Efficacy of Methylprednisolone in Preventing Lung Injury Following Pulmonary Thromboendarterectomy

Kim M. Kerr, MD, FCCP; William R. Auger, MD; James J. Marsh, PhD; Gehan Devendra, MD; Roger G. Spragg, MD; Nick H. Kim, MD; Richard N. Channick, MD, FCCP; Stuart W. Jamieson, MB; Michael M. Madani, MD; Gerard R. Manecke, MD; David M. Roth, MD, PhD; Gordon P. Shragg, MA; and Peter F. Fedullo, MD, FCCP

Background: We sought to determine the efficacy and safety of perioperative treatment with methylprednisolone on the development of lung injury after pulmonary thromboendarterectomy.

Methods: This was a randomized, prospective, double-blind, placebo-controlled study of 98 adult patients with chronic thromboembolic pulmonary hypertension who were undergoing pulmonary thromboendarterectomy at a single institution. The patients received either placebo (n = 47) or methylprednisolone (n = 51) (30 mg/kg in the cardiopulmonary bypass prime, 500 mg IV bolus following the final circulatory arrest, and 250 mg IV bolus 36 h after surgery). The primary end point was the presence of lung injury as determined by two independent, blinded physicians using prospectively defined criteria. The secondary end points included ventilator-free, ICU-free, and hospital-free days and selected levels of cytokines in the blood and in BAL fluid.

Results: The incidence of lung injury was similar in both treatment groups (45% placebo, 41% steroid; $P = .72$). There were no statistical differences in the secondary clinical end points between treatment groups. Treatment with methylprednisolone, compared with placebo, was associated with a statistically significant reduction in plasma IL-6 and IL-8, a significant increase in plasma IL-10, and a significant reduction in postoperative IL-1ra and IL-6, but not IL-8 in BAL fluid obtained 1 day after surgery.

Conclusions: Perioperative methylprednisolone does not reduce the incidence of lung injury following pulmonary thromboendarterectomy surgery despite having an antiinflammatory effect on plasma and lavage cytokine levels.

CHEST 2012; 141(1):27–35

Abbreviations: CPB = cardiopulmonary bypass; mPAP = mean pulmonary artery pressure; NYHA = New York Heart Association; PTE = pulmonary thromboendarterectomy; PVR = pulmonary vascular resistance

Lung injury is a common complication of pulmonary thromboendarterectomy (PTE), typically developing within the first 48 h after surgery and characterized by a high-permeability edema that results in hypoxemia and radiographic opacities in areas of the lung that have been reperfused. Currently, treatment is limited to supportive measures.^{1–3}

High-dose perioperative methylprednisolone has been used for patients undergoing PTE at our institution. This therapeutic intervention was based on the observation that perioperative corticosteroids can reduce complement activation and the release of inflammatory cytokines associated with cardiopulmonary bypass (CPB).^{4–8} However, the clinical benefit

of this intervention is uncertain. Studies assessing the use of corticosteroids in patients who undergo CPB are limited by a small number of patients or an absence of physiologic or clinical correlates.⁹ Furthermore, most studies focus on patients undergoing cardiac bypass grafting with short CPB times and mild hypothermia, which is dissimilar to the prolonged CPB times, total circulatory arrest, and profound hypothermia associated with PTE.

The primary purpose of this study was to determine whether perioperative methylprednisolone would reduce the incidence and/or severity of lung injury following PTE. Secondary end points included clinical outcomes (mortality; ventilator-free, ICU-free,

and hospital-free days; lung injury scores) and biologic end points (selected cytokine levels in both plasma and BAL fluid).

MATERIALS AND METHODS

After University of California, San Diego, Human Subjects Committee approval (Project 011306) and written informed consent were obtained, consecutive adult (>18 years old) patients scheduled for PTE at the University of California, San Diego, were prospectively enrolled between April 2000 and October 2004. Patients were excluded if they had received systemic (oral or IV) corticosteroids, other immunosuppressive drugs, or any investigational drug within the previous 30 days. Other exclusion criteria included a history of previous sternotomy, preexisting neurologic disease (previous stroke, seizure disorder), diabetes (treated with diet or medication), current pregnancy or lactation, current use of epoprostenol, or an additional planned cardiothoracic procedure (eg, coronary artery bypass grafting, valve replacement) to be performed at the time of the PTE. The anesthetic care and surgical procedure have been described elsewhere.^{10,11}

Study Design

This was a randomized, double-blind, placebo-controlled, parallel study of patients undergoing PTE. Computer-based randomization was performed by the investigational pharmacist. The investigators and site personnel (with the exception of the investigational pharmacist) were blinded to the assigned treatment group. Fifty-one patients were randomized to receive corticosteroids, and 50 were randomized to receive placebo. Patients who were treated received 30 mg/kg methylprednisolone (Pfizer Pharmacia Upjohn) IV push bolus delivered in the CPB prime solution, 500 mg methylprednisolone (62.5 mg/mL) IV over 15 min upon rewarming while on CPB following PTE, and 250 mg methylprednisolone diluted in 50 mL 0.9% normal saline IV over 15 min at 36 h following the start of surgery. The control group received a similar volume of normal saline as placebo at the same time points. All study medications were prepared by the investigational pharmacist, who otherwise was not involved in patient care, and were concealed in foil to maintain blinding. All other aspects of care were identical between the two treatment groups.

Manuscript received January 31, 2011; revision accepted June 7, 2011.

Affiliations: From the Division of Pulmonary and Critical Care Medicine (Drs Kerr, Auger, Marsh, Spragg, Kim, and Fedullo), the Division of Cardiothoracic Surgery (Drs Jamieson and Madani), the Department of Anesthesiology (Drs Manecke and Roth), and the General Clinical Research Center (Mr Shragg), University of California, San Diego, CA; Kaiser Permanente (Dr Devendra), Sacramento, CA; and Massachusetts General Hospital (Dr Channick), Boston, MA.

Funding/Support: This study was supported by the National Institutes of Health [Grants NHLBI HL23584 and MO1-RR0827 from the National Center for Research Resources for the University of California, San Diego, General Clinical Research Center].

Correspondence to: Kim M. Kerr, MD, FCCP, Pulmonary and Critical Care Medicine Division, University of California San Diego Medical Center, 9300 Campus Point Dr, M/C 7381, La Jolla, CA 92037; e-mail: kmkerr@ucsd.edu

© 2012 American College of Chest Physicians. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (<http://www.chestpubs.org/site/misc/reprints.xhtml>).

DOI: 10.1378/chest.10-2639

Blood for plasma cytokine samples was drawn from the radial arterial line at the following time points: after induction of anesthesia and prior to incision (T1), 60 min after the final circulatory arrest was completed (T2), 2 h after discontinuation of CPB (T3), and 24 h (T4) and 48 h (T5) following the start of surgery.

Bronchoscopy with BAL was performed immediately before surgery (day 1) and approximately 24 h later (day 2). BAL was performed on a single lung segment at risk for developing acute lung injury. A different endarterectomized segment was lavaged on day 2. In patients who sustained lung injury, segments apparently injured were selected for BAL on day 2. Three 30-mL aliquots of normal saline were instilled sequentially, aspirated with hand suction after each instillation, and then placed immediately on ice. The three specimens were subsequently pooled and processed as described in the "Sample Processing" section.

Arterial blood gas values, $\text{PaO}_2/\text{FiO}_2$, and positive end expiratory pressure were measured every 6 h on days 1 and 2 and then daily until the time of extubation. The tidal volume and average ratio of tidal volume to predicted body weight were recorded daily on days 1 to 3. Chest radiographs were obtained at baseline and daily on days 1 to 3. A single radiologist blinded to the treatment group and clinical condition of each subject scored the chest radiographs for the presence of new pulmonary infiltrates using a scoring system previously described.¹ A lung injury score was calculated using the $\text{PaO}_2/\text{FiO}_2$, positive end expiratory pressure, and chest radiograph (modified from Murray et al¹² and described in e-Appendix 1) on days 1 to 3.

Each patient was evaluated daily on days 1 to 3 by two independent blinded investigators for the presence of lung injury using criteria used in a previous study.¹ Subjects with hypoxemia ($\text{PaO}_2/\text{FiO}_2 < 300$), a new lung infiltrate on chest radiograph in an area that had been reperfused, and no other cause for hypoxemia or other acute chest radiograph abnormality on any individual study day from 1 to 3 were defined as having lung injury. Those not meeting the criteria for lung injury were identified as not having lung injury.

Ventilator-free days, ICU-free days, and hospital-free days were recorded for each subject. Mortality and adverse events for the entire hospitalization period were recorded for each patient.

Sample Processing

Cytokine assays (IL-1ra, IL-6, IL-8, and IL-10) were performed on plasma and BAL samples (40,000 g supernatant) using enzyme-linked immunosorbent assay kits (Quantikine; R&D Systems) according to the manufacturer's instructions. For BAL samples, the cell culture supernatant protocol was followed. The total protein in BAL samples (40,000 g supernatant) was measured as previously described.¹

Data Analysis

The development of lung injury was the primary end point of this study and was used to power the study. Based on our previous research,¹ we expected a 60% incidence of lung injury following PTE in the treated (corticosteroid) group. We hypothesized that 85% of the nontreated (placebo) group would experience lung injury. To test the hypothesis that the proportion of lung injury in the two groups is different, we used a Pearson χ^2 test of association. A minimal sample size of 49 for each group was calculated a priori, with a setting of $\beta = 0.20$ (power = 0.80) and $\alpha = 0.05$, hypothesizing an absolute difference of 25% (85% in the placebo group, 60% in the corticosteroid group) between the two groups.

Secondary end points of interest in this study included the number of ventilator-free, ICU-free, and hospital-free days, lung injury scores, BAL findings, plasma cytokine levels, and hospital

mortality. Data are presented as mean $\pm$ SD unless noted otherwise. Numerical secondary end point differences between the two treatment groups in regard to numerical secondary end points were assessed using a Student independent groups *t* test or a mixed-model analysis of variance when measurements were repeated (eg, plasma cytokines levels). When the within-group factor was significant in the analysis of variance, subsequent post hoc analyses were performed using a Student paired *t* test, using a Bonferroni correction for multiple comparisons. All numerical baseline patient characteristics (presented in Table 1) were analyzed using a Student independent groups *t* test. Categorical variables (eg, sex and New York Heart Association [NYHA] class distributions) were analyzed using a Pearson χ^2 test of association. Patients were categorized primarily by their treatment group, however, for some analyses, we separated patients on the basis of whether they had subsequent lung injury. All patients who received any study drug were included in all of the efficacy and safety analyses.

RESULTS

Patient Characteristics

Four hundred eleven patients were screened for study participation, 170 were eligible, 69 declined to participate, and 101 were enrolled. All patients who received a single dose of study medication were included in the analysis. Three patients were withdrawn from the study after enrollment: two patients because of a change in the surgery schedule and one because of the inadvertent administration of corticosteroids into the CPB prime. These three subjects were excluded from the analysis, leaving a total of 98 evaluable patients (Fig 1).

The baseline characteristics of the two treatment groups were similar (Table 1). Subjects who developed

lung injury demonstrated more severe symptoms, as reflected in the NYHA class distribution, and had more severe pulmonary hypertension than those who did not; patients with lung injury had significantly higher preoperative pulmonary vascular resistance (PVR) and mean pulmonary artery pressure (mPAP). Subjects who developed lung injury also had a significantly higher postoperative PVR and mPAP as well as a greater change in PVR after surgery compared with those without lung injury (Table 1).

Efficacy End Points

There was no statistically significant difference between the treatment groups in the incidence of lung injury (41% in the corticosteroid group and 45% in the placebo group, $P = .727$). The secondary end points (ventilator-free days, ICU-free days, and hospital-free days) were also similar between the treatment groups (Table 2). The severity of hypoxemia as assessed by the $\text{PaO}_2/\text{FIO}_2$ was similar in both treatment groups on each study day (Table 3). The total lung injury score as well as the individual components of the lung injury scores were not statistically different (Table 4).

Safety Analysis

Adverse events were similar in both treatment groups. Specific categories of adverse events and the number of each reported adverse event are detailed in Table 5. More patients in the steroid group required exogenous insulin in the first 3 study days

Table 1—Patient Characteristics

Characteristic	Patient Groups					
	Corticosteroid (n = 51)	Placebo (n = 47)	P Value	No Injury (n = 56)	Injury (n = 42)	P Value
Sex, male (female)	23 (28)	22 (25)	NS	28 (28)	17 (25)	NS
Mean age, y	51 $\pm$ 13	47 $\pm$ 14	NS	48 $\pm$ 14	53 $\pm$ 13	NS
Preoperative NYHA class distribution, No. (%)			NS			.035
NYHA class I	0 (0)	0 (0)		0 (0)	0 (0)	
NYHA class II	7 (13.7)	7 (14.9)		12 (21.4)	2 (4.8)	
NYHA class III	40 (78.4)	40 (85.1)		43 (76.8)	37 (88)	
NYHA class IV	4 (7.8)	0 (0)		1 (1.8)	3 (7.1)	
Preoperative PVR, dyne/s/cm ⁵	918 $\pm$ 493	813 $\pm$ 387	NS	727 $\pm$ 342 (n = 55)	1,052 $\pm$ 502	.001
Postoperative PVR, dyne/s/cm ⁵	304 $\pm$ 247	284 $\pm$ 143	NS	235 $\pm$ 106 (n = 55)	371 $\pm$ 267	.003
Change in PVR (preoperative-postoperative), dyne/s/cm ⁵	614 $\pm$ 355	516 $\pm$ 355	NS	480 $\pm$ 319 (n = 54)	681 $\pm$ 374	.006
Preoperative mPAP, mm Hg	44 $\pm$ 11	44 $\pm$ 10	NS	41 $\pm$ 9 (n = 55)	47 $\pm$ 11	.003
Postoperative mPAP, mm Hg	28 $\pm$ 10	28 $\pm$ 8	NS	26 $\pm$ 7	31 $\pm$ 11	.013
Change in mPAP (preoperative-postoperative), mm Hg	16 $\pm$ 12	16 $\pm$ 11	NS	16 $\pm$ 10 (n = 55)	17 $\pm$ 13	NS
Pulmonary artery obstruction, %	55% (n = 50)	50% (n = 46)	.066	52% (n = 55)	53% (n = 41)	NS
Duration of CPB, min	217 $\pm$ 47	220 $\pm$ 38	NS	218 $\pm$ 48	219 $\pm$ 38	NS
Total circulatory arrest time, min	35 $\pm$ 13	36 $\pm$ 10	NS	35 $\pm$ 11	36 $\pm$ 12	NS
Tidal volume/predicted body weight, mL/kg ^a	12 $\pm$ 2	12 $\pm$ 2	NS	12 $\pm$ 2	12 $\pm$ 2	NS

Data are presented as mean $\pm$ SD unless noted otherwise. CPB = cardiopulmonary bypass; mPAP = mean pulmonary artery pressure NS = not significant; NYHA = New York Heart Association; PVR = pulmonary vascular resistance.

^aAveraged over study days 1 to 4 or until extubation, if prior to day 4.

FIGURE 1. Chart shows the flow of the study. PTE = pulmonary thromboendarterectomy.

(27 vs six, $P < .01$). There were two deaths in the corticosteroid group (anoxic brain injury, persistent pulmonary hypertension) and three deaths in the placebo group (persistent pulmonary hypertension, lung injury, lung injury with sepsis).

Biologic Markers

Corticosteroid vs Placebo: Twenty-four hours after surgery, levels of IL-1ra and IL-6 were markedly lower in the steroid group compared with the placebo group, but the IL-8 levels were not significantly different. (Fig 2) The percentage of polymorphonuclear leukocytes in BAL cells was significantly less in patients treated with corticosteroids. There were no significant differences in BAL protein levels or cellularity between the patient groups treated with corticosteroids or placebo (Table 6).

Dramatic increases in plasma IL-1ra, IL-6, IL-8, and IL-10 were observed in both groups during the perioperative period, in particular 2 h after discontinuation of CPB. Significantly lower levels of IL-6 and IL-8 were observed in the corticosteroid group compared with the placebo group from 2 h after discontinuation of CPB to 48 h after surgery. Higher levels of IL-10 were observed in the corticosteroid group compared with the placebo group at 60 min after circulatory arrest, 2 h after discontinuation of CPB, and 48 h after surgery. IL-1ra levels were similar in both treatment groups (Fig 3).

Injury vs No Injury: Twenty-four hours after surgery there was a trend toward higher levels of BAL IL-1ra, IL-6, and IL-8 in patients who developed lung injury compared with those who did not, although the differences did not reach statistical

Table 2—Primary and Secondary End Points

Characteristic	Patient Groups		P Value
	Corticosteroid (n = 51)	Placebo (n = 47)	
Patients with lung injury, No. (%)	21 (41.2)	21 (44.7)	NS
Ventilator-free days	23.1 ± 7.0	22.3 ± 7.2	NS
ICU-free days	21.6 ± 6.8	20.5 ± 7.4	NS
Hospital-free days	15.8 ± 6.4	14.6 ± 6.8	NS
Mortality, No. (%)	2 (3.9)	3 (6.4)	NS

Data are presented as mean ± SD unless noted otherwise.

Table 3— P_{aO_2}/F_{iO_2} Distribution of Mechanically Ventilated Patients

Day	Patient Groups	P_{aO_2}/F_{iO_2}		
		< 200	200-299	≥ 300
Day 1	Corticosteroid (n = 51)	49.0	31.4	19.6
	Placebo (n = 47)	55.3	21.3	23.4
Day 2	Corticosteroid (n = 50)	38.0	44.0	18.0
	Placebo (n = 47)	48.9	40.4	18.0
Day 3	Corticosteroid (n = 17)	58.8	23.5	17.6
	Placebo (n = 20)	70	30	0

Data given as percentage for subjects in each treatment group on mechanical ventilation. Spontaneously breathing subjects not included.

Table 4—Lung Injury Scores

Score	Patient Group		P Value
	Corticosteroid	Placebo	
Chest radiograph score			
Day 1	0.60 ± 0.67 (n = 50)	0.53 ± 0.65 (n = 47)	NS
Day 2	0.98 ± 0.52 (n = 50)	0.94 ± 0.60 (n = 47)	NS
Day 3	1.06 ± 0.93 (n = 16)	0.80 ± 0.52 (n = 20)	NS
Day 4	1.13 ± 0.641 (n = 8)	1.00 ± 0.00 (n = 14)	NS
Hypoxemia score			
Day 1	1.86 ± 1.28 (n = 51)	1.77 ± 1.27 (n = 47)	NS
Day 2	1.59 ± 1.17 (n = 51)	2.00 ± 1.16 (n = 47)	NS
Day 3	2.06 ± 1.34 (n = 17)	2.60 ± 1.05 (n = 20)	NS
Day 4	3.00 ± 1.12 (n = 9)	2.93 ± 0.70 (n = 15)	NS
PEEP score			
Day 1	0.43 ± 0.67 (n = 51)	0.45 ± 0.92 (n = 47)	NS
Day 2	0.54 ± 0.86 (n = 51)	0.62 ± 0.99 (n = 47)	NS
Day 3	0.82 ± 1.23 (n = 17)	1.00 ± 1.08 (n = 20)	NS
Day 4	1.44 ± 1.42 (n = 9)	0.93 ± 1.10 (n = 15)	NS
Total lung injury score			
Day 1	0.98 ± 0.70 (n = 51)	0.91 ± 0.68 (n = 47)	NS
Day 2	1.04 ± 0.72 (n = 51)	1.18 ± 0.71 (n = 47)	NS
Day 3	1.34 ± 0.95 (n = 17)	1.47 ± 0.62 (n = 20)	NS
Day 4	1.91 ± 0.94 (n = 9)	1.64 ± 0.56 (n = 15)	NS

Values are mean of entire treatment group. See e-Appendix 1 for score calculation. PEEP = positive end expiratory pressure. See Table 1 legend for expansion of other abbreviation.

significance (Fig 4). There were no significant differences in BAL protein levels, cellularity, or the percentage of polymorphonuclear cells between patient groups that developed lung injury and those that did not (Table 6). Seven patients (four from the corticosteroid group, three from the placebo group) were too hypoxemic to safely undergo bronchoscopy on day 2.

Large increases in plasma IL-1ra, IL-6, IL-8, and IL-10 were observed in both groups during the perioperative period, in particular 2 h after discontinuation of CPB. The levels of IL-1ra did not differ between groups. There was a trend toward higher levels of IL-6, IL-8, and IL-10 in patients who developed lung injury compared with those who did not (Fig 5).

Table 5—Adverse Events

Event	Patient Groups		P Value
	Corticosteroid (n = 51)	Placebo (n = 47)	
Neurologic	15 events	13 events	...
	15 subjects	11 subjects	.82
Bleeding	4 events	8 events	...
	4 subjects	6 subjects	.57
Pleuropericarditis	4 events	4 events	...
	4 subjects	4 subjects	.90
Infection	13 events	16 events	...
	9 subjects	11 subjects	.51
Exogenous insulin	27 subjects	6 subjects	<.01
Mortality	2	3	.59

DISCUSSION

In this prospective, randomized, controlled clinical trial, we found that methylprednisolone did not prevent lung injury following PTE. Furthermore, there was no significant difference in secondary end points and adverse events between treatment groups, suggesting that methylprednisolone does not affect the severity of lung injury or the development of other postoperative complications.

PTE is a potentially lifesaving procedure for patients with chronic thromboembolic pulmonary hypertension. However, the perioperative mortality is relatively high, with reperfusion lung injury reported to occur in 60% of patients undergoing the procedure, contributing to prolonged mechanical ventilation, prolonged ICU stay, and mortality.^{1,2,13,14} CPB is known to be associated with an undesirable systemic inflammatory response that likely contributes to the development of postoperative complications, including respiratory failure, bleeding disorders, and renal, hepatic, and neurologic dysfunction. Corticosteroids have been used in patients undergoing cardiac surgery with CPB to reduce the systemic inflammatory response syndrome induced by CPB, despite the fact that few well-controlled studies exist to support their use.¹⁵ Their use is based on limited studies suggesting that corticosteroids may mitigate the inflammatory response associated with CPB through the reduction of complement activation and the release of inflammatory cytokines,^{5,6,8} and an increase in IL-10⁸ and antiinflammatory cytokines.

FIGURE 2. BAL cytokine levels in patients treated with methylprednisolone (gray bars) or placebo (white bars). Time points represented are before surgery (1) and 24 h after surgery (2). Median values are shown. Error bars represent the 25th and 75th percentiles. * $P < 0.05$ compared with placebo.

Our plasma cytokine findings are similar to those of others. We demonstrated a rise in IL-1ra, IL-6, IL-8, and IL-10 after surgery, most pronounced at 2 h after the discontinuation of CPB. Langer et al¹⁶ also measured IL-6 and IL-10 in 14 patients who underwent a PTE, and they found a similar peak of IL-6 and IL-10 levels immediately following surgery, with a return toward baseline at 24 h. Similar to other studies, we found that methylprednisolone did reduce the rise in the proinflammatory cytokines IL-6 and IL-8 and increased the rise in the antiinflammatory cytokine IL-10. However, as in other studies,^{4,5,7,17} no significant clinical benefit was associated with the administration of methylprednisolone in PTE surgery. Blunting the rise in proinflammatory cytokines IL-6 and IL-8 and increasing the levels of antiinflammatory cytokine IL-10 with methylprednisolone does not appear sufficient to prevent acute lung injury following PTE. It is likely that numerous other inflammatory events such as complement activation, leukocyte activation, the expression of adhesion molecules, and the production of oxygen free radicals, arachadonic acid metabolites, nitric oxide,

platelet-activating factor, and endothelins contribute to the inflammatory response to surgery and CPB¹⁸ as well as to the development of acute lung injury following PTE.

An unexpected finding was the lack of difference in postoperative BAL results between patients with and without lung injury. Previous studies have demonstrated lung injury following PTE to be a high-permeability edema associated with an influx of neutrophils and protein into the alveolar fluid.¹ Our lack of statistical difference may be due to sampling error; seven patients with lung injury were unable to undergo postoperative bronchoscopy because of the severity of their hypoxemia. Hence, the sickest of the patients with lung injury were not included in the postoperative BAL analysis.

Another notable finding of this study is the statistical association between the severity of preoperative pulmonary hypertension (preoperative NYHA class, preoperative mPAP and PVR) and the degree of residual postoperative pulmonary hypertension (postoperative mPAP and PVR) with the development of postoperative lung injury, suggesting that

Table 6—BAL

Results	Patient Groups					
	Steroid (n = 50)	Placebo (n = 46)	P Value, t Test	No Injury (n = 53)	Injury (n = 43)	P Value, t Test
Preoperative protein, $\mu\text{g/mL}$	59.8 $\pm$ 50.6 (n = 47)	51.4 $\pm$ 28.3 (n = 45)	NS	56.6 $\pm$ 49.2 (n = 52)	54.6 $\pm$ 28.2 (n = 40)	NS
Postoperative protein, $\mu\text{g/mL}$	148.8 $\pm$ 168.7 (n = 42)	165.5 $\pm$ 296.0 (n = 41)	NS	111.3 $\pm$ 89.7 (n = 49)	223.0 $\pm$ 349.8 (n = 34)	.077
Preoperative WBC, 10^5 cells/mL	1.03 $\pm$ 0.80 (n = 49)	0.95 $\pm$ 0.89 (n = 46)	NS	1.04 $\pm$ 1.02 (n = 52)	0.92 $\pm$ 0.57 (n = 43)	NS
Postoperative WBC, 10^5 cells/mL	2.10 $\pm$ 3.06 (n = 43)	1.58 $\pm$ 1.46 (n = 42)	NS	2.06 $\pm$ 2.95 (n = 49)	1.54 $\pm$ 1.31 (n = 36)	NS
Preoperative % PMN	7.88 $\pm$ 14.60 (n = 50)	5.54 $\pm$ 6.87 (n = 44)	NS	8.34 $\pm$ 14.3 (n = 52)	4.86 $\pm$ 6.68 (n = 42)	NS
Postoperative % PMN	12.57 $\pm$ 18.48 (n = 44)	22.34 $\pm$ 22.8 (n = 41)	.03	14.82 $\pm$ 19.59 (n = 49)	20.63 $\pm$ 22.91 (n = 36)	NS

Data are presented as mean $\pm$ SD unless noted otherwise. PMN = polymorphonuclear leukocyte. See Table 1 legend for expansion of the other abbreviation.

FIGURE 3. Plasma cytokine levels in patients treated with methylprednisolone (gray bars) or placebo (white bars). Time points represented are before surgery (1), 60 min after circulatory arrest (2), 2 h after discontinuation of cardiopulmonary bypass (CPB) (3), 24 h after surgery (4), and 48 h after surgery (5). Median values are shown. Error bars represent the 25th and 75th percentiles. * $P < 0.05$ compared with placebo.

hemodynamic and/or mechanical factors may play a role in the development of lung injury following PTE.

