
Primary Graft Failure
Who Is at Risk?

One of the most intriguing complications encountered following lung transplantation (LT) is the pulmonary reimplantation response (PRR). PRR develops in the immediate posttransplant period (4 to 6 h up to 72 h) and is characterized by the development of alveolar infiltrates in the graft(s), a reduction in lung compliance, and impairment in gas exchange.

Originally described in the animal model by Siegelman et al,1 the spectrum of PRR is synonymous with many other terms, including reperfusion injury, ischemia-reperfusion injury, reperfusion edema, primary graft failure (PGF), and early or primary graft dysfunction. The presentation of PRR exhibits variable incidence and clinical presentation. In the mildest form, PRR may affect nearly 60% of transplant recipients to some degree.2 The most severe form, more recently referred to as PGF, may have an incidence of up to 15%.3 According to the 2002 registry of the International Society of Heart and Lung Transplantation,4 primary/nonspecific graft failure is one of the leading causes of early (within 30 days) mortality following LT, accounting for 16.4% of deaths in this time period.

PRR is a diagnosis of exclusion, and one must consider other entities in the differential diagnosis, including acute rejection, hyperacute rejection, donor-borne or recipient-harbored infection, a complication at the venous anastomosis, and volume overload. Acute rejection can be diagnosed by transbronchial biopsy with the characteristic findings of lymphocytic vasculitis. Hyperacute rejection, while not uncommon in other solid-organ transplant recipients, has only been rarely described in isolated case reports following LT.5 A venous anastomotic complication is often associated with localized pulmonary edema, and can be evaluated by transesophageal echocardiography.

Primary treatment for PRR is supportive with mechanical ventilation and diuresis. More recently, newer critical care innovations have been used to combat PRR. The use of inhaled nitric oxide, directed at increasing depleted levels of endogenous nitric oxide, thereby reducing pulmonary vascular resistance, improving gas exchange, and breaking the cycle of increased production of biochemical mediators of lung injury, has been described in small case series with beneficial results.6–8 Extracorporeal membrane oxygenation, surfactant, and independent lung ventilation strategies have also been used to support patients through this process.9–12

The outcome of those transplant recipients with PRR or PGF is compromised. Investigators5 have found that the development of PGF has been associated with prolonged mechanical ventilation, longer hospital length of stay, poorer 1-year actuarial survival (40% vs 69%), and decreased exercise function in survivors. Another group of investigators2 observed prolonged mechanical ventilation requirements, as well as ICUs stay, but did not observe a survival difference between patients with or without PRR. A third study12 found that PGF was associated with prolonged mechanical ventilation and higher ICU mortality, 29% vs 10.9%.

Despite active clinical research in this area, the cause of PRR remains incompletely understood. The leading physiologic and molecular explanation for PRR is ischemia-reperfusion injury to the lung graft(s) resulting in the release of free-radical and inflammatory cytokine mediators, with resulting cellular injury and pulmonary vessel dilatation and alveolar flooding.14 The net result is high-protein membrane permeability edema, with normal pulmonary artery occlusion pressures.15 The lung pathology is consistent with diffuse alveolar damage. Based on the likely contribution of free-radical injury to PRR, both animal and human studies16,17 have attempted to address the addition of various free-radical scavengers to the donor-preservation solution, with variable impact on PRR.

Risk factors for the development of PRR have been difficult to define by the available literature. Based on the molecular mechanisms, it might be logical to expect that prolonged ischemic times might lead to increased production of free-radical mediators and consequently more severe forms of PRR with reperfusion. Similarly, one might hypoth-
esize that patients with a pretransplant diagnosis of pulmonary hypertension might suffer greater injury following reperfusion. Cardiopulmonary bypass with the associated anticoagulation, cytokine production, and inflammatory response might also be expected to exaggerate PRR.

Several of the risk factors thought to contribute to the development of PRR have been examined in large (by LT study standards), retrospective studies. Risk factors that have been examined include graft ischemic times, donor and recipient age, donor and recipient gender, single vs bilateral LT procedures, use of cardiopulmonary bypass during the transplant, and recipient diagnoses, particularly pulmonary hypertension. Cardiopulmonary bypass was identified as a risk factor in one study\(^2\) but was not confirmed in others.\(^3\) Likewise, prolonged graft ischemic times were found to correlate with the development of PRR in one study, but not in others.\(^4\)

In the article in this issue of CHEST (see page 1232), Christie and co-workers have retrospectively identified some of the possible risk factors for the development of the most severe subset of PRR, those patients who acquire PGF. The authors defined PGF as diffuse alveolar opacities involving the allograft(s) developing within 72 h of transplant, a ratio of \(\text{Pa}_2\) to fraction of inspired oxygen < 200 beyond 48 h postoperatively, and no other secondary causes of graft dysfunction identified. In a prior study,\(^3\) these authors examined several risk factors and were able to identify only the lack of induction lympholytic therapy as a possible independent variable associated with the development of PGF. Now with further analysis and a larger patient population, several factors have been identified: recipient diagnosis of primary pulmonary hypertension, donor African-American race, donor female sex, and donor age < 21 years or > 45 years also were variables independently associated with the development of PGF. It is difficult to postulate a pathophysiologic mechanism as to why some of these specific variables might increase the incidence of PGF, and this deserves further study.

