment has not been robustly tested previously and represents a change to current approaches designed to treat ALI/ARDS once established.

What This Study Adds to the Field: Patients undergoing esophagectomy were randomized to perioperative inhaled long-acting β-agonists (salmeterol, 100 μg twice daily) or placebo. Treatment was well tolerated. This study found some reduced biomarkers of alveolar inflammation and epithelial injury but no effect on the development of ALI/ARDS.

Acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) are common after esophagectomy (1), which is used to treat esophageal cancer, the fifth most common cancer worldwide accounting for nearly half a million deaths a year (2). The most common surgical approach is to perform a transthoracic esophagectomy. Access to the esophagus is achieved through the deflation of one of the lungs, and gas exchange maintained with one-lung ventilation. During one-lung ventilation, the inflated lung is exposed to high-inspired oxygen concentrations and high inflation pressures, risking the development of ventilator-associated lung injury (3). At the same time, the deflated lung sustains a period of ischemia followed by reperfusion. Together these insults are likely to contribute to the high incidence of postoperative ALI observed among this patient group.

Experimental studies spanning the last 30 years suggested that β-agonists might be an effective treatment for ALI through decreasing inflammatory cell infiltration and cytokine release, augmenting alveolar fluid clearance, and improving alveolar capillary barrier function (4, 5). The Beta Agonist Lung Injury Trial (BALTI-1) showed that a sustained infusion of intravenous salbutamol reduced extravascular lung water (EVLW) and improved pulmonary mechanics in a group of 40 patients with ARDS (6). Two further small human studies showed that inhaled β-agonists could prevent high-altitude pulmonary edema (7) and reduce postoperative lung injury after pulmonary resection (8). These findings led to a series of phase 3 studies investigating the role of β-agonists in ALI.

Two studies examined the role of β-agonists in the treatment in ALI. The ARDSnet trial of nebulized albuterol in ALI was terminated after enrolling 282 patients because there was no difference in overall number of ventilator-free days between arms (9). In the subgroup of patients with shock before randomization, the number of ventilator-free days was less in the albuterol-treated arm (9). The larger multicenter BALTI-2 study, which used intravenous salbutamol, was stopped early because the intervention arm had a higher rate of tachycardias, arrhythmias, and lactic acidosis and a lower survival rate (10).

Prior studies suggest that ALI can be prevented and outcomes improved in patients at risk of but without established disease (11). Recommendations from the critical care community stress the need to explore new treatments to prevent the onset of ALI. This paper reports the results of the first multicenter trial to evaluate β-agonists in the prevention of ALI in patients undergoing esophagectomy (Beta Agonist Lung Injury Prevention [BALTI-p]). Some of the results of these studies have been previously reported in the form of an abstract (12).

Methods

Patients were enrolled from April 1, 2008 until June 30, 2011 at 12 tertiary academic (teaching) hospitals in the United Kingdom. National Research Ethics approval was provided by South Birmingham Research Ethics Committee (reference 07/H1207/233). The trial was approved by the Research and Development Department at each hospital. The study is registered with the International Standard Randomized Controlled Trial Register (ISRCTN47481946) and European Union database of randomized Controlled Trials (EudraCT 2007-004096-19). The study was conducted in accordance with the detailed study protocol, which has been previously published (13).

Patients

Patients aged 18 or older undergoing an elective transthoracic esophagectomy who could use an inhaler with spacer device and were willing to give written informed consent were eligible for inclusion. Patients were ineligible if they were pregnant, receiving current treatment with long-acting β-agonist, allergic to excipients contained in the salmeterol inhaler (HFA 134a), receiving current treatment with noncardioselective β-blockers, or enrolled in a trial of an investigational medicinal product in the last 30 days. Patients were enrolled and data collected by dedicated research staff.

Randomization and Masking

Drug (salmeterol, 25-μg metered dose inhaler) and matching placebo were supplied by Bilcare (Powys, UK) and Modepharma (London, UK). Inhalers and spacer devices were packed into sequentially numbered treatment packs according to a secure randomization sequence. The randomization sequence was produced by the senior study statistician (S.G.) and sent securely to the treatment pack suppliers. Randomization was done according to a block size of 10 with equal allocation between active and placebo groups. Treatment packs were supplied in groups of 10 to centers thus ensuring an equal allocation between active and placebo groups at each center. Treatment packs were held by the pharmacy at each center and issued sequentially for each randomized patient. Research staff, clinical teams, and patients were masked to randomization and treatment allocation.

Drug Administration

Subjects received either 100-μg inhaled salmeterol or placebo by a spacer device 2 hours before surgery and then every 12 hours for 72 hours (including the evening after surgery). Subjects requiring ventilation postoperatively received 100 μg of the drug by an in-line chamber inserted into the inspiratory limb of the ventilator circuit.

Primary and Secondary Outcomes

The primary outcome was the development of ALI within 72 hours of esophagectomy. Lung injury was defined by the American European Consensus Conference definition

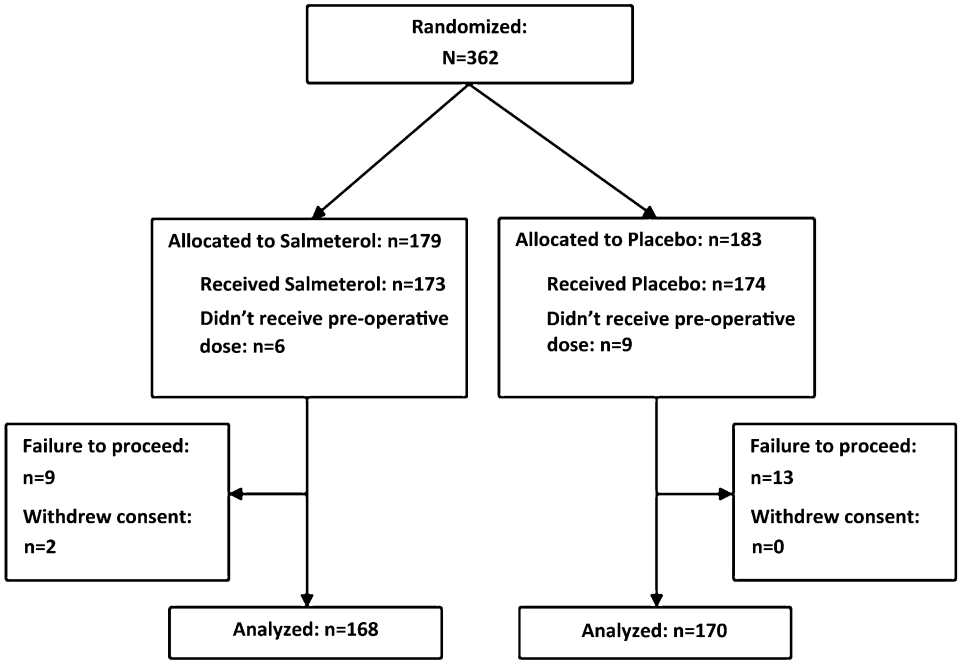

Figure 1. CONSORT flow diagram.

as the acute onset of bilateral infiltrates on the chest radiograph and hypoxemia (Pa_{O_2}/FI_{O_2} ratio of <300 mm Hg) in the absence of clinical evidence of left atrial hypertension (14). Site investigators recorded the Pa_{O_2}/FI_{O_2} ratio and presence or absence of left atrial hypertension daily. A clinical endpoint committee comprised of a respiratory physician (D.R.T.) and radiologist (B.H.) independently reviewed all chest radiographs where Pa_{O_2}/FI_{O_2} ratio was less than 300 mm Hg and there was no clinical evidence of left atrial hypertension to determine if there was radiologic evidence of ALI. Where the reviewers

Table 1: Participant Baseline Characteristics

		Salmeterol (*n = 179*)	Placebo (*n = 183*)
Age, yr	Mean (SD)	63.9 (9.8)	63.3 (10.0)
Sex	Male	142 (79.3%)	146 (79.8%)
Ethnicity	White	178 (99.4%)	182 (99.5%)
Height, cm	Mean (SD)	170.9 (11.9)	171.0 (9.3)
Weight, kg	Mean (SD)	80.7 (18.6)	79.5 (18.0)
Diagnosis	Adenocarcinoma	133 (74.3%)	139 (76.0%)
	Squamous cell	31 (17.3%)	29 (15.9%)
	Other malignant	3 (1.7%)	1 (0.6%)
	Barrett esophagus	10 (5.6%)	9 (4.9%)
	Missing	2 (1.1%)	5 (2.7%)
Preoperative chemotherapy	Number (%)	134 (74.9%)	151 (82.5%)
Chemotherapy part of OE05 trial	Number (%)	23 (12.8%)	25 (13.7%)
TNM staging tumor	1	13 (7.3%)	7 (3.8%)
	2	45 (25.1%)	46 (25.1%)
	3	112 (62.6%)	120 (65.6%)
	4	2 (1.1%)	2 (1.1%)
	Missing	7 (3.9%)	8 (4.4%)
TNM staging nodes	0	70 (39.1%)	60 (32.8%)
	1	103 (57.5%)	108 (59.0%)
	Missing	6 (3.4%)	15 (8.2%)
FVC, L	Mean (SD)	4.1 (1.0)	3.9 (1.0)
FEV_1, L/s	Mean (SD)	2.8 (0.8)	2.8 (0.8)
EQ-5D score	Mean (SD)	0.85 (0.20)	0.85 (0.18)
EQ-5D VAS	Mean (SD)	75.1 (17.7)	72.6 (18.5)

Table 2: Operation Characteristics

		Salmeterol (*n* = *179*)	Placebo (*n* = *183*)
Tumor location	Cervical	3 (1.7%)	2 (1.1%)
	Mid esophagus	39 (21.8%)	54 (29.5%)
	Esophageal/gastric junction	127 (71.0%)	117 (63.9%)
	Missing	10 (5.6%)	10 (5.5%)
Surgical approach	Laparoscopic	38 (21.2%)	43 (23.5%)
	Open	133 (74.3%)	133 (72.7%)
	Missing or did not proceed	8 (4.5%)	7 (3.8%)
Open stage; if open surgical approach	Two stage	96 (72.2%)	98 (73.7%)
	Three stage	4 (3.0%)	11 (8.3%)
	Missing or did not proceed	33 (24.8%)	24 (18.0%)
Thoracotomy; if open surgical approach	Right	102 (76.7%)	94 (70.7%)
	Left	22 (16.5%)	23 (17.3%)
	Missing or did not proceed	9 (6.8%)	16 (12.1%)
American Society of Anesthesiologists grade	I	9 (5.0%)	9 (4.9%)
	II	118 (65.9%)	112 (61.2%)
	III	37 (20.7%)	45 (24.6%)
	IV	1 (0.6%)	1 (0.6%)
	V	0	0
	Missing	14 (7.8%)	16 (8.7%)
Duration of one-lung ventilation, min	Mean (SD)	143.0 (53.6)	144.2 (55.2)
Cumulative fluid balance at end of surgery, L			
	Median (interquartile range)	2.7 (2–3.7)	2.5 (1.6–3.6)
Duration of surgery, min	Mean (SD)	384.2 (104.6)	380.3 (121.1)
Maximum F_{IO_2}	Mean (SD)	0.79 (0.18)	0.79 (0.19)
Tidal volume, ml/kg	Mean (SD) actual weight	7.2 (2.0)	6.6 (1.8)
	Mean (SD) predicted weight	7.5 (1.7)	7.2 (2.0)
Positive end-expiratory pressure, cm H_2O	Mean (SD)	4.38 (2.3)	4.8 (1.1)
Peak airway pressure, cm H_2O	Mean (SD)	23.5 (5.4)	22.9 (2.9)

disagreed a third reviewer (G.D.P.) provided arbitration. Reviewers were unaware of treatment allocation.

The trial secondary outcomes were the development of ALI during the first 28 days postoperatively, Pa_{O_2}/F_{IO_2} ratio, the number of ventilator-free and organ failure–free days, 28- and 90-day survival, and adverse events. Given the link between the development of ALI and impaired health-related quality of life, we included the generic health outcome questionnaire EuroQol (EQ-5D).

Ventilator-free days were defined as previously (15). Organ failure–free days were defined in a similar manner, with an organ failure–free day being a day without evidence of nonrespiratory organ failure. Organ failure was defined by a Sequential Organ Failure Assessment score of greater than 3 (16).

Lung Water and Plasma Measurements

Consecutive patients at two sites (Birmingham Heartlands Hospital [n = 14] and University Hospital Birmingham [n = 39]) were coenrolled into an exploratory substudy. The substudy was overseen personally by one of the authors (D.P.) who administered drug before surgery in a standardized manner and undertook all the measurements and laboratory analyses. In these patients, EVLW and pulmonary vascular permeability index (PVPI) were measured by thermodilution (PiCCO; Pulsion Medical, London, UK) preoperatively, at the end of the procedure, and the first postoperative day as previously described (17). EVLW was measured as an indirect assessment of the accumulation of fluid in the interstitium and alveolar space (18). PVPI reflects alveolar capillary permeability (19). Plasma was collected preoperatively, at the end of the procedure, and the morning after surgery (8–10 AM). Samples were processed and frozen at −80°C (20). Inflammatory mediators (IL-6, IL-8, IL1-β, tumor necrosis factor [TNF]-α) and markers of endothelial (s-ICAM-1) and epithelial damage (soluble receptor for advanced glycation endproducts [sRAGE]) were measured by multiplex ELISA (Millipore, Watford, UK) at a central

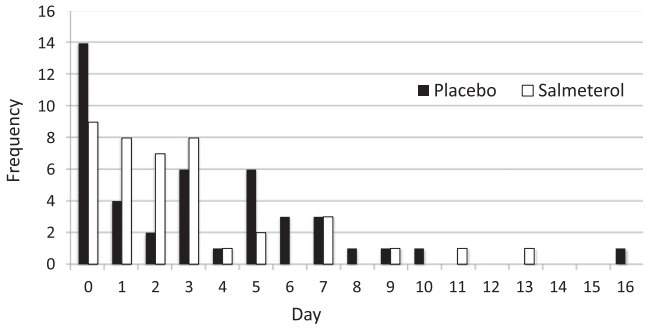

Figure 2. Timing of development of acute lung injury (ALI) (one patient with missing day of ALI; one placebo [early ALI]).

laboratory according to manufacturer's instructions. Surface protein-D was measured by ELISA (Hycult Biotech, Plymouth, UK).

Perioperative Care

Clinical teams were briefed to adopt a lower tidal volume and fluid-conservative hemodynamic management approach. Patients were extubated at the end of the procedure whenever possible. The following medications were not permitted for the duration of the clinical study: long-acting β-agonists, noncardioselective β-blockers, or another investigational medicinal product. Inhaled or nebulized short-acting β-agonists were not permitted except in the event of severe bronchospasm.

Trial Design and Statistical Analysis

Detailed information about the sample size estimate is provided in the trial protocol (13). In brief, we sought to determine a reduction in the event rate of ALI from 25 to 12.5% based on consultation with the British Society of Esophageal Gastric Surgeons. We calculated this would require 336 patients to provide 80% power at a significance level of 0.05. We included a 5% failure to proceed with surgery and a 2% loss to follow-up rate. This gave an overall sample size of 180 per arm. The exploratory substudy sought to recruit a minimum of 46 patients (23 in each arm), to provide 80% power to detect a 25% change in EVLW index (from a baseline of 9.7 ml/kg, standard deviation 2.7 ml/kg (21) at a significance level of 0.05).

The primary analysis was based on intention-to-treat. Patients found to have an inoperable malignancy after randomization were considered no longer at risk of ALI and were withdrawn from

Table 3: Study Outcomes

		Salmeterol (*n = 168*)	Placebo (*n = 170*)	Statistics (*95% CI*)
Early ALI (Day 0–3)	Yes	32 (19.2%)	27 (16.0%)	OR = 1.25 (0.71 to 2.19)*
	No	135 (80.8%)	142 (84.0%)	OR = 1.24 (0.69 to 2.22)†
	Missing	1	1	
Late ALI (Day 4–28)	Yes	9 (5.4%)	17 (10.1%)	OR = 0.51 (0.22 to 1.18)*
	No	157 (94.6%)	151 (89.9%)	OR = 0.47 (0.20 to 1.11)†
	Missing	2	2	
All ALI (Day 0–28)	Yes	41 (24.7%)	44 (26.2%)	OR = 0.92 (0.56 to 1.51)*
	No	125 (75.3%)	124 (73.8%)	OR = 0.89 (0.54 to 1.48)†
	Missing	2	2	HR = 0.97 (0.63 to 1.49)*
				HR = 0.95 (0.62 to 1.46)†
Severity of respiratory illness: lowest recorded Pa_{O_2}/FI_{O_2} ratio	Mean	30.6 (13.7)	28.6 (13.2)	Difference = 2.00 (−0.93 to 4.93)*
	Median (IQR)	28.2 (19.8 to 37.2)	27.5 (18.6 to 36.3)	Difference = 1.94 (−1.00 to 4.87)†
	Range	3.1 to 82.5	4.3 to 80.9	
	Missing	10	4	
Any organ failure on Day 0–28	Yes	53 (31.5%)	61 (36.1%)	RR = 0.87 (0.65 to 1.18)
	No	115 (68.5%)	108 (63.9%)	
	Missing	0	1	
Organ failure–free days	Mean	26.2 (4.1)	25.6 (5.1)	Difference = 0.61 (−0.38 to 1.60)*
	Median (IQR)	28 (26 to 28)	28 (25 to 28)	Difference = 0.61 (−0.38 to 1.60)†
	Range	1 to 28	2 to 28	
	Missing	0	1	
Any ventilator support on Day 0–28	Yes	63 (37.5%)	64 (37.6%)	RR = 1.00 (0.76 to 1.31)
	No	105 (62.5%)	106 (62.4%)	
	Missing	0	0	
Ventilator-free days	Mean	25.2 (6.4)	25.4 (6.1)	Difference = −0.17 (−1.50 to 1.16)*
	Median (IQR)	28 (26.5 to 28)	28 (27 to 28)	Difference = −0.08 (−1.38 to 1.23)†
	Range	0 to 28	0 to 28	
	Missing	0	0	
Mortality	Alive at 28 d	164 (98.8%)	165 (97.6%)	HR = 0.48 (0.09 to 2.64)*
	Dead at 28 d	2 (1.2%)	4 (2.4%)	HR = 0.53 (0.09 to 3.03)†
	Missing	2	1	*P* value = 0.3886‡
EQ-5D score	Mean	0.526 (0.30)	0.521 (0.30)	Difference = 0.006 (−0.068 to 0.079)*
	Median (IQR)	0.62 (0.329 to 0.76)	0.587 (0.293 to 0.76)	Difference = 0.015 (−0.060 to 0.090)†
	Range	−0.331 to 1	−0.594 to 1	
	Missing	34	38	
EQ-5D VAS	Mean	61.0 (17.1)	61.2 (17.9)	Difference = −0.21 (−4.44 to 4.01)*
	Median (IQR)	60 (50 to 75)	62 (50 to 75)	Difference = 0.22 (−4.04 to 4.44)†
	Range	5 to 100	0 to 90	
	Missing	35	38	

Definition of abbreviations: ALI = acute lung injury; CI = confidence interval; HR = hazard ratio; IQR = interquartile range; OR = odds ratio; RR = relative risk.
*Unadjusted treatment effect.
†Treatment effect adjusted for hospital and age at randomization.
‡Calculated using log-rank test.

further participation. The primary outcome was compared using a logistic regression model, with the dependent variable as ALI/no ALI within 72 hours and the independent variables as treatment and other important predictors (center and age) and reported as an odds ratio (95% confidence interval [CI]). Categorical data were analyzed using logistic regression models. Continuous data were analyzed using linear regression models, with treatment group as an independent variable along with other important predictors and reported as adjusted mean estimates and 95% CI's.
Time-to-event data were analyzed using a log-rank test. The *P* values and a hazard ratio with its 95% CI from a Cox proportional hazards model were also calculated. The proportional hazard assumption across treatment arms was checked graphically using a log-cumulative hazard plot.

Results

Enrollment and Patient Characteristics

A total of 362 patients (288 [79.6%] male) were enrolled in the study up until June 30, 2011 when the target sample size was achieved. Follow-up of outcomes and collation of chest radiographs continued until March 2012. A total of 179 were randomly assigned to the salmeterol arm and 183 to placebo. Participant flow is summarized in Figure 1. The patient's baseline characteristics were well matched (Table 1). Most patients had an open procedure via right thoracotomy for an esophageal or gastric junctional tumor. One-fifth had minimally invasive (laparoscopic) procedures. Groups were well matched with respect to operative and anesthetic interventions (Table 2). Eight patients (4.5%) in the salmeterol arm and 13 (7.0%) in the placebo arm had inoperable malignancy and were withdrawn from the study. Two patients in the salmeterol arm withdrew consent.

Outcomes

The proportion of patients who met the primary outcome (development of ALI within 72 h of surgery) was similar between the salmeterol and placebo arms (salmeterol 32 [19.2%] of 168 vs. placebo 27 [16.0%] of 170; odds ratio, 1.25; 95% CI, 0.71–2.22). There was also no difference in ALI rates during the first 28 days after surgery (placebo 41 [24.7%] of 168 compared with salmeterol 44 [26.2%] of 167; odds ratio, 0.98; 95% CI, 0.59–1.60). Most cases (72%) of ALI occurred in the first 72 hours, most frequently in the first 24 hours after surgery. There was no difference in the time to development of ALI (Figure 2). The degree of impairment in oxygenation (Pa_{O_2}/FI_{O_2}) was similar as were the number of ventilator-free and organ failure–free days (Table 3). There was no difference in 28-day survival.

Compared with baseline, health-related quality of life was impaired in both groups at 28 and 90 days, although there was no difference between the salmeterol- and placebo-treated groups.

Lung Water and Alveolar Inflammation

A total of 53 patients were enrolled in the translational substudy (26 placebo, 27 salmeterol). Salmeterol treatment significantly reduced PVPI compared with placebo (Figure 3). However, this did not attenuate the increase in EVLW seen after surgery (immediately postoperation EVLWI for placebo mean 9.8 [SD, 3.1] vs. salmeterol mean 10.4 [SD 3.1], difference −0.6 [95% CI, −2.1 to 1.0] ml/kg, P = 0.458 or at postoperative Day 1 placebo 9.2 [3.6] vs. salmeterol 8.5 [2.4], difference 0.68 [95% CI, −0.9 to 2.3], P = 0.397).

Soluble ICAM-1, a marker of endothelial injury, was reduced immediately postoperatively among patients treated with salmeterol as were the circulating inflammatory cytokines IL-1β and TNF-α. There was no difference in IL-6 or IL-8 between groups. sRAGE (a marker of type I epithelial cell damage) was also reduced at postoperative Day 1 but there was no difference in the type II cell marker surfactant protein D (Table 4).

Safety and Adverse Events

The frequency of serious adverse events, suspected unexpected serious adverse reaction, and adverse events was less in the salmeterol group (placebo 70 vs. salmeterol 55; odds ratio, 0.63; 95% CI, 0.39–0.99) (Table 5). This was mainly caused by a lower rate of pneumonia (17 [9.9%] placebo vs. 7 [4.1%] salmeterol; odds ratio, 0.39; 95% CI, 0.16–0.96). The rate of cardiovascular adverse events was similar between groups (salmeterol 8 [4.7%] vs. placebo 9 [5.3%]).

Discussion

The main findings of this randomized, clinical trial were that in adult patients at high risk of ALI because of elective esophagectomy, perioperative treatment with inhaled salmeterol (100 μg twice daily) did not prevent the development of ALI.

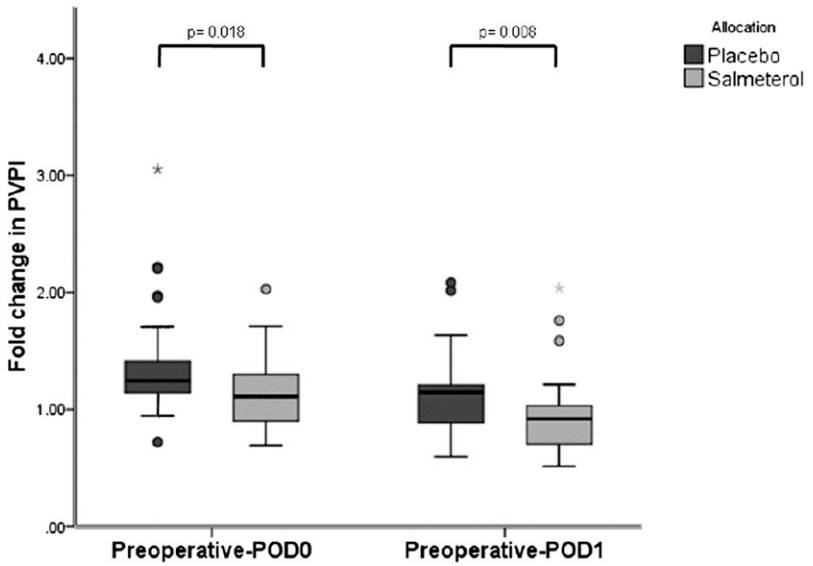

Figure 3. Box-and-whisker plot showing fold change in pulmonary vascular permeability index (PVPI). *Circles* and *asterisks* represent outlying values.

Table 4: Systemic Inflammatory and Endothelial–Epithelial Markers

	Baseline		Postoperative		Day 1	
	Placebo (*n* = 23)	Salmeterol (*n* = 27)	Placebo (*n* = 23)	Salmeterol (*n* = 27)	Placebo (*n* = 23)	Salmeterol (*n* = 27)
TNF-α, pg/ml	9.6 (6–35.6)	9.7 (5.4–12.4)	3.9 (2.6–7.9)	3.4 (2.6–4.9)	10.2 (7.1–18)	7.4 (4.7–10.5)*
IL1-β, pg/ml	0.47 (0.01–12.7)	0.01 (0.01–1.03)*	0.01 (0.01–1.03)	0.05 (0.05–0.05)	0.05 (0.04–5.7)	0.04 (0.04–1.4)*
IL-6, pg/ml	10.2 (5.5–47.3)	5.8 (1.7–21)	459.4 (233.2–727.3)	491 (227.9–666.2)	387.3 (209.4–452.6)	224.3 (157–389.6)
IL-8, pg/ml	20.2 (13–62.9)	19.2 (9.9–40.4)	49.4 (34.8–108.9)	49 (22.5–86)	65.5 (35.2–101.1)	46.5 (22.5–86.1)
sRAGE, pg/ml	26.5 (18.4–41.9)	33.4 (15.2–59.6)	748 (232.2–1017.5)	424.6 (142.9–1014.3)	74.3 (44.3–117.2)	44.3 (28.7–61.7)*
SP-D, pg/ml	896 (587–1,612)	825 (575–1,428)	936 (614–1,465)	986 (554–1,322)	634 (472–1,028)	650 (495–1,087)
sICAM-1, pg/ml	82.3 (51.6–110.8)	57.9 (36–90.3)	51.2 (39.9–74.5)	37.5 (30.6–54.3)†	88.6 (71–128.4)	87.6 (68.4–110.3)
vWF, pg/ml	112.6 (58.3–162.6)	79.4 (43–154.6)	184.7 (123.9–290.2)	180.6 (121.9–213.6)	204.8 (155.5–277.6)	207.9 (176.5–255.5)

Definition of abbreviations: sICAM = soluble intracellular adhesion molecule-1; SP-D = surface protein D; sRAGE = soluble receptor for advanced glycation endproducts; TNF = tumor necrosis factor; vWF = von Willebrand factor.
*$P < 0.05$.
†$P < 0.01$.

Treatment with salmeterol did not improve oxygenation or alter the number of ventilator- or organ failure–free days. Patients randomized to salmeterol had a lower rate of serious adverse events predominantly through a reduction in the rate of nosocomial pneumonia.

There are several potential reasons why perioperative treatment with inhaled salmeterol did not prevent lung injury. First, the timing and dose may not have been optimal. In a high-altitude pulmonary edema study, which showed that 125 μg of salmeterol reduced the rate of high-altitude pulmonary edema from 74 to 33%, salmeterol was administered 24 hours before ascent. It is possible that because the peak rate of ALI was observed in the first 24 hours after the esophagectomy, pretreatment 2 hours before surgery may have been too short a time interval (7). The dose selected for the present study was consistent with prior human studies, which showed that salmeterol reduced neutrophil recruitment and alveolar TNF-α (22) and enhanced pulmonary fibrinolysis (23) after an inhaled LPS challenge. It is possible, however, that higher doses may have been effective. This has important implications for future studies of ARDS prevention. Consideration is needed to understand the time interval between the insult and development of ARDS for a given population to inform when it is most appropriate to intervene. In addition, smaller proof of principal dose finding studies should be considered to determine if the intervention has efficacy on surrogate biologic outcomes before embarking on a large trial powered for clinical outcomes.

Second, despite adopting a randomized controlled trial design to minimize imbalances between the treatment and control arm we observed numerically higher tidal volumes during surgery in the salmeterol arm. In rat models of ALI, even short periods (1–5 h) of high tidal volume ventilation are associated with increased diffuse alveolar damage and reductions in c-AMP–dependent alveolar fluid clearance linked at least in part to reduced Na/K ATPase expression and function (24, 25). Because the duration of exposure to ventilation was on average 6 hours it is plausible that this led to worse lung injury in the salmeterol group, mitigating any therapeutic benefit from the drug.

We chose esophagectomy as a clinical model of ALI because the population was identifiable in advance, the timing of the "insult" (surgery) was predictable, and esophagectomy is associated with one of the highest incidences of postoperative ALI (25–40%) (1, 26). From a pathophysiologic perspective, many of the changes observed after esophagectomy (activation of the inflammatory cascade [27] and increase in alveolar-capillary permeability [28]) mirror those in the early phase of ALI (29). On the basis of the data from this current study it is likely that β agonists are ineffective as a treatment to prevent ALI. However, it is possible that the severity of insult associated with esophagetcomy (biotrauma, hyperoxia, mechanical manipulation of the lung, ischemia-reperfusion, infection) may have overwhelmed the effects of salmeterol. We cannot therefore exclude different results in other groups of at-risk patients.

In light of the findings of ALTA (9) and BALTI-2 (10) we paid close attention to the safety and tolerability of β-agonists during the present trial. In contrast to the former studies, the rate of serious adverse events in BALTI-prevention was lower in the salmeterol arm. This was caused predominantly by a lower rate of nosocomial pneumonia. Although this finding was unexpected it is not unprecedented because salmeterol has also been observed to reduce the frequency of exacerbations of obstructive lung diseases (30). *In vitro* salmeterol reduced epithelial cell damage after exposure to *Pseudomonas auroginosa* and *Haemophilus influenza* and reduced *Pseudomonas* adhesion to epithelial cells (31, 32). In addition, salmeterol enhances ciliary beat frequency and reduces pyocyanin-induced slowing of ciliary beat frequency (33). The observation of a reduced rate of nosocomial pneumonia could potentially be explained by the cytoprotective effects of salmeterol on respiratory epithelial cells, most likely related to maintaining structural integrity and function of the epithelial cells.

This study measured biomarkers that are linked to the pathophysiology and outcome from ALI. We observed a reduction in the early inflammatory mediators IL-1β and TNF-α. IL-6 and IL-8 were numerically lower, although this was not statistically significant. These findings are similar to the experimental human LPS model whereby salmeterol reduced alveolar TNF-α but did not have a statistically significant effect on IL-8 or IL-6. Because IL-8 and IL-6 are released later in the inflammatory response it is possible that our sample timing may have been too early to observe changes in these levels;

Table 5: Safety Summarized by Treatment Group

		Salmeterol (*n* = *170*)	Placebo (*n* = *171*)
SAE and SUSARs	Total SAEs	48 (28.2%)	66 (38.6%)
	Related to study drug	0	2 (1.2%)
	Related to study drug and unexpected	0	1 (0.6%)
SAE	Anastomotic leak	10 (5.9%)	9 (5.3%)
	Other surgical complication	7 (4.1%)	10 (5.9%)
	Pneumonia	7 (4.1%)	17 (9.9%)
	Other respiratory	13 (7.6%)	11 (6.4%)
	Inoperable tumor	0	1 (0.6%)
	Sepsis	5 (2.9%)	5 (2.9%)
	Arrhythmia	1 (0.6%)	5 (2.9%)
	Other	5 (2.9%)	7 (4.1%)
Adverse events	Atrial fibrillation	4 (2.4%)	4 (2.3%)
	Bigeminy	1 (0.6%)	0
	Hypokalemia	1 (0.6%)	0
	Sinus tachycardia	1 (0.6%)	0

Definition of abbreviations: SAE = serious adverse event; SUSAR = suspected unexpected serious adverse reaction.

alternatively, salmeterol may differentially modulate the inflammatory cascade.

We observed a reduction in alveolar capillary barrier dysfunction as measured by the PiCCO PVPI. These findings were consistent with our BALTI-1 study in patients with ARDS, which also observed reduced pulmonary vascular permeability after β-agonist administration (17). The lower levels of RAGE released into the circulation perioperatively supports the hypothesis that epithelial damage during surgery was lower as a result of salmeterol treatment. RAGE is preferentially expressed on alveolar type I epithelial cells, which are more prone to ventilator-induced injury than type II cells. RAGE has been shown to be an independent predictor of outcome in patients who develop ALI and be elevated in patients with sepsis with ARDS versus control subjects (34).

There are several possibilities that may explain why the changes in biologic markers failed to translate into differences in clinical outcomes. First, the methods used to quantify cytokine measurements reflect antigenic levels rather than biologic activity so the observed findings may not reflect the biologic effects *in vivo*. Second, although clinical evaluations of PVPI have shown that it is able to differentiate between cardiogenic and noncardiogenic pulmonary edema (35) and is related to the severity of underlying lung injury (36), its measurement is sensitive to changes in pulmonary blood flow that are unrelated to alveolar-capillary permeability. Thus, it is possible that the pulmonary vasodilatatory effects of β-agonists may have been responsible for the observed reduction in PVPI. Finally, the biologic effects of salmeterol may be insufficient to overcome the severity of insult associated with esophagectomy. The present study draws attention to the limitations of relying solely on biomarkers when evaluating prophylactic treatments for ALI. Furthermore, it highlights the need for further research to identify and characterize alternative biomarkers that could serve as potential surrogate outcomes measures in future trials. Such research should consider the challenges of interpretation of biomarkers relative to the sex and timing of specimen retrieval.

This study has strengths and weaknesses. The choice of esophagectomy had the advantage of a greater degree of homogeneity in case mix (predominantly male, white patients, with esophageal cancer), insult, and frequency of developing of ALI than selecting a broader range of surgical procedures. Nevertheless, even within this population there is variation in preoperative risk factors for ALI (e.g., smoking status, alcohol use, chronic obstructive pulmonary disease, diabetes) and perioperative risk factors. Future studies could consider the use of risk prediction tools, such as the Surgical Lung Injury Prediction (37) model, to reduce variation, enrich the population to patients at highest risk of ALI, and enhance generalizability of the findings. Clinical teams were advised to adopt a protective ventilation and conservative fluid management strategy. Although this enhanced the generalizability of findings to clinical practice, it introduced variation between cases. The development of a more proscriptive surgical, ventilation, and fluid management protocol may reduce such variation and might be considered in future trials. Finally, we demonstrated the feasibility of using a clinical endpoint committee to determine that the primary outcome improved consistency and reduced the chance of reporter bias.

In summary, β-agonists cannot be recommended as a prophylactic treatment to prevent ALI after esophagectomy. Salmeterol did show signs of biologic efficacy in terms of reducing markers of inflammation and epithelial damage perioperatively. In contrast to the results of ALTA and BALTI-2 there were reduced adverse events postoperatively in the salmeterol-treated patients that may be caused by a reduced incidence of pneumonia. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

BALTI-Prevention Collaborators: Trial Coordination Team: Coordinators (Beverly Hoddell, Elizabeth Ball, Claire Daffern), Management and quality assurance (Sarah Duggan, Claire Daffern). Clinical support: Teresa Melody, Chris Bassford, Aisling Clarkson. Contracts: Navdeep Bains. Sponsor representatives: Elizabeth Adey, Bethan Bishop (Heart of England NHS Foundation Trust). Site study teams: Teresa Melody, Keith Couper, Aisling Clarkson. Birmingham Heartlands Hospital – Heart of England NHS Trust, Derek Alderson (PI), Judith Wilde, Louise Williams. Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust,

Joseph Marzouk (PI), Geraldine Ward, Steven Clay. University Hospitals Coventry and Warwickshire, James Ryan (PI), Louise Cawthorn, Kerry Colling. The James Cook University Hospital – South Tees Hospitals NHS Foundation Trust, Danny McAuley (PI), Chris Burnett, Sonia Derbyshire. Royal Victoria Hospital, Belfast, Jonathan Thompson (PI), Natalie Rich, Sarah Bowrey. Leicester Royal Infirmary – University Hospitals of Leicester NHS Trust, Duncan Beardsmore (PI), Mark Deakin, Sarah Dawson. University Hospital of North Staffordshire – University Hospital of North Staffordshire NHS Trust, Akesh Dhrampal (PI), Melissa Rosbergen. Norfolk and Norwich University Hospital NHS Foundation Trust, Prasad Lanka (PI), Neil Smith, Castle Hill Hospital – Hull and East Yorkshire Hospitals NHS Trust, Shondipon Laha (PI), Jackie Baldwin, Janet Mills, Angela Walsh. Royal Preston Hospital – Lancashire Teaching Hospitals NHS Foundation Trust, Tom Durcan (PI), Sue Smolen. Broomfield Hospital, Mid Essex Hospital Services NHS Trust, Carl Waldmann (PI), Nicola Jacques. Royal Berkshire NHS Foundation Trust, Patient and Public Involvement Representative: Mr. Barry Williams, Chairman Intensive Care Patient and Relatives Committee. Data Monitoring Committee: Bill Tunnicliffe, Jasmeet Soar.

References

1. Park DP, Welch CA, Harrison DA, Palser TR, Cromwell DA, Gao F, Alderson D, Rowan KM, Perkins GD. Outcomes following oesophagectomy in patients with oesophageal cancer: a secondary analysis of the ICNARC Case Mix Programme Database. *Crit Care* 2009;13:S1.
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011;61:69–90.
3. Michelet P, D'Journo XB, Roch A, Doddoli C, Marin V, Papazian L, Decamps I, Bregeon F, Thomas P, Auffray JP. Protective ventilation influences systemic inflammation after esophagectomy: a randomized controlled study. *Anesthesiology* 2006;105:911–919.
4. Bassford CR, Thickett DR, Perkins GD. The rise and fall of β-agonists in the treatment of ARDS. *Crit Care* 2012;16:208.
5. Perkins GD, McAuley DF, Richter A, Thickett DR, Gao F. Bench-to-bedside review: beta2-agonists and the acute respiratory distress syndrome. *Crit Care* 2004;8:25–32.
6. Perkins GD, McAuley DF, Thickett DR, Gao F. The Beta-Agonist Lung Injury Trial (BALTI): a randomized placebo-controlled clinical trial. *Am J Respir Crit Care Med* 2006;173:281–287.
7. Sartori C, Allemann Y, Duplain H, Lepori M, Egli M, Lipp E, Hutter D, Turini P, Hugli O, Cook S, *et al*. Salmeterol for the prevention of high-altitude pulmonary edema. *N Engl J Med* 2002;346: 1631–1636.
8. Licker M, Tschopp JM, Robert J, Frey JG, Diaper J, Ellenberger C. Aerosolized salbutamol accelerates the resolution of pulmonary edema after lung resection. *Chest* 2008;133:845–852.
9. Matthay MA, Brower RG, Carson S, Douglas IS, Eisner M, Hite D, Holets S, Kallet RH, Liu KD, MacIntyre N, *et al*.; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Randomized, placebo-controlled clinical trial of an aerosolized β_2-agonist for treatment of acute lung injury. *Am J Respir Crit Care Med* 2011;184:561–568.
10. Gao Smith F, Perkins GD, Gates S, Young D, McAuley DF, Tunnicliffe W, Khan Z, Lamb SE; BALTI-2 study investigators. Effect of intravenous β-2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicentre, randomised controlled trial. *Lancet* 2012;379:229–235.
11. Serpa Neto A, Cardoso SO, Manetta JA, Pereira VG, Espósito DC, Pasqualucci MdeO, Damasceno MC, Schultz MJ. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. *JAMA* 2012;308: 1651–1659.
12. Parekh D, Dancer R, Park D, Perkins GD, Thickett D. Salmeterol prevents pneumonia and reduces biomarkers of inflammation/ epithelial damage but not acute lung injury following oesophagectomy: the results of BALTI prevention trial. Abstract 18. Barcelona: European Respiratory Society; 2013 [accessed 2014 Feb 13]. Available from: http://www.ersnet.org/learning_resources_player/abstract_print_13/files/Abstract_book_2013.pdf
13. Perkins GD, Park D, Alderson D, Cooke MW, Gao F, Gates S, Lamb SE, Mistry D, Thickett DR. The Beta Agonist Lung Injury Trial (BALTI): prevention trial protocol. *Trials* 2011;12:79.
14. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, LeGall JR, Morris A, Spragg R; Consensus Committee. Report of the American-European Consensus conference on acute respiratory distress syndrome: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *J Crit Care* 1994;9:72–81.
15. Schoenfeld DA, Bernard GR; ARDS Network. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. *Crit Care Med* 2002;30:1772–1777.
16. Vincent JL, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F, Blecher S. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med* 1998;26:1793–1800.
17. Perkins GD, Gao F, Thickett DR. In vivo and in vitro effects of salbutamol on alveolar epithelial repair in acute lung injury. *Thorax* 2008;63:215–220.
18. Craig TR, Duffy MJ, Shyamsundar M, McDowell C, McLaughlin B, Elborn JS, McAuley DF. Extravascular lung water indexed to predicted body weight is a novel predictor of intensive care unit mortality in patients with acute lung injury. *Crit Care Med* 2010;38:114–120.
19. Tagami T, Kushimoto S, Atsumi T, Matsuda K, Miyazaki Y, Oyama R, Koido Y, Kawai M, Yokota H, Yamamoto Y. Investigation of the pulmonary vascular permeability index and extravascular lung water in patients with SIRS and ARDS under the PICCO system. *Crit Care* 2006;10:352.
20. Perkins GD, Nathani N, McAuley DF, Gao F, Thickett DR. In vitro and in vivo effects of salbutamol on neutrophil function in acute lung injury. *Thorax* 2007;62:36–42.
21. Oshima K, Kunimoto F, Hinohara H, Hayashi Y, Kanemaru Y, Takeyoshi I, Kuwano H. Evaluation of respiratory status in patients after thoracic esophagectomy using PICCO system. *Ann Thoracic Cardiovasc Surg* 2008;14:283–288.
22. Maris NA, de Vos AF, Dessing MC, Spek CA, Lutter R, Jansen HM, van der Zee JS, Bresser P, van der Poll T. Antiinflammatory effects of salmeterol after inhalation of lipopolysaccharide by healthy volunteers. *Am J Respir Crit Care Med* 2005;172:878–884.
23. Maris NA, de Vos AF, Bresser P, van der Zee JS, Jansen HM, Levi M, van der Poll T. Salmeterol enhances pulmonary fibrinolysis in healthy volunteers. *Crit Care Med* 2007;35:57–63.
24. Lecuona E, Saldías F, Comellas A, Ridge K, Guerrero C, Sznajder JI. Ventilator-associated lung injury decreases lung ability to clear edema and downregulates alveolar epithelial cell Na, K-adenosine triphosphatase function. *Chest* 1999;116(Suppl. 1): 29S–30S.
25. Hirsch J, Hansen KC, Sapru A, Frank JA, Chalkley RJ, Fang X, Trinidad JC, Baker P, Burlingame AL, Matthay MA. Impact of low and high tidal volumes on the rat alveolar epithelial type II cell proteome. *Am J Respir Crit Care Med* 2007;175:1006–1013.
26. Paul DJ, Jamieson GG, Watson DI, Devitt PG, Game PA. Perioperative risk analysis for acute respiratory distress syndrome after elective oesophagectomy. *ANZ J Surg* 2011;81:700–706.
27. Sato N, Koeda K, Kimura Y, Ikeda K, Ogawa M, Saito K, Endo S. Cytokine profile of serum and bronchoalveolar lavage fluids following thoracic esophageal cancer surgery. *Eur Surg Res* 2001;33:279–284.
28. Rocker GM, Wiseman MS, Pearson D, Shale DJ. Neutrophil degranulation and increased pulmonary capillary permeability following oesophagectomy: a model of early lung injury in man. *Br J Surg* 1988;75:883–886.
29. Perkins GD, Chatterjie S, McAuley DF, Gao F, Thickett DR. Role of nonbronchoscopic lavage for investigating alveolar inflammation and permeability in acute respiratory distress syndrome. *Crit Care Med* 2006;34:57–64.

30. Niewoehner DE. TORCH and UPLIFT: what has been learned from the COPD "mega-trials"? *COPD* 2009;6:1–3.
31. Dowling RB, Johnson M, Cole PJ, Wilson R. Effect of salmeterol on *Haemophilus influenzae* infection of respiratory mucosa *in vitro*. *Eur Respir J* 1998;11:86–90.
32. Dowling RB, Rayner CF, Rutman A, Jackson AD, Kanthakumar K, Dewar A, Taylor GW, Cole PJ, Johnson M, Wilson R. Effect of salmeterol on *Pseudomonas aeruginosa* infection of respiratory mucosa. *Am J Respir Crit Care Med* 1997;155:327–336.
33. Piatti G, Ambrosetti U, Santus P, Allegra L. Effects of salmeterol on cilia and mucus in COPD and pneumonia patients. *Pharmacol Res* 2005; 51:165–168.
34. Ware LB, Koyama T, Zhao Z, Janz DR, Wickersham N, Bernard GR, May AK, Calfee CS, Matthay MA. Biomarkers of lung epithelial injury and inflammation distinguish severe sepsis patients with acute respiratory distress syndrome. *Crit Care* 2013;17:R253.
35. Kushimoto S, Taira Y, Kitazawa Y, Okuchi K, Sakamoto T, Ishikura H, Endo T, Yamanouchi S, Tagami T, Yamaguchi J, *et al*.; The PiCCO Pulmonary Edema Study Group. The clinical usefulness of extravascular lung water and pulmonary vascular permeability index to diagnose and characterize pulmonary edema: a prospective multicenter study on the quantitative differential diagnostic definition for acute lung injury/acute respiratory distress syndrome. *Crit Care* 2012;16:R232.
36. Kushimoto S, Endo T, Yamanouchi S, Sakamoto T, Ishikura H, Kitazawa Y, Taira Y, Okuchi K, Tagami T, Watanabe A, *et al*.; the PiCCO Pulmonary Edema Study Group. Relationship between extravascular lung water and severity categories of acute respiratory distress syndrome by the Berlin definition. *Crit Care* 2013;17:R132.
37. Kor DJ, Warner DO, Alsara A, Fernández-Pérez ER, Malinchoc M, Kashyap R, Li G, Gajic O. Derivation and diagnostic accuracy of the surgical lung injury prediction model. *Anesthesiology* 2011;115:117–128.