Ventilation-Perfusion Inequalities in a Patient With Obliterative Bronchiolitis After Single-Lung Transplantation for Primary Pulmonary Hypertension

To the Editor:

The assessment of graft rejection after single-lung transplantation (SLT) is often difficult. Therefore, it was with great interest that we read the article by Levine et al., which appeared in the February 1992 issue of Chest. The authors described their experience with ventilation-perfusion (V/Q) inequalities during graft rejection after SLT for primary pulmonary hypertension (PPH). We recently had a similar experience.

A 49-year-old white woman with a history of PPH underwent right SLT in June 1991. Immunosuppression therapy consisted of cyclosporine, azathioprine, and corticosteroids. During the first 2 months after transplantation she was given four courses of methylprednisolone for rejection suspected on clinical grounds. Patient and donor were both seropositive for cytomegalovirus (CMV). Four weeks after transplantation, CMV reactivation was observed; the virus was isolated from bronchoalveolar lavage fluid and pleural fluid. Transbronchial biopsies showed some infiltration of plasma cells in the submucosa of the walls of the bronchioles, but there were no signs of acute vascular rejection, bacterial infection, or CMV infection. The patient was treated by lowering the dosage of azathioprine, and subsequently anti-CMV immunoglobulin G was seen to be increased. She made a full clinical recovery from this episode.

Approximately 5 months after SLT, the patient began complaining of slowly progressive dyspnea on exertion and a low-grade fever. Spirometric values were unchanged, and the cardiologic status was normal. Although there was no clear diagnosis, the patient was treated with pulse corticosteroids for suspected rejection, but without effect. There was progression of her dyspnea, and the spirometric values deteriorated, suggesting increasing airflow limitation (Fig 1). A histologic diagnosis could not be established. Again she was treated with pulse corticosteroids, together with anti-CMV hyperimmune globulin, but without improvement. Nine months after SLT, a V/Q scan showed a decline in ventilation of the transplanted lung, while the perfusion did not change as a percentage of total (Fig 1). Open-lung biopsy revealed obliterative bronchiolitis without evidence of acute rejection. Treatment with rabbit antithymocyte globulin had no clinical effect. Repeat V/Q scans showed a further decline in ventilation of the transplanted lung leading to further V/Q mismatch.

As in the patients presented by Levine et al, this case of small airway disease due to obliterative bronchiolitis after SLT for PPH showed progressive V/Q mismatching on repeated V/Q scans. However, concurrent spirometry showed a progressive decline in vital capacity with concomitant progressive bronchoconstriction. Although experience with obliterative bronchiolitis in this setting is still limited, we feel that repeated spirometry is a good method for routinely following the function of the transplanted lung in these patients and that repeated V/Q scanning does not provide extra information in such situations.

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REFERENCE

Elevation of Cardiac Output and Oxygen Delivery Improves Outcome in Septic Shock

To the Editor:

It was with great interest that I read the article by Tuchschmidt et al., which appeared in the July 1992 issue of Chest. There were however, a couple of errors in the abstract that confuse their message. In both cases, a careful reading of the text reveals what I hope is the truth. In lines 21 and 22, it should read that 72 percent of the normal treatment (NT) patients died versus 50 percent of the optimal treatment (OT) patients. These numbers were switched, which makes their optimal treatment sound like a killer. In line 29, the oxygen delivery (DO₂) of the NT <4.5 group is shown as 10.9 ml/min/kg, which is even higher than the original group's DO₂. The authors' point was that they were excluding those spontaneously hyperdynamic patients; the correct DO₂ should be 7.2±0.7 ml/min/kg. Since abstracts are so widely read, I thought this clarification important.

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REFERENCE

To the Editor:

We would like to comment on the use of the statistical information in the article by Tuchschmidt et al., which appeared in the July 1992 issue of Chest.

Under "Methods," the authors state that "statistical significance is reported at a p<0.05," the usual level for statistical significance. Under "Results," they state that "in the NT patients, mortality rate was 72 percent and 50 percent in the OT patients (p=0.14)"—that
is, the two groups are not statistically different, even though the authors do not state that fact in that sentence.

Under "Discussion," the authors say that "a 28 percent reduction in hospital mortality was observed when CI [cardiac index] was titrated to 6 L/min/m²"—the latter being the definition of the OT group. This statement is misleading; since the two groups are not different, there is no demonstrable reduction in mortality.

In the next paragraph, they continue: "The lack of statistical significance in the overall mortality rates probably reflects the spontaneously higher CIs . . ." We would like to offer a much simpler explanation for the lack of statistical significance: lack of statistical power, which we estimated at 60 percent. The usually accepted level of statistical power is 80 percent, in order to achieve it, we calculate that the authors would have needed a sample size of 95 total patients, provided that all other factors, including the mortality rates in the two groups, remain equal.

Since there was no statistically significant difference between the mortality rates in the two groups, and since this comparison did not achieve sufficient statistical power, the authors cannot make any statement with regard to survival and mortality in the two groups.

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REFERENCES

To the Editor:

In the July 1992 issue of Chest, Dr. Tuchschmidt and colleagues present a provocative article showing a therapeutic benefit of augmenting cardiac output and oxygen delivery in patients with septic shock.

In the "Results" section, the authors contrast the difference in outcome between the NT and OT groups. Twice as many patients in the OT group received dobutamine at 2.6 times larger dosages to achieve the predetermined therapeutic endpoint of 6 L/min/m².

Mortality rate correlated strongly with postresuscitation oxygen delivery (r = 0.94, p = 0.016) in all patients. However, when analyzed by "intention to treat," there was no statistically significant difference in survival between the two groups (p = 0.14). Most likely the lack of statistical significance is related to a small sample size (ie, type II error), rather than the inability to achieve the desired endpoint in a portion of the patients in the OT group, as the authors postulate. Furthermore, their subset analysis is misleading by comparing patients in the OT group with a CI greater than 4.5 L/min/m² (ie, responders) to the patients in the NT group with a CI less than 4.5 L/min/m². Although a significant difference in mortality was observed, this subgroup analysis does not represent a look at the data according to treatment received. A comparison of all patients who achieved a CI greater than 4.5 L/min/m² (n = 25) with those with a CI less than 4.5 L/min/m² (n = 20) would have been more helpful to address the question of therapeutic impact on survival. However, even using this approach, there appears to be no statistically significant difference in survival—again, likely due to a small sample size.

I regret that the investigators discontinued the study prematurely based on a trend favoring the OT group and the "wrong" subgroup analysis. Further randomized, prospective, and preferably multi-center studies are needed before we routinely flog the hearts of our patients and call this "optimal treatment."

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REFERENCES

To the Editor:

We appreciate the letters in response to our article. The letter by Dr. Bredle is quite correct. The abstract erroneously transposed mortality data for the NT and OT groups. Clearly, this was our oversight.

The letters by Drs. Petrinka and Norman and by Dr. Schuller refer to the same issue. They correctly point out that the difference in mortality between the NT and OT groups fails to reach statistical significance primarily because of the small sample size. A power analysis of our data by intention to treat suggests that the difference in mortality, were it to remain unchanged, would become significant if twice as many patients were in each group. Our study was prospective, randomized, and controlled but could not have been blinded, for obvious reasons. As we discussed, the study was stopped to avoid the potential for bias and because subset analysis of our data suggested a benefit to optimizing CI.

From the inception of this study, we realized that some hyperdynamic patients with high cardiac outputs would be randomized to the NT group and that a few patients in the OT group would not raise their CI in response to therapy. These outliers thus end up having achieved CI values much closer to those of the treatment group opposite to the one to which they were randomized. Thus, we performed our subset analysis in order to compare two groups of patients who met our treatment goals. We believe moving the NT group outliers to the OT group and the OT group outliers to the NT group would have been statistically inappropriate. Interestingly, patients randomized to the NT group who achieved a CI greater than 4.5 mL/min/m² on their own had a mortality rate (50 percent) very similar to that in those patients in the OT group whose cardiac output was improved through therapeutic intervention (40 percent).

Finally, we agree with Dr. Schuller's comment that a multicenter, randomized, prospective, and controlled trial is warranted. A number of studies suggest that there is a benefit to raising CI in patients with septic shock to greater than normal values, but all these studies have limitations, and we suspect that a multicenter study would too.

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Communications to the Editor