Intraoperative Solumedrol Helps Prevent Postpneumonectomy Pulmonary Edema

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Background. **Postpneumonectomy pulmonary edema and pneumonia are life threatening and seemingly unavoidable complications after pneumonectomy. We theorized that an intraoperative dose of intravenous steroids (as a prophylactic measure to reduce pulmonary injury to the remaining lung) just before pulmonary artery ligation might decrease this problem.**

Methods. **Seventy-two patients (52 men) who had pneumonectomy during two time periods were studied prospectively. Thirty-five patients received 250 mg of methylprednisolone sodium succinate (Solumedrol; Upjohn, Kalamazoo, MI) just before pulmonary artery ligation (S group) and 37 did not (non-S group). Groups were matched for known or suspected preoperative, intraoperative, and postoperative risk factors for postpneumonectomy pulmonary edema.**

Results. **The incidence of postpneumonectomy pulmonary edema or adult respiratory distress syndrome was less in the S group (0 of 35, 0% versus 5 of 37, 13.5%, $p = 0.049$), the overall major complication rate was less in the S group (7 of 35, 20% versus 16 of 37, 43%, $p = 0.04$), and the length of hospital stay was shorter in the S group (6.1 days versus 11.9 days, $p = 0.02$). In addition, there were no bronchopleural fistulas in the S group compared with two (both right-sided) in the non-S group.**

Conclusions. **The intraoperative intravenous administration of 250 mg of methylprednisolone sodium succinate just before pulmonary artery ligation during pneumonectomy may reduce the incidence of postpneumonectomy pulmonary edema and adult respiratory distress syndrome as well as decrease other major complications and shorten the hospital stay. It does not seem to increase the incidence of bronchopleural fistula. Further randomized trials are needed.**

(Ann Thorac Surg 2003;76:1029–35)

One of the most devastating problems after pneumonectomy is postpneumonectomy pulmonary edema (PPE), first described by Gibbon in 1942 [1, 2]. Most reports quote the incidence of PPE after pneumonectomy to be about 5% [3–7]. Several theories for the cause of PPE have been reported; they include excessive preoperative, intraoperative, and postoperative fluids; lymphatic injury secondary to thoracic lymphadenectomy; volotrauma and barotrauma to the lung from positive pressure ventilation; right ventricular dysfunction; or circulating vasoactive mediators [7–12]. However, the precise mechanism has never been fully delineated, and hence prevention is difficult. At times it seems to occur despite careful preoperative, intraoperative, and postoperative management. Most disturbing, however, is that when PPE develops the mortality rate ranges from 80% to 100% [7]. Recently Mathisen and colleagues [13] described the use of nitrous oxide to help treat PPE, but few studies have evaluated ways to prevent it. Because we believed that PPE was probably some type of pulmonary, capillary, endothelial damage, we theorized that a 250-mg dose of steroids given just before pulmonary artery ligation might help prevent this devastating clinical problem.

Patients and Methods

This study was planned as a safety trial with prospective collection of data. Our initial goal was to show that the intraoperative use of a suprapharmacologic dose of methylprednisolone sodium succinate (Solumedrol, Upjohn, Kalamazoo, MI) was safe and was not associated with complications, with a potential subsequent prospective randomized trial. Between September 1996 and November 30, 1999, a single general thoracic surgeon in an academic institution performed 37 consecutive pneumonectomies. These patients had standard operative procedures and did not receive intraoperative steroids. Between December 1, 1999 and October 31, 2002 the same surgeon, in the same setting, with the same anesthesiologists performed 35 consecutive pneumonectomies. All patients in the second group received 250 mg of methylprednisolone sodium succinate (Solumedrol) intraoperatively 5 minutes before ligating the pulmonary artery. This dose was chosen based on our previous clinical

Presented at the Thirty-ninth Annual Meeting of The Society of Thoracic Surgeons, San Diego, CA, Jan 31–Feb 2, 2002.

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Published by Elsevier Inc

0003-4975/03/$30.00
PII S0003-4975(03)00879-8

experience. Sleeve lobectomy or standard lobectomy was attempted first, if appropriate, in all patients. Because it was not known whether patients required a pneumonectomy to obtain a complete resection with negative frozen section margins until operative exploration, the steroid dose was not given until just before pulmonary artery clamping. Both groups had standard preoperative evaluations, including pulmonary function testing, ventilation perfusion scans, preoperative stress test, echocardiogram, and standard staging studies if malignancy was suspected or confirmed preoperatively. Preoperatively all patients received an epidural, identical preoperative antibiotics, limited amounts of intravenous fluids, posterior-lateral thoracotomy, and attempts at lobectomy or sleeve resection of the bronchus, artery, or both. Intraoperative fluids were limited in both groups of patients, and the same type of anesthetic agents and the same anesthesiologists were used. If pneumonectomy was performed for cancer, patients in both groups had a complete thoracic lymphadenectomy.

All patients were extubated in the operating room and went to the intensive care unit where they received 0.6 mL/kg per hour of D5LR. Identical computerized order sets for both groups of patients were used to help guide the postoperative management. All patients received the same type and dose of intravenous calcium-channel blockers immediately postoperatively to help decrease the incidence of arrhythmias. Patients received similar postoperative treatment, which included early physical therapy, the removal of the chest tube (that was placed to water seal only) on postoperative day 1, transfer to the floor on postoperative day 1, advancement of diet with the discontinuation of intravenous fluids when oral intake was 600 mL or greater without nausea, the weaning of oxygen, similar pain management, and strict aspiration precautions. All patients had a standing posterior-anterior and lateral chest roentgenogram in the radiology department each day.

The institutional review board at the University of Alabama at Birmingham approved this study. Baseline characteristics of patients were compared using Pearson χ^2, Fisher's exact test, Student's t test, or Wilcoxin two-sample test, where appropriate. Summary statistics for continuous variables were recorded as means and standard deviations and analyzed using a Student's t test; categorical data were summarized as frequencies and percentages, and comparisons between the two treatment groups were performed with the Pearson χ^2 test or Fischer's exact test. Analysis of the treatment effect of Solumedrol in the prevention of PPE and adult respiratory distress syndrome was performed also using Fischer's exact test. All analyses were conducted according to the intention-to-treat principle unless otherwise stated, and all p values are two sided. A p value of 0.05 or less was considered to represent a statistically significant difference between two groups unlikely to be due to chance. Data entry was performed using ACCESS (Microsoft, Redmond, WA), and the analysis was done using SAS software version 8.02 (SAS Institute, Cary, NC).

Definitions

Because PPE can be at times difficult to distinguish from pneumonia, pulmonary edema, congestive heart failure, pulmonary emboli, aspiration, or a small bronchopleural fistula with aspiration, strict definitions were used for respiratory complications. PPE and adult respiratory distress syndrome are often defined synonymously; therefore, we labeled an event as PPE (the same as adult respiratory distress syndrome, defined as PPE in this paper) if there was no evidence to support the other diagnoses. In addition, patients were required to have profound hypoxia with a minimum fraction of inspired oxygen requirement of at least 0.8, a positive end-expiratory pressure of at least 7.5 mm Hg, and a maximum arterial oxygen tension of 65 mm Hg. Patients with acute respiratory compromise were reintubated, transferred to the surgical intensive care unit, and underwent bronchoscopy, broncholaveolar lavage, echocardiography, and helical chest computed tomography when they were hemodynamically stable. The diagnosis of a bronchopleural fistula was eliminated by bronchoscopy and in selected patients by replacement of a chest tube in the pneumonectomized space with or without the use of Xenon ventilation scans. The diagnosis of pneumonia was eliminated by the lack of at least two of the following: a positive sputum culture, an elevated white blood cell count, or a new segmental or lobar infiltrate. The diagnosis of pulmonary emboli was eliminated by the presence of normal-appearing pulmonary arteries and their branches on helical chest tomography. The diagnosis of cardiogenic pulmonary edema was eliminated by the use of transsternal echocardiography and in selected patients transesophageal echocardiography. Cardiac isoenzymes and serial electrocardiograms eliminated the diagnosis of myocardial infarction. Any patient who had profound hypoxia and did not have the above diagnoses was considered to have PPE. All efforts and diagnostic tests were used to try to rule out other possible causes of hypoxia.

