

Primary Graft Failure Following Lung Transplantation: Is There Hope for Improvement?

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Cystic fibrosis associated with end-stage respiratory failure is one of the most relevant indications for lung transplantation. Patients are young and lung transplantation offers them an acceptable quality of life and a chance of survival that is also acceptable, given the low perioperative mortality rate. This issue of ARCHIVOS DE BRONCONEUMOLOGÍA includes a report of excellent results in cystic fibrosis patients treated by the Valencia group,¹ who have ample experience with lung transplantation. The authors conclude that the variable that significantly affects perioperative mortality is primary graft failure (PGF), defined as a ratio of PaO₂ to inspired oxygen fraction less than 200 mm Hg in the first 72 hours following implantation. PGF is also associated with greater risk of acute rejection and, in the medium and long term, development of bronchiolitis obliterans as an expression of chronic rejection. In spite of all their difficulties, cystic fibrosis patients comprise the group with better short- and long-term survival. What is the situation, however, with other types of transplant patients? Reviewing our own experience recently, we noticed that the complication most influencing mortality was PGF, followed by infectious and renal complications. Patients with restrictive diseases and obese patients had greater risk of PGF. Patients receiving organs from male head-injury donors older than 53 years of age, smokers, transfused donors, and donors with radiographic infiltrates or positive culture were also at greater risk. Also associated with a higher incidence of PGF were a need for extracorporeal circulation or transfusion during transplantation and an ischemic period longer than 6 hours.

Thus, morbidity and mortality associated with lung transplantation is caused in part by PGF, which can be seen to be arising from diverse factors involving the recipient, the donor, and the surgical event itself. But, in addition, it should be mentioned that lung grafts require preservation from explantation to implantation and their

metabolic activity should be slowed to a minimum during the ischemic period.

What is being done at present to reduce PGF? The most recent literature on the subject suggests that action is moving in 3 directions:

1. Increasing the number of donors by applying techniques that improve lung graft function, even of organs from donors designated as marginal or suboptimal.
2. Exploring the possibility of incorporating donors in asystole (so-called non-heart-beating donors) into the pool of brain-dead donors.
3. Assessing lungs *ex vivo* in an isolated circuit where they are ventilated and reperfused and, in