What are the clinical implications of these findings? With our current limited organ donor population and with this low number continuing to represent the single rate-limiting factor to the performance of additional LT procedures, it is unlikely that one would turn down a potential lung donor based on these results or apply these results to donor-recipient matching at this time. For example, should we hesitate in offering a lung from a suitable 19-year-old African-American female donor to a recipient with pulmonary hypertension? Most would say, of course not. Likewise, many transplant physicians have encountered patients who have acquired PRR and even PGF even though they met none of the at-risk criteria, for example, a 55-year-old man undergoing single LT for chronic obstructive lung disease, who did not require cardiopulmonary bypass, and who received a lung from a 30-year-old white donor.

Clearly, this is an area of interest that requires further investigation. However, if these findings hold true in further analyses of larger patient groups as well as in multicenter data analyses, then the implications may be of great importance. Now that newer critical care techniques can be applied to this group of patients, then perhaps prophylactic strategies can be instituted in those recipients thought to be at risk for the development of PRR, thus minimizing or preventing this potentially devastating posttransplant complication.\(^18–20\)

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Interaction of Angiotensin-Converting Enzyme Inhibition and Aspirin in Congestive Heart Failure

Long Controversy Finally Resolved?

Not long after the initial findings of the positive effects of angiotensin-converting enzyme (ACE) inhibition on prognosis for patients with congestive heart failure (CHF), a controversy commenced as to whether there is a negative interaction between ACE inhibition and aspirin. Since one of the most important underlying causes of CHF is coronary artery disease, this question is of utmost clinical importance. The fact that this topic is still relevant > 10 years after the initiation of the controversy indicates the difficulty inherent in resolving the question. In this issue of CHEST (see page 1250), Aumégage et al present their data showing no negative interaction in their CHF cohort. Does this mean that the controversy is finally resolved?

It is important to understand the theoretic basis for this potential interaction. ACE not only converts angiotensin I to angiotensin II, but it is also responsible for the degradation of kinins. Thus, the inhibition of ACE increases bradykinin levels. Bradykinin, a potent vasodilator on its own, activates vascular endothelial B2-kinin receptors, which promote the formation of vasodilatory prostaglandins through the action of phospholipase-A2 and cyclooxygenase (COX). Accordingly, drugs that inhibit endothelial COX, such as aspirin, may reduce the synthesis of vasodilatory prostaglandins. Accordingly, the inhibition of COX may reduce the efficacy of ACE inhibition, if this pathway is of importance. Indeed, although it is also a matter of controversy, there is some indirect evidence that this is the case. Thus, the clinical benefits of ACE inhibition persist despite the fact that angiotensin II levels may return to pretreatment levels. These findings suggest that mechanisms other than the inhibition of angiotensin II formation (ie, increased levels of bradykinin and vasodilatory prostaglandins) are at least in part responsible for the effects of ACE inhibitors. Similarly, the lack of superiority of angiotensin II receptor type 1 blockade compared to ACE inhibition in patients with CHF, despite the more complete inhibition of the angiotensin II-transmitted effects, suggests that additional mechanisms are responsible for the effects of ACE inhibitors. Furthermore, experimental data suggest that the positive effects of ACE inhibition on postmyocardial remodeling are mediated by bradykinin, although the data in this regard are not consistent. Cardioprotection against free radicals by ACE inhibition depends on the activation of bradykinin type 2 receptors and prostaglandin synthesis. In humans, several hemodynamic studies showed that the inhibition of endothelial COX by nonsteroidal antiinflammatory drugs may result in a substantial reduction of the effects of ACE inhibition. Also, the antihypertensive potential of ACE inhibitors was found to be reduced with concomitant use of nonsteroidal antiinflammatory drugs. However, for obvious reasons, the issue of whether long-term endothelial COX inhibition is prognostically harmful in patients with cardiovascular diseases has never been prospectively evaluated.

There are, however, also reasons for a positive rather than negative interaction between ACE inhibition and aspirin. Thus, angiotensin II may exert its vasoconstrictive effect in part via the COX product thromboxane-A2. Opposing the production of angiotensin II by ACE inhibition may result in vasodilation, in part by the attenuation of thromboxane-A2 production. Since aspirin inhibits COX and thereby thromboxane A2 production, the two agents may act synergistically. Furthermore, bradykinin has been described as enhancing the release of norepinephrine by sympathetic nerve endings. This may be particularly important in the heart since cardiac

References: