Reperfusion Edema after Lung Transplantation: Radiographic Manifestations[1]

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Abbreviations:
A-a = alveolar-arterial
DLT = double-lung transplant
FIO_2 = fraction of inspired oxygen
PO_2 = partial pressure of oxygen
SLT = single-lung transplant

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PURPOSE: To characterize the radiographic manifestations of reperfusion edema after lung transplantation and to correlate the severity of the radiographic findings with pulmonary physiology.

MATERIALS AND METHODS: Chest radiographs obtained after 45 lung transplantation procedures (20 single, 25 double) were reviewed retrospectively. Physiologic parameters (alveolar-arterial gradient, ratio of partial pressure of oxygen to fraction of inspired oxygen) were noted in patients who underwent intubation.

RESULTS: Reperfusion edema appeared on day 1 in 39 transplants and by day 3 in 44. One patient's lungs remained clear. Peak severity occurred by day 4 in 43 of 44 transplants. At peak severity, reperfusion edema appeared as reticular interstitial disease in the upper (19%), middle (33%), and lower (34%) lung zones or air-space disease in the upper (31%), middle (61%), and lower (57%) zones. Reperfusion edema was asymmetric after double-lung transplantation in nine patients. The process cleared by day 10 in five transplants and by day 21 in another seven. There was a poor correlation between the severity of radiographic findings and physiologic measurements.

CONCLUSION: Reperfusion edema is almost invariable after lung transplantation and most often appears as air-space disease in the middle and/or lower lung zones. The severity of radiographic findings is a poor indicator of pulmonary physiology.

After lung transplantation, patients are prone to a number of specific complications, including reperfusion edema, acute rejection, and opportunistic infection associated with immunosuppression, as well as all of the usual complications seen in patients undergoing thoracotomy. Reperfusion edema is a form of noncardiogenic pulmonary edema associated with all types of lung transplantation, including autotransplantation. This entity has been summarized as "the morphologic, roentgenographic and functional changes that occur in a lung transplant in the early postoperative period as a result of surgical trauma, ischemia, denervation, lymphatic interruption and other injurious processes (exclusive of rejection) that are unavoidable aspects of transplant operation" (1).

It is important to differentiate reperfusion edema from the other complications of lung transplantation, as the latter require specific therapy but reperfusion edema does not. The purpose of this study was to characterize the radiographic patterns of reperfusion edema, including how it evolves and clears, and to determine if there is any correlation between the severity of this process on radiographs and the physiologic status of the patient.

MATERIALS AND METHODS

The results of 50 consecutive lung transplantation procedures in 49 patients were reviewed. Twenty-one patients received a single-lung transplant (SLT); 28 received a double-lung transplant (DLT). One patient received a right SLT initially and a left SLT 1 year later. The transplantation procedures were performed between December 1987 and June 1992. The patients were aged 17–63 years (mean, 40.6 years); 23 were male and 26 were female. Pulmonary allografts were harvested and preserved according to established criteria (2,3). The preservation solution most commonly used was modified Euro-Collins solution; the allografts were immersed in this solution at 4°C for transport.

The patient charts for the 1st month after transplantation were reviewed by one of the authors (S.K.) to exclude complications that mimic reperfusion edema (eg, fluid overload, mucous plugging, pneumonia, acute rejection). The fluid balance, wedge pressure, blood pressure, oximetric and bronchoscopic results, temperature, microbiologic features of sputum, and physicians' progress notes were reviewed to determine if a complication was present and the dates on which it occurred. Patients with a complication that was present continually during the first 4 postoperative days were excluded from the analysis. Five patients were excluded: Four had persistent fluid overload and/or a wedge pressure above 15 mm Hg, and one had missing data.

A study population of 44 patients remained: 23 female and 21 male patients aged 17–63 years (mean, 40.8 years). Twenty of these patients received SLTs, and 25 received DLTs. The underlying lung diseases were cystic fibrosis ($n = 12$), idiopathic pulmonary fibrosis ($n = 8$), primary pulmonary hypertension ($n = 6$ [one of these patients received two SLTs]), α_1-antitrypsin deficiency ($n = 6$), emphysema ($n = 6$), and miscellaneous conditions ($n = 6$).

The plain chest radiographs of each patient were reviewed in a blinded fashion by one of the authors (S.J.H.) without knowledge of any clinical information, including the patient's physiologic status. These readings were performed in multiple sessions with each patient's radiographs assessed together. Although the reader had been involved in the care of these patients, their names were not revealed to him and the retrospective readings took place 2–5 years after the surgery. All radiographs from the first 2 postoperative days were reviewed, as were daily radiographs from days 2–7 and radiographs obtained every other day during days 9–21. In general, the radiographic protocol was as follows: During the 1st week, bedside radiographs were obtained with the patient supine (first 3 or 4 days) or upright. During weeks 2 and 3, upright posteroanterior and lateral radiographs were obtained. On each radiograph, the presence and location (upper, middle, or lower lung) of pulmonary parenchymal reticular interstitial or air-space disease were noted. In DLT recipients, these features were noted for each lung; in SLT recipients, only the transplanted lung was investigated (it was always clear from the radiograph alone which lung had been transplanted).

Radiographs obtained during the occurrence of a known complication were excluded from the analysis. The diagnosis of rejection was based on the results of the clinician's evaluation (which included such criteria as new-onset tachypnea, hypoxemia, characteristic radiographic changes, and lymphocytosis) and commonly on the results of transbronchial biopsy or bronchoalveolar lavage, in the absence of clinical evidence of infection or pulmonary edema. Characteristically, the diagnosis of rejection was supported by improvement in the clinical and radiographic abnormalities 24–48 hours after intravenous administration of corticosteroids. Pneumonia was considered present on clinical grounds based on the physician's assessment, which usually included fever, microorganisms in sputum or bronchoalveolar lavage specimens, and focal radiographic changes of consolidation. Radiographs obtained after diagnosis of pneumonia were excluded from the analysis. Mucous plugging was diagnosed with bronchoscopy and resolved after therapeutic bronchoscopy. Pneumothorax was diagnosed in the usual fashion; radiographs that showed a large pneumothorax or pleural effusion were excluded from the analysis.

Diagnosis of fluid overload (pulmonary edema) was particularly difficult. Fluid overload was defined as a positive fluid balance above 1 L during the preceding 24 hours or a wedge pressure above 15 mm Hg that persisted until 24 hours after a diuretic response. Lung transplant recipients are generally considered to have fluid depletion after transplantation and are given large amounts of fluid in the early postoperative period. Therefore, any positive fluid balance that occurred within the first 24 hours after transplantation was excluded from the analysis.

Overall, there were 17 episodes of fluid overload, 28 of acute rejection, seven of pneumonia, and four of mucous plugging; no episodes of a large pneumothorax or pleural effusion occurred. Radiographs obtained when any of these complications were present were not analyzed, and any changes seen on these radiographs were therefore excluded. Although 16 radiographs were obtained in each patient, after these exclusions an average of only 13.7 radiographs were analyzed.

TABLE 1
Radiographic Findings in Lungs at First Appearance of Reperfusion Edema

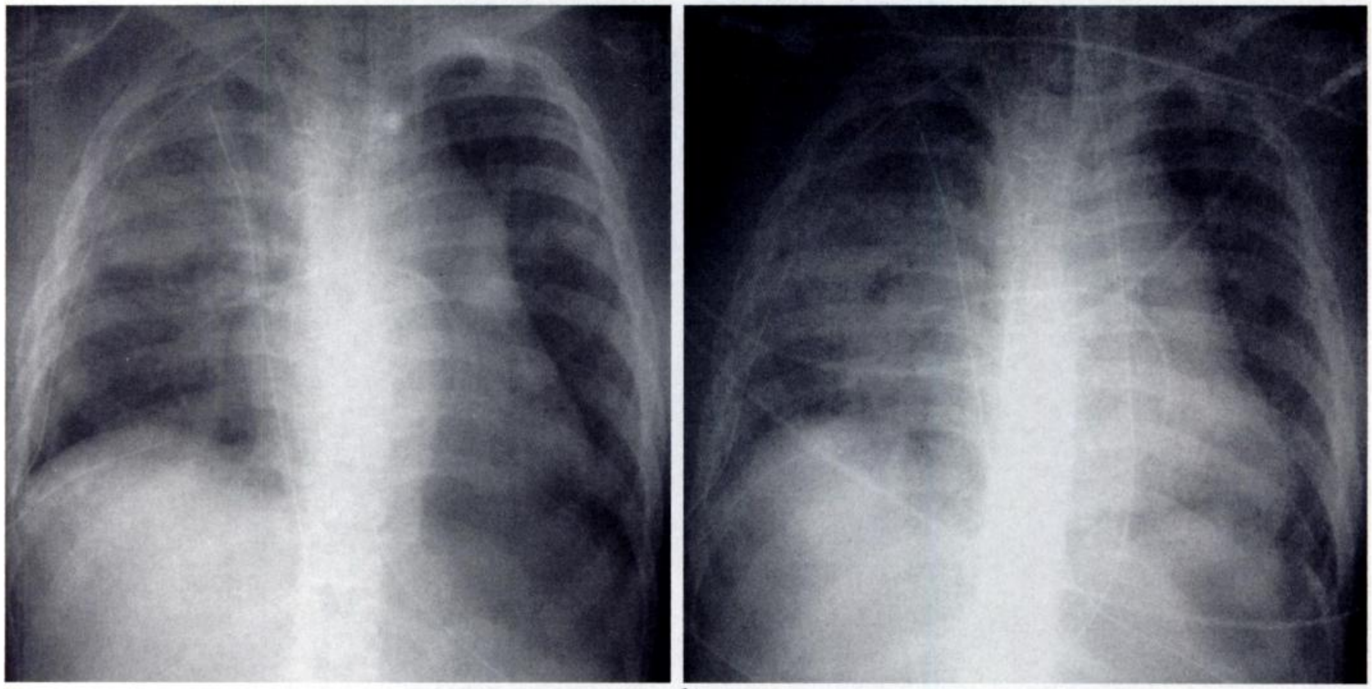
Lung Zone	Interstitial Disease (%)	Air-Space Disease (%)
Upper	19	26
Middle	43	44
Lower	53	39

TABLE 2
Radiographic Findings in Lungs at Peak Severity of Reperfusion Edema

Lung Zone	Interstitial Disease (%)	Air-Space Disease (%)
Upper	19	31
Middle	33	61
Lower	34	57

The radiographic patterns, including worsening or resolution and disease locations and radiographic features, were recorded at two times: when an abnormality first appeared and when it was most severe. We also noted when the lungs began to clear and when they returned to a normal appearance. At the time of peak severity, a radiographic severity score was assigned to each patient. In each lung zone, a score of 3 was assigned to air-space disease and a score of 1 was assigned to interstitial disease. Therefore, the maximal score was 9 for an SLT recipient and 18 for a DLT recipient.

To determine the physiologic status of each lung transplant, the fraction of inspired oxygen (F_{IO_2}), partial pressure of oxygen (P_{O_2}), and partial pressure of carbon dioxide were noted. These values were noted only in patients who underwent intubation (10 SLT and 14 DLT recipients) to be certain that the F_{IO_2} was accurate. The values were obtained and recorded many times each day. We selected measurements obtained as close to the time of reference radiography as possible, usually within 1 hour and always within 3 hours. From these data, the alveolar-arterial (A-a) gradient and P_{O_2}/F_{IO_2} ratio were calculated. These are accepted methods of determining the functional status of transplanted lungs. The radiographic score was compared with the A-a gradient and P_{O_2}/F_{IO_2} ratio by using the Kendall τ test. This comparison was performed separately for



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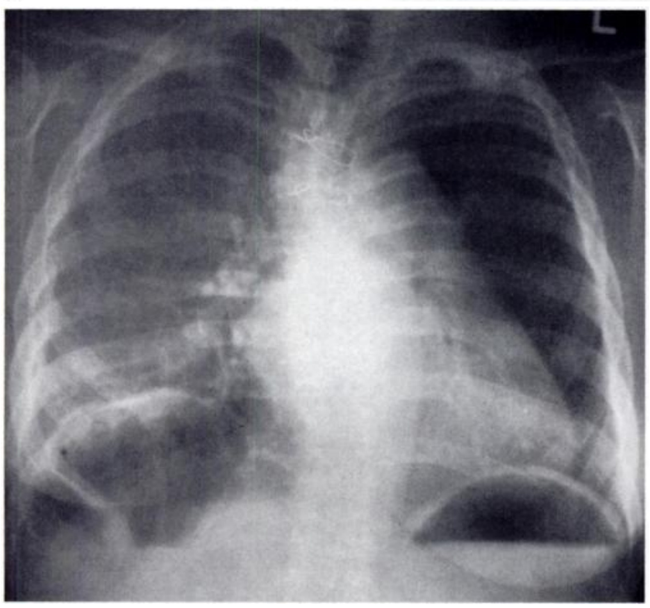

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Figure 1. Right SLT in a 42-year-old woman with Eisenmenger syndrome. **(a)** Radiograph obtained on day 1 shows diffuse mild air-space disease in the transplanted lung. There is a large basal pneumothorax on the left. **(b)** Radiograph obtained on day 3 (peak severity) shows worsening air-space disease in all three lung zones. The radiographic score was 9. **(c)** Radiograph obtained on day 20 shows residual mild reticular interstitial disease in all three zones.

SLTs and DLTs. In addition, to confirm the validity of the physiologic measurements, the A-a gradient and Po_2/Fio_2 ratio were compared.

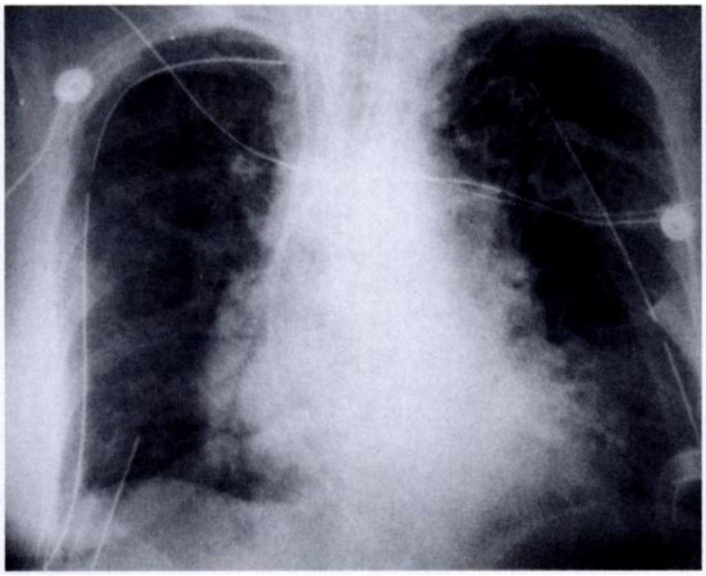
RESULTS

Interstitial or air-space disease was noted in the early postoperative period in 44 of 45 lung transplants (Figs 1a, 2a). One patient's lungs remained clear throughout the posttransplantation period. Interstitial or air-space disease appeared on day 1 in 39 transplants, on day 2 in four, and on day 3 in one. The radiographic findings in the lungs at the first appearance of reperfusion edema are summarized in Table 1.

The radiographic findings in the lungs at peak severity of reperfusion edema are summarized in Table 2 (Figs 1b, 2b). The process peaked in severity on day 1 in 17 transplants, day 2 in eight, day 3 in 15, day 4 in three, and day 5 in one. Among the DLT recipients, the process was symmetric in 16. In the other nine DLT recipients, there was air-space disease on one side and interstitial disease on the other or the process involved more zones on one side than the other.

Clearing of the process was first seen radiographically on days 1–5 in 27 transplants, on days 6–10 in 14, and after day 11 in three. The process cleared completely by day 10 in five transplants and by day 21 in another seven. In the remaining 32 transplants, the lungs remained abnormal at the end of the 21-day observation period. When air-space disease was present, it cleared first by changing into reticular interstitial disease (Figs 1c, 2c). It appeared as reticular disease in all 32 transplants in which disease was still present on day 21.

The results of correlating the radiographic score and physiologic status are summarized in Table 3. For the SLT recipients, the mean radiographic score was 7.4 (range, 4–9); the mean A-a gradient was 140.4 mm Hg (range, 12–249 mm Hg); and the mean Po_2/Fio_2 ratio was 281 (range, 162–562). For the DLT recipients, the mean radiographic score was 10.9 (range, 4–18); the mean A-a gradient was 175.2 mm Hg (range, 17–311 mm Hg); and the mean Po_2/Fio_2 ratio was 267



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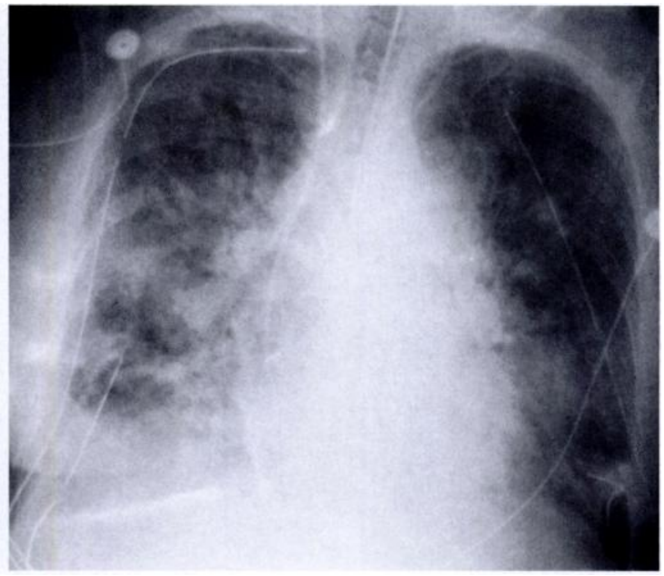

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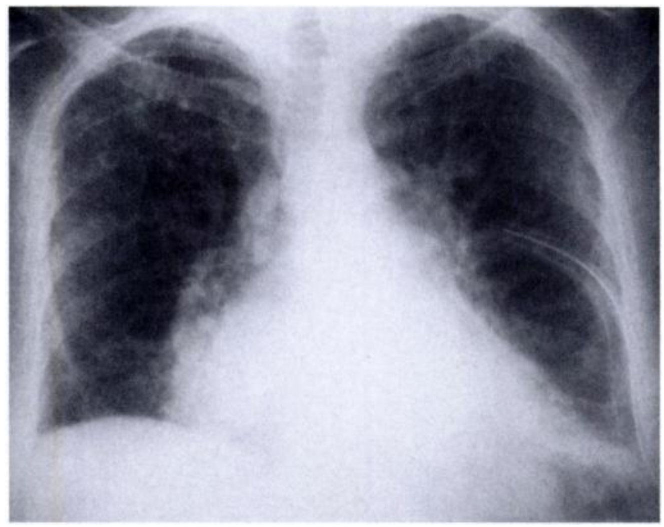

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Figure 2. DLT in a 53-year-old woman with emphysema. **(a)** Radiograph obtained on day 1 shows reticular interstitial disease in all six lung zones. **(b)** Radiograph obtained on day 2 (peak severity) shows air-space disease in the middle and lower zones and reticular interstitial disease in the upper zones bilaterally. The radiographic score was 14. **(c)** Radiograph obtained on day 18 shows residual reticular interstitial disease in all six lung zones.

(range, 162–562). There was no correlation between the radiographic score and the A-a gradient or Po_2/Fio_2 ratio in the SLT and DLT recipients (Fig 3). However, there was a strong correlation between the two physiologic parameters.

DISCUSSION

Our observations on reperfusion edema after lung transplantation agree with those in previous studies. During the first 3 postoperative days, Anderson et al (4) found that almost all transplanted lungs had infiltrates in the perihilar and basal regions, consistent with reperfusion edema. In studies by Herman et al (2,3) of patients not included in the current study, the patterns seen most frequently included perihilar and basal reticular interstitial disease and/or air-space consolidation.

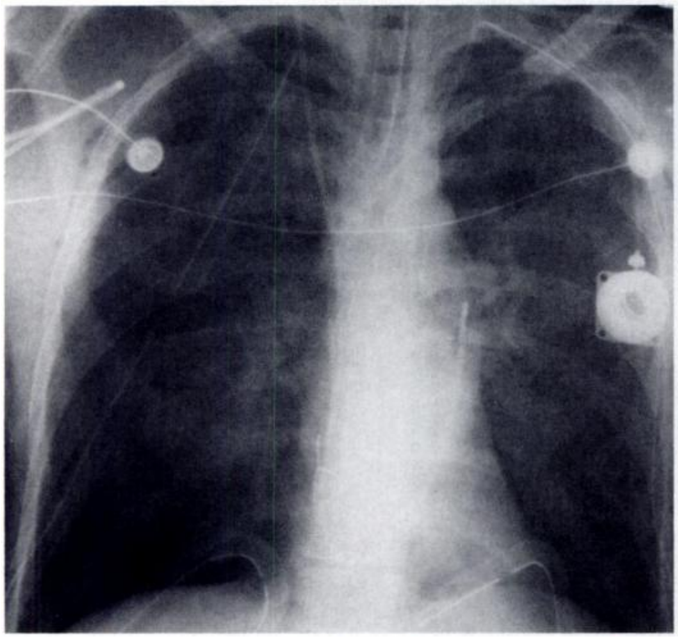
Reperfusion edema has been studied in a number of animal models, including canines (5,6), rodents (7), and primates (8). In a dog model, Siegelman et al (6) noted an alveolar infiltrate, which was predominantly perihilar and basal.

According to our study and animal studies (9), there is a poor correlation between the radiographic manifestations of reperfusion edema and physiologic parameters. However, we found an excellent correlation between the A-a gradient and Po_2/Fio_2 ratio, suggesting that these physiologic parameters are an accurate measure of lung function. There are several possible reasons for the poor correlation with radiographic features.

TABLE 3
Comparison of Radiographic Score and Physiologic Parameters

Patient Group and Comparison	Kendall τ	*P* Value
SLT recipients (n = 10)		
Radiographic score vs A-a gradient	−.105	.696
Radiographic score vs Po_2/Fio_2 ratio	.053	.845
A-a gradient vs Po_2/Fio_2 ratio	−.644	.010
DLT recipients (n = 14)		
Radiographic score vs A-a gradient	.076	.677
Radiographic score vs Po_2/Fio_2 ratio	−.192	.298
A-a gradient vs Po_2/Fio_2 ratio	−.760	<.0001

The reliability of chest radiography in estimating the extent of excessive fluid accumulation in the lung is limited. Although animal studies have shown a statistically significant relationship between extravascular lung water and pulmonary edema at chest radiography, it was possible to diagnose excess lung water only when the level was more than 35% above



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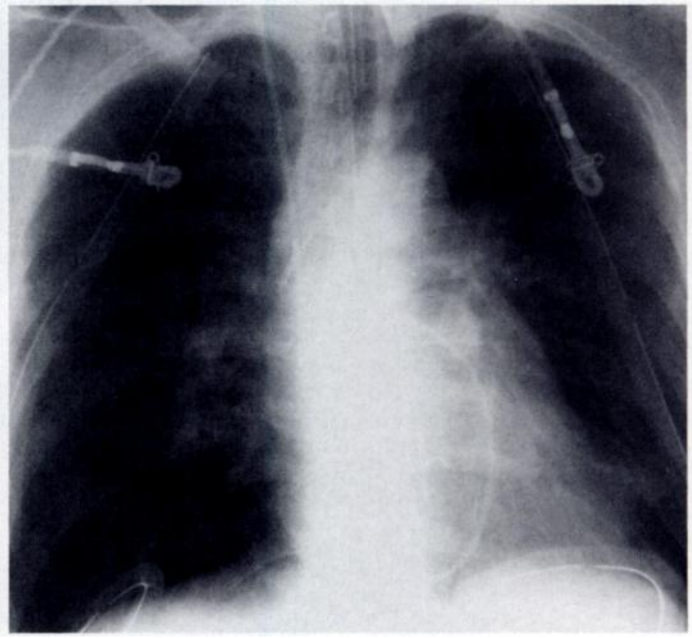

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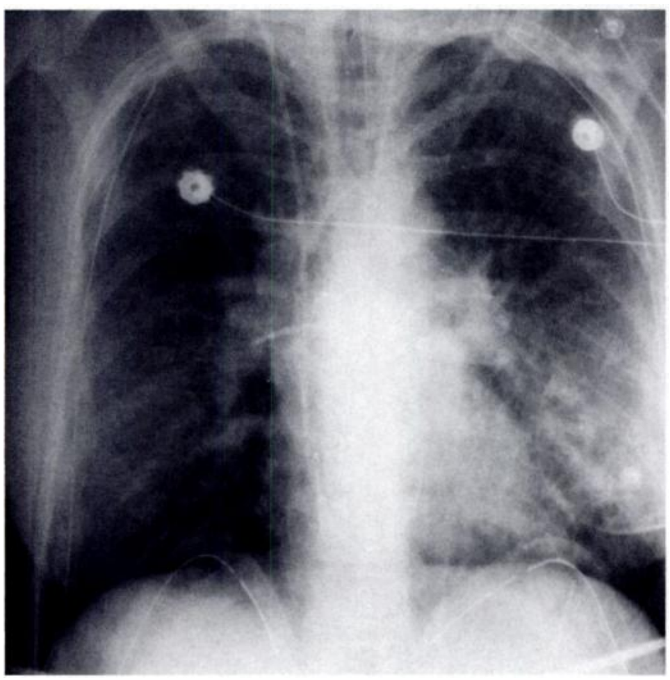

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Figure 3. Correlation between radiographic score and physiologic parameters in DLT recipients. **(a)** Good correlation between radiographic score and physiologic parameters in a 27-year-old man with cystic fibrosis. Peak severity radiograph (day 1) shows air-space disease in all three zones on the left and the upper and middle zones on the right (radiographic score of 15). The A-a gradient was 241 mm Hg, and the Po_2/Fio_2 ratio was 250. **(b)** Mild radiographic changes with severe physiologic abnormalities in a 37-year-old man with cystic fibrosis. Peak severity radiograph (day 1) shows reticular interstitial disease in the middle and lower zones bilaterally (radiographic score of 4). The A-a gradient was 264 mm Hg, and the Po_2/Fio_2 ratio was 263. **(c)** Severe radiographic changes with good pulmonary physiology in a 38-year-old woman with cystic fibrosis. Peak severity radiograph (day 1) shows air-space disease in all six lung zones. The A-a gradient was 17 mm Hg, and the Po_2/Fio_2 ratio was 526.

normal (10). In addition, there is controversy about whether radiography can even allow distinction between cardiogenic and noncardiogenic pulmonary edema (11,12).

Because reperfusion edema is a dynamic, transient process, a major cause of the poor correlation with radiographic features may be the delay between the onset of pulmonary edema and the development of radiographic findings. The physiologic parameters change within hours of development of fluid overload, but it may take several hours to an entire day for the radiographic appearance to change (13). By the time radiographic manifestations appear, treatment and clinical resolution of the fluid overload may well be under way. In cardiogenic pulmonary edema, the severity of radiographic abnormalities generally correlates well with the wedge pressure (14). However, it has been suggested that, in acute cardiac disease states, there is a phase lag between elevation of the wedge pressure and radiographic signs of pulmonary edema, possibly because of slow transudation of fluid into the extravascular space (13). Another study also demonstrated considerable phase lags (15). Therefore, the chest radiographic manifestations tend to be delayed due to the transient nature of reperfusion edema.

Another cause of the poor correlation may be the scoring system used in our study, which did not include grading the severity of air-space disease. For example, a lower lung zone with mild air-space disease would have received a score of 3, as would one that demonstrated total opacification. One would expect the former situation to be associated with better physiologic function than the latter. However, we believe that the scoring system may not have been an important factor, as demonstrated by Figure 3a, which shows a patient with much milder air-space disease than the one in Figure 3c but worse physiologic parameters.

A number of conditions, including fluid overload, left ventricular failure, rejection, infection, and atelectasis, can mimic reperfusion edema. Because these entities cannot be completely excluded, we assumed that all chest radiographic changes not obviously due to these processes represented reperfusion edema. Although we reviewed the fluid balance, wedge pressure, blood pressure, bronchoscopic results, and physicians' progress notes, some of the episodes of reperfusion edema in our study may actually have represented one of the above complications (especially fluid overload, which is particularly difficult to diagnose). Lung transplant recipients are generally considered to have fluid depletion postoperatively and are given large amounts of fluid intravenously; they therefore have a propensity toward fluid overload. Because of the fluid depletion preoperatively, calculations based on input and output volumes alone are not an accurate means of assessing fluid balance. Therefore, some of the episodes of reperfusion edema in our study may actually have represented fluid overload. However, the difficulty in distinguishing between fluid overload and reperfusion edema on posttransplantation chest radiographs is commonly also a problem for the clinicians treating such patients in the immediate perioperative period.

The causes of reperfusion edema are uncertain and probably multifactorial. They include increased vascular permeability (16), uptake of calcium by the cells (in an in vitro study) (17), free radical production (18,19), and possibly the vasoconstrictive effects of prostaglandin E_2 (20).

In summary, reperfusion edema is a form of noncardiogenic pulmonary edema that occurs in virtually all transplanted lungs within 48 hours of transplantation. This entity appears as perihilar and/or basal interstitial and/or air-space disease that peaks in severity by day 4. There is a poor correlation between radiographic severity and physiologic parameters. Nevertheless, chest radiography is clearly important in lung transplant recipients because of its usefulness in the diagnosis of many other conditions. Because reperfusion edema is similar in appearance to many other conditions, it is a diagnosis of exclusion. However, any pulmonary process beginning or worsening after day 5 should be assumed to be due to some other cause and investigated accordingly.

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