Results

There were 72 patients in this trial. The demographics and possible risks of PPE for both groups of patients are shown in Table 1. Table 1 attempts to delineate all known or suspected preoperative risks for PPE. Table 2 shows a similar analysis for known or suspected intraoperative and postoperative risk factors. As shown, there was no statistically significant difference between these two groups for any of these previously identified or suspected variables. Table 3 shows the results for the two groups. We found a statistically significant advantage favoring the group that received intraoperative steroids for the incidence of PPE or adult respiratory distress syndrome, overall complications (not including arrhythmias), and for length of stay. Table 4 outlines the fate of the 5 patients who had PPE, and Table 5 describes the circumstances surrounding the deaths of the 5 operative mortalities.

Comment

The key to any postoperative complication is prevention. Unfortunately, PPE seems not only to be difficult to prevent, but once it develops it is difficult to treat. Even when one carefully follows the many techniques purported to prevent it, it still develops in approximately 5% of patients, as in our untreated group. Once PPE develops it is often fatal, in some reports up to 100% of the time. For these reasons prevention of this particular postoperative complication is paramount. Because PPE can be indistinguishable from postoperative adult respiratory distress syndrome, noncardiogenic pulmonary edema, or sometimes even pneumonia, we wanted to ensure that we were not missing it or any subtle form of PPE. Therefore, we used a relatively broad definition of PPE for this analysis.

We found two relatively well-matched groups for the previously identified variables that may be causative factors for PPE. We then found a statistically significant different incidence of PPE and in pneumonia in the group

Table 1. Potential Preoperative Risk Factors for the Development of Complications After Pneumonectomy

	S Group (n = 35)	Non-S Group (n = 37)	*p* Value
Age (y)	54.9 ± 11.7	55.6 ± 10.9	0.801
Gender			
Male	(26) 74%	(26) 70%	0.795
Female	(9) 26%	(11) 30%	
Race			
White	(28) 80.0%	(31) 83.8%	
Black	(5) 14.3%	(4) 10.8%	0.803
Other	(2) 4.7%	(2) 5.4%	
Pulmonary function test			
FEV_1 (%)	71.0 ± 18.3	74.1 ± 23.3	0.604
MVV (%)	63.0 ± 26.4	71.3 ± 25.6	0.284
DLCO (%)	66.2 ± 19.1	75.4 ± 23.5	0.133
Blood flow to removed lung (%)	21.0 ± 14	33.0 ± 17	0.086
POP FEV_1 (%)	29.9 ± 16.6	42.8 ± 28.1	0.113
POP DLCO (%)	30.7 ± 19.7	43.0 ± 26.8	0.154
Hx CAD[a]	(2) 5.7%	(4) 10.8%	0.675
History of smoking	(27) 79%	(26) 72%	0.737
History of arrhythmia	(3) 8.6%	(3) 8.1%	0.987
History of chemotherapy or radiation	(5) 14.3%	(2) 5.4%	0.424
Patent foramen ovale	0	0	—
Echocardiographic data (in mean)	50%	55%	0.853
RVEF	52%	50%	0.922
LVEF	1/3	1/3	0.947
MV regurg	1/3	1/3	0.956
TV regurg	0/3	0/3	0.937
PV regurg	0/3	0/3	0.958
AV regurg	0/3	0/3	0.923

[a] CAD defined as a history of a previous MI, and/or a history of a coronary artery stent or a coronary artery bypass graft operation.

Data are given as mean ± standard deviation, n (%), or as specified.

AV = atrioventricular; CAD = coronary artery disease; DLCO = diffusion of the lung carbon monoxide; FEV_1 = forced expiratory volume in 1 second; LVEF = left ventricular ejection fraction; MV = mitral valve; MVV = maximal voluntary ventilation; POP = postoperative predictive; PV = pulmonary valve; regurg = regurgitation; RVEF = right ventricular ejection fraction; TV = tricuspid valve.

Table 2. Potential Intraoperative Risk Factors for the Development of Complications After Pneumonectomy

	S Group (n = 35)	Non-S Group (n = 37)	*p* Value
Weight (kg) ± SD	71.7 ± 16.5	81.0 ± 21.5	0.313
Perioperative fluids (mL)			
Hetastarch	440	425	0.885
Normal saline	1157	1163	0.984
D5W	275	208	0.482
Estimated blood loss (mL)	421	339	0.457
Urinary output (mL)	185	170	0.854
Number of patients transfused with PRBC	(7) 20%	(6) 16%	0.817
Total anesthesia time	3:25	2:59	0.614
	(26) 74% cancer	(30) 81% cancer	
Indication for pneumonectomy	(9) 26% destroyed lung[a]	(7) 9% destroyed lung[a]	0.573
Type of pneumonectomy			
Standard	80%	81.1%	
Completion	14.3%	8.1%	0.692
Cuff atrium	5.7%	10.8%	
HCT, middle operation	35.8% ± 7.4	36.3% ± 1.7	0.906
HGB, middle operation	11.9% ± 2.5	12.2% ± 0.6	0.834
Lung removed			
Right	(22) 63%	(25) 68%	0.638
Left	(13) 37%	(12) 32%	
Postop fluids (mL/kg/hour)	0.6 mL	0.65 mL	0.924
Postoperative blood transfusions	(6) 17%	(7) 19%	0.835
Urinary output, mean per postoperative day	420 mL	460 cmc	0.675
Mean serum creatinine (mg/dL)	1.7	2.0	0.754
Tumor stage			
I	2.9%	8.1%	
II	17.1%	18.9%	
IIIa	40%	37.8%	0.514
IIIb	5.7%[b]	8.1%[b]	
IV	5.7%[c]	2.7%[c]	
Lasix given on postoperative day 3	(32) 92%	(33) 89%	0.986
Mean days in SICU	1.0	1.0	0.935

[a] Destroyed lung was defined by a persistently positive cultures for a fungus from the lung despite adequate medical treatment for 6 months with a ventilation perfusion scanning showing less than 15% blood flow to the affected side and chest tomography identifying severely scarred pulmonary parenchyma. [b] T4 tumors involving a cuff of atrium. [c] Metasectomy.

HCT = hematocrit; HGB = hemoglobin; PRBC = packed red blood cells; SD = standard deviation; SICU = surgical intensive care unit.

Table 3. Postoperative Results

	S Group N = 35	Non-S Group N = 37	*p* Value
PPE/ARDS	(0) 0%	(5) 13.5%	**0.049**
Pneumonia	(1) 2.8%	(4) 10.8%	0.354
Overall complications	(11) 31.3%	(17) 46%	0.237
Overall complications excluding arrhythmia	(7) 20%	(16) 43.2%	**0.040**
Mortality	(1) 2.8%	(4) 10.8%	0.354
Bronchopleural fistulas	(0) 0%	(2 pt. both right sided) 5.4%	0.496
Mean length of hospital stay, days	6.1 days	11.9 days	**0.020**

ARDS = pulmonary adult respiratory edema distress syndrome; PPE = postpneumonectomy; S = solumedrol.

Table 5. Causes of Death In All Six Operative Mortalities

Patient	Group	Death on POD	Cause of Death
1	Non-S	6	Pneumonia, MOS failure, made DNR
2	Non-S	15	PPE/ARDS
3	Non-S	39	Discharged on POD #5, returned POD #29 with pneumonia, had an MI, MOS failure
4	Non-S	14	Discharged on POD #5, home working in garage sudden death, no autopsy
5	S	7	Had pneumonectomy, destroyed lung, developed DIC, MOS failure, made DNR

DIC = disseminated intravascular coagulopathy; DNR = do not resuscitate; MOS = multi-organ system; Non-S = non-solumedrol group; POD = postoperative day; S = solumedrol.

that received intraoperative steroids. The obvious flaw to this study is that is not randomized, and the two groups were operated on over two different periods of time. There could be some unknown difference between the two groups that we failed to recognize, and the first group was done earlier so we were less experienced. Despite this very important criticism, we consider the results of this study important. We believe that a phase III prospective, randomized, multi-institutional trial is indicated with a larger number of patients to corroborate or disprove this study's finding.

Elsewhere it has been suggested that attaching the chest tubes to underwater seal after pneumonectomy could be harmful [14]. The cause of the lung injury is theorized to be acute hyperinflation of the remaining lung aggravated by the active removal of air from the pneumonectomized space. In an interesting study on puppies, Ramenofsky [14] demonstrated that all animals that had a chest tube placed on water seal after pneumonectomy developed PPE. This variable has also been found to be a risk factor in humans, as shown by Deslauriers and associates [7]. In our series, however, all patients had a chest tube placed the day of operation and it was attached to water seal until the next morning. It was then removed on postoperative day 1. This did not seem to lead to PPE in our patients.

Table 4. Outcomes of Patients with PPE/ARDS

Patient	Group	Outcome
1	Non-S	Treated nitrous oxide, developed PPE on POD 3, survived, left hosp POD #30
2	Non-S	Treated nitrous oxide, developed PPE on POD 3, died POD #15 respiratory failure
3	Non-S	Treated nitrous oxide, developed PPE on POD 2, developed pneumonia, discharged POD 11
4	Non-S	Treated nitrous oxide, developed PPE on POD 2, discharged POD #71
5	Non-S	Treated nitrous oxide, developed PPE on POD 3, discharged POD #29

ARDS = pulmonary adult respiratory edema distress syndrome; POD = postoperative day; PPE = post-pneumonectomy pulmonary edema.

If this study's findings are true, the mechanism of action of how methylprednisolone sodium succinate (Solumedrol) helps prevent PPE needs to be elucidated. This is especially true because the cause of the increased vascular permeability that is a hallmark of PPE has never been definitively outlined. However, there are good data that capillary stretching [15] and injury to the spaces between endothelial cells may be an early event in PPE. Steroids are known to help stabilize cellular membranes as well as help prevent the propagation of cellular injury and the subsequent cascade of mediators that follows. The preemptive administration of methylprednisolone may help slow or even arrest the flow of some of these mediators that lead to PPE.

In conclusion, the intraoperative administration of 250 mg of methylprednisolone sodium succinate (Solumedrol, UpJohn, Kalamazoo, MI) 5 minutes before the ligation of the pulmonary artery at the time of pneumonectomy seems to reduce the incidence of postpneumonectomy pulmonary edema or adult respiratory distress syndrome. It may also decrease major complications, including operative mortality rate and hospital stay. A prospective randomized trial is warranted to corroborate or disprove this study's results.

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DISCUSSION

DR KEITH S. NAUNHEIM (St. Louis, MO): I congratulate Dr Cerfolio on his excellent personal results with a 5.5% operative mortality rate for pneumonectomy over a 6-year interval in this trial. The manuscript is interesting and bound to raise questions and incite controversy for some time to come. I do, however, have some questions and criticisms regarding the manuscript. Most important is the characterization of this trial as a prospective comparison of a treatment variable. In fact, it is more like a phase I safety trial utilizing perioperative Solumedrol.