Although we did not see a difference in adverse events associated with corticosteroid treatment, significantly more patients who were randomized to the corticosteroid group required exogenous insulin therapy compared with the placebo group. Hyperglycemia in patients who underwent CPB and were treated with steroids has been noted in other trials.¹⁷ Additional detrimental effects of corticosteroids have been noted by others, including increased blood loss, increased requirements for postoperative ventila-

tion, and larger alveolar-arterial oxygen gradients.^{19,20} With the exception of higher insulin requirements, we did not observe any detrimental effects of steroid treatment in the population.

This study has several limitations. While postoperative care was provided by a small group of intensivists and surgeons with similar practice patterns and extensive experience with this population, postoperative treatment was not tightly controlled. In particular, there were no strict guidelines for extubation, transfer from the ICU, or hospital discharge, which could have affected the number of ventilator-free,

FIGURE 4. BAL cytokine levels in patients who developed lung injury (gray bars) or had no lung injury (white bars). Time points represented are before surgery (1) and 24 h after surgery (2). Median values are shown. Error bars represent the 25th and 75th percentiles.

FIGURE 5. Plasma cytokine levels in patients who developed lung injury (gray bars) or had no lung injury (white bars). Time points represented are before surgery (1), 60 min after circulatory arrest (2), 2 h after discontinuation of CPB (3), 24 h after surgery (4), and 48 h after surgery (5). Median values are shown. Error bars represent the 25th and 75th percentiles. * $P < 0.05$ compared with no injury. See Figure 3 legend for expansion of the abbreviation.

ICU-free, and hospital-free days. In addition, the sample size was estimated assuming an 85% incidence of lung injury in the placebo group and a 60% incidence of lung injury in the treatment group. However, the actual incidence of lung injury in both groups was significantly lower than predicted, resulting in a decrease in the power of the study. Because of the sample size, it is possible that a small but clinically important difference in the primary outcome may have been missed. Last, steroid therapy was started at the time of initiation of CPB. Perhaps initiating steroid therapy earlier would have a different effect on the development of lung injury.

The central conclusion of this study is that the administration of perioperative methylprednisolone does not reduce the incidence of lung injury for patients undergoing PTE. Methylprednisolone does mitigate the rise in proinflammatory cytokines IL-6 and IL-8 and enhances the rise in the antiinflammatory cytokine IL-10, but has no effect on the development of lung injury or the severity of lung injury as assessed by ventilator-free, ICU-free, and hospital-free days. The role of preoperative and postoperative pulmonary hemodynamic variables in the develop-

ment of postoperative lung injury requires further evaluation.

ACKNOWLEDGMENTS

Author contributions: *Dr Kerr:* contributed to the study conception and design; the acquisition, analysis, and interpretation of data; and the drafting, review, and final approval of the manuscript.

Dr Auger: contributed to the study conception and design; the acquisition of data; and the drafting, review, and final approval of the manuscript.

Dr Marsh: contributed the study design, the acquisition of data, the analysis and interpretation of data, and the review and final approval of the manuscript.

Dr Devendra: contributed to the study conception and design, the acquisition of data, and the review and final approval of the manuscript.

Dr Spragg: contributed to the study conception and design, the analysis and interpretation of data, and the review and final approval of the manuscript.

Dr Kim: contributed to the acquisition of data, and the review and final approval of the manuscript.

Dr Channick: contributed to the study conception and design, the acquisition of data, and the review and final approval of the manuscript.

Dr Jamieson: contributed to the study conception and design and the review and final approval of the manuscript.

Dr Madani: contributed to the acquisition of data and the review and final approval of the manuscript.

Dr Manecke: contributed to the acquisition of data and the review and final approval of the manuscript.

Dr Roth: contributed to the study conception and design, the acquisition of data, and the review and final approval of the manuscript.

Mr Shragg: contributed to the analysis and interpretation of data and the review and final approval of the manuscript.

Dr Fedullo: contributed to the study conception and design, the acquisition of data, and the review and final approval of the manuscript.

Financial/nonfinancial disclosures: The authors have reported to CHEST the following conflict of interest: Dr Spragg served as a consultant to Nycomed GmbH. Drs Kerr, Auger, Marsh, Devendra, Kim, Channick, Jamieson, Madani, Manecke, Roth, and Fedullo and Mr Shragg have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or in the preparation of the manuscript.

Other contributions: This study was conducted at the University of California, San Diego. The authors thank Barbara Munden, RN, and Laura Gabel, AS, for their assistance with specimen and data collection; Kathy Harris for specimen processing; Linda Olson, MD, for scoring of chest radiographs; and Andrew Ries, MD, and Joel Dimsdale, MD, for serving on the Data Safety Monitoring Board.

Additional information: The e-Appendix can be found in the Online Supplement at <http://chestjournal.chestpubs.org/content/141/1/27/suppl/DC1>.

REFERENCES

1. Kerr KM, Auger WR, Marsh JJ, et al. The use of cylexin (CY-1503) in prevention of reperfusion lung injury in patients undergoing pulmonary thromboendarterectomy. *Am J Respir Crit Care Med*. 2000;162(1):14-20.
2. Adams A, Fedullo PF. Postoperative management of the patient undergoing pulmonary endarterectomy. *Semin Thorac Cardiovasc Surg*. 2006;18(3):250-256.
3. Levinson RM, Shure D, Moser KM. Reperfusion pulmonary edema after pulmonary artery thromboendarterectomy. *Am Rev Respir Dis*. 1986;134(6):1241-1245.
4. Jorens PG, De Jongh R, De Backer W, et al. Interleukin-8 production in patients undergoing cardiopulmonary bypass. The influence of pretreatment with methylprednisolone. *Am Rev Respir Dis*. 1993;148(4 pt 1):890-895.
5. Hill GE, Alonso A, Spurzem JR, Stammers AH, Robbins RA. Aprotinin and methylprednisolone equally blunt cardiopulmonary bypass-induced inflammation in humans. *J Thorac Cardiovasc Surg*. 1995;110(6):1658-1662.
6. Engelman RM, Rousou JA, Flack JE III, Deaton DW, Kalfin R, Das DK. Influence of steroids on complement and cytokine

generation after cardiopulmonary bypass. *Ann Thorac Surg*. 1995;60(3):801-804.

7. Tassani P, Richter JA, Barankay A, et al. Does high-dose methylprednisolone in aprotinin-treated patients attenuate the systemic inflammatory response during coronary artery bypass grafting procedures? *J Cardiothorac Vasc Anesth*. 1999;13(2):165-172.
8. Celik JB, Gormus N, Okesli S, Gormus ZI, Solak H. Methylprednisolone prevents inflammatory reaction occurring during cardiopulmonary bypass: Effects on TNF- α , IL-6, IL-8, IL-10. *Perfusion*. 2004;19(3):185-191.
9. Whitlock RP, Chan S, Devereaux PJ, et al. Clinical benefit of steroid use in patients undergoing cardiopulmonary bypass: A meta-analysis of randomized trials. *Eur Heart J*. 2008;29(21):2592-2600.
10. Manecke GR Jr. Anesthesia for pulmonary endarterectomy. *Semin Thorac Cardiovasc Surg*. 2006;18(3):236-242.
11. Thistlethwaite PA, Kaneko K, Madani MM, Jamieson SW. Technique and outcomes of pulmonary endarterectomy surgery. *Ann Thorac Cardiovasc Surg*. 2008;14(5):274-282.
12. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis*. 1988;138(3):720-723.
13. Auger WR, Kim NH, Kerr KM, Test VJ, Fedullo PF. Chronic thromboembolic pulmonary hypertension. *Clin Chest Med*. 2007;28(1):255-269.
14. Jamieson SW, Kapelanski DP, Sakakibara N, et al. Pulmonary endarterectomy: Experience and lessons learned in 1,500 cases. *Ann Thorac Surg*. 2003;76(5):1457-1462.
15. Chaney MA. Corticosteroids and cardiopulmonary bypass: a review of clinical investigations. *Chest*. 2002;121(3):921-931.
16. Langer F, Schramm R, Bauer M, Tscholl D, Kuniyara T, Schäfers HJ. Cytokine response to pulmonary thromboendarterectomy. *Chest*. 2004;126(1):135-141.
17. Liakopoulos OJ, Schmitt JD, Kazmaier S, et al. Cardiopulmonary and systemic effects of methylprednisolone in patients undergoing cardiac surgery. *Ann Thorac Surg*. 2007;84(1):110-118.
18. Warren OJ, Smith AJ, Alexiou C, et al. The inflammatory response to cardiopulmonary bypass: part 1—mechanisms of pathogenesis. *J Cardiothorac Vasc Anesth*. 2009;23(2):223-231.
19. Coffin LH, Shinozaki T, DeMeules JE, Browdie DA, Deane RSD, Morgan JG. Ineffectiveness of methylprednisolone in the treatment of pulmonary dysfunction after cardiopulmonary bypass. *Am J Surg*. 1975;130(5):555-559.
20. Chaney MA, Nikolov MP, Blakeman B, Bakhos M, Slogoff S. Pulmonary effects of methylprednisolone in patients undergoing coronary artery bypass grafting and early tracheal extubation. *Anesth Analg*. 1998;87(1):27-33.