Doctor Cerfolio and colleagues have indeed demonstrated that administering a single perioperative dose of Solumedrol is a relatively safe maneuver. The complications one might anticipate, including stump fistula and an increased incidence of pneumonia, did not occur. This certainly seems to set the stage for a subsequent prospective randomized trial but is far less than definitive evidence for several reasons.

First, although the Solumedrol group may well have been a prospective cohort, the non-Solumedrol group is in fact a retrospective or historical control. While these two cohorts were matched with regard to age, gender, and other demographic or perioperative variables, the pitfalls of historical controls are well documented and include varying personnel, changing institutional resources, evolving technology and, perhaps most importantly, the operator's learning curve regarding patient selection, operative technique, and postoperative care. This learning curve phenomenon applies to everyone involved in the care of such patients and can lead to significant differences in outcome not attributable to treatment variables alone.

Second, I have some difficulty with the certainty of diagnosis of postpneumonectomy pulmonary edema in this study. In the definition section, the authors state that PPE is the "acute respiratory compromise" characterized by "profound hypoxia" and the elimination, as best as possible, of competing diagnoses of pneumonia, stump breakdown, infarction, congestive failure, and pulmonary embolus. Yet nowhere is there a quantitative definition of hypoxia. Is it an oxygen tension less than 60 mm Hg? A saturation of less than 90%? A ratio of oxygen tension to fraction of inspired oxygen less than .6? Any future study will have to quantify such definitions.

Also, there was no mention of pulmonary infiltrates seen on chest x-ray. This is a finding most practitioners would think essential for the diagnosis of PPE, and yet one cannot tell whether it was identified in any patient.

Other issues of concern regarding the accuracy of diagnosis are the incidence and outcome of PPE. In this series, PPE occurred in 5 of 37 patients in the non-Solumedrol group, thus yielding an incidence of 14% for this disorder, a frequency which one must consider surprisingly high. Even more remarkable is the mortality rate after PPE, which was 1 in 5, or 20% in this series, an unbelievably low rate virtually unequaled in the literature at this time.

One must wonder whether the diagnosis of PPE or adult respiratory distress syndrome was correct in each instance, and the lack of a quantitative definition may have contributed to this. These issues call into question any conclusion regarding efficacy within this trial. They also highlight the critical importance of establishing firm, quantitative, and consistent criteria for the diagnosis of PPE should a future study be undertaken as suggested by the authors. Such a trial should also require the diagnosis of PPE to be made by blinded investigators, a methodologic maneuver not utilized in this current study. Finally, I would like to pose a few questions to Dr Cerfolio.

Number one, in light of these current results, how should we define PPE for future studies? What combination of radiographic, hemodynamic, and oxygenation parameters should be required for the diagnosis?

Number two, how did you choose a single dose of 250 mg of methylprednisolone as the treatment? Should this be the dosage in subsequent trials?

And number three, in your experience over 20% of the pneumonectomies performed were for the indication of destroyed lung. This incidence seems rather high, and it really was undefined in the manuscript. Could you better characterize what the diagnoses were in these cases of destroyed lung and whether these patients had ongoing low-grade infections at the time of operation? I wonder if you believe such patients should be included in a subsequent trial with perioperative steroid administration?

Once again, I would like to thank the Society for the privilege of discussing the manuscript and would also like to congratulate

Doctor Cerfolio and their colleagues on a stimulating and provocative paper.

DR JOSEPH B. SHRAGER (Philadelphia, PA): I would like to congratulate Dr Cerfolio on a potentially important paper. My specific question is, how many sleeve resections were done during this same period of time? The basis for that question is that, obviously, the best way to avoid the complications of a pneumonectomy is not to do a pneumonectomy. I do not believe, although I am not sure, that the author would like to give the impression that a pneumonectomy with Solumedrol is safer than a sleeve resection.

DR DOUGLAS E. WOOD (Seattle, WA): This is a great study and a well-documented background on the patients and the results. I have a couple of questions, one of which relates to the preoperative factors. One thing I did not see is the incidence of preoperative treatment with chemotherapy or radiation that may be an important risk factor as well, and then the intraoperative factor of the extent of lymphadenectomy, which is another risk factor or potential etiology of PPE. Do you have that data regarding these differences between those two groups?

And lastly, do you think that the complication rate and the PPE rate are potentially surrogates for each other in your outcomes between the two groups?

DR TIMOTHY M. ANDERSON (Buffalo, NY): I enjoyed your paper. I noticed that you managed to get patients through the early postoperative period, but I am concerned about the long-term effects of giving steroids. We know from the Japanese literature that tumor cells are seeding through the pulmonary veins at the time of operation. Presumably, these cells are undergoing surveillance and interactions with the immune system during their transit. We also know that cancer patients who receive blood transfusions in the perioperative period are at increased risk for reduced survival, thought secondary to tolerance or some manipulation of the immune system. By giving steroids just before resecting cancer you may be altering the immune system's ability to handle systemic metastases during a critical time interval. So I wonder how you view the steroid effect in the long term?

DR DUANE S. BIETZ (Portland, OR): Some years ago when anesthesiologists were interested in the fast track, doses of steroids were given to hasten early extubation. We noticed a decrease in atrial fibrillation. We have had some programs in which our incidence of atrial fibrillation after coronary artery bypass grafting has been as low as 5% to 6%. I noticed you had a difference in arrhythmias. How much of that was atrial fibrillation? What are our observations for future use of steroids for prophylaxis atrial fibrillation?

DR MARK K. FERGUSON (Chicago, IL): I enjoyed the paper very much. I am interested if you could comment on your method of managing the postpneumonectomy space? It has been described by Jean Deslauriers that reducing overexpansion of the remaining lung may eliminate volotrauma and thus eliminate the problem of PPE.

DR CERFOLIO: Those are all great questions, and I want to thank everyone for coming to the microphone. We could probably talk about this for hours but unfortunately we do not have the time. So I will try to be succinct.

First, I want to thank Dr Naunheim very much for not only being kind enough to review my first poor manuscript but for allowing me to rewrite it after his initial comments and make it better. That is the way this system can work best. However, after listening to his comments this morning it obviously needs more work.

To answer his first question about the design, we really had planned to study 35 or 36 patients in the first group and double that in the second. When we finished doing about 35 patients in the second group we decided to take a look at our statistics now and see how we are doing, because I knew we had no PPEs since we started using steroids. When we found it was statistically significant, we decided that although the numbers were small and it is not a perfect study, we thought it was too important to sit on these data. We decided to write the abstract and submit it. Yes, it is a safety study, and we clearly stated that. We wanted to discuss this issue at the next meeting and see what everybody thinks about a multi-institutional trial. It would have been better if we had waited 5 or 6 years to do a prospective randomized trial, but it takes so long to do a large number of pneumonectomies that it would have been years away, and that takes me to Dr Shrager's question.

The answer to your question Dr Shrager is that we have done 19 sleeve resections during this time period. We are always trying to do a sleeve of either the bronchus or the pulmonary artery or both. We, like everybody else, are always trying to avoid a pneumonectomy, especially a right-sided pneumonectomy, which I think is a very high-risk procedure, but in people with N1 disease and in people who have had neoadjuvant treatment, I think that can be difficult to do.

I will now try to answer the rest of Dr Naunheim's questions. How should we define PPE in future studies? Well, although we did not have it in the manuscript, we can add it. We did look at radiologic data, and we looked at patients who had the classic pulmonary infiltrates, fluffy infiltrates, who had negative results of at least one bronchoalveolar lavage. Hemodynamically, these were patients who were stable, had negative blood cultures, and had no evidence of sepsis. The diagnosis was not just mine but that of the intensive care unit attendings, and the radiologist; and they were all classic PPE. I am very confident that the diagnosis was correct in all patients.

And your third question was oxygen parameters. That is a very good point. We would have to go back and retrospectively look at that. We did not collect that prospectively. I always worry about retrospectively collected data, because I truly believe it is less accurate then prospectively collected data, but the oxygen is probably all in the charts and we could go back and get arterial gradients, but they were enormous. These are patients on 100% oxygen, with positive end-expiratory pressure of 15 mm Hg, and with arterial oxygen tension around 50 and 60 mm Hg.

Your second question was, how did I choose a dose of 250 mg of Solumedrol? To be honest we just made it up. I have nothing else to really say about it—there are other reports out there that we read and I spoke with other surgeons—but essentially based on how it comes from the pharmacy, I just made it up and guessed.

Your third question is about the 20% of patients who had pneumonectomies that were performed for destroyed lung. You wanted me to characterize them just briefly. They were all the kind of cases all of us dread: the ones where you have to carve the lung out of then pleural space and where taking the vessels intrapericardially is the easy part of the case. They are in general for tuberculosis; either they have had previous operations and a resection and now they have no functional lung left that has no blood flow left but is seeding the other good lung. The chest has no recognizable structures. They have all had long-term antibiotics for at least 6 months, most a year. Those are the majority of those patients.

The reason we have such a low mortality rate for PPE is because this study is in the era of nitric oxide. We very quickly used nitric oxide in these patients, sometimes even within minutes after the Swan-Ganz catheter went in under fluoroscopic guidance and determined high pulmonary artery pressures. I believe it was the nitric oxide that led to such a low mortality rate.

Doctor Wood's questions are excellent. In terms of radiation and chemotherapy, that is discussed in the report but for time's sake it was eliminated from this morning's presentation. There was no statistically significant difference between the two groups. One would expect there would be more radiation and

chemotherapy in the second cohort, and there was, but it was not significant. In terms of lymph node dissection, all patients who have cancer get a complete thoracic lymphadenectomy. That is how I was trained, and that is how I practice. The number of patients who had cancers were similar in the two groups so the two groups had similar thoracic lymphadenectomies.

You then asked about the complications and the statistics. If we threw out the complications, the length of stay was still statistically significant, which was surprising to me but according to the statistician is true.

The next question was from Dr Anderson about the long-term effects of steroids on survival. I cannot answer that. I have no data as to whether the survivability or the presence of local or systemic recurrence is higher in the patients who received the steroids versus those who did not. It is an interesting and provocative question. However, I think that one shot of 250 mg of Solumedrol would make little to no difference because it was a one-time dose, but we could go back and look at that since we did not think of that.

The next question is from Dr Bietz concerning atrial fibrillation. I intentionally left out this fact, in this presentation, but he was too astute and inferred it from other data I presented. There indeed were fewer arrhythmias in the Solumedrol patients. I was afraid it would open up a whole can of worms. It is interesting to find that you have had a similar observation. However, we did see less incidence of atrial fibrillation, but I did not want to start answering questions that maybe every patient who undergoes coronary artery bypass grafting should get intraoperative steroids to help prevent that problem because I do not have data not do I have a pathophysiological mechanism to explain it, if true. Further prospective studies in are needed and they would be very easy to do.

And the final question is, how did we handle the pleural space? Dr Ferguson, you are correct, and I have read Dr Deslauriers' studies and have much repsect for his expertise in the problem of PPE. His chapter in the Surgical Clinic of North America covers that issue of volotrauma and so does our journal article. However, I do place a chest tube after most every pneumonectomy, and I like to leave it in for about 24 hours to monitor bleeding. I place them to water seal overnight. We did not put them to suction. I am not sure if it makes a difference, but we no longer use the balance drainage system because it confused the nursing staff and led to too many questions. Then it seems that every week or two we have a whole new set of nurses. We now use a regular drainage system and tape a sign on it that covers up the suction attachment and says "no suction." To be honest I do not think suction is really that harmful, but that is what we did for this trial and still do. The tubes were removed the next day except in 1 or 2 patients, and we found that that this process did not seem to be an independent variable of the incidence of PPE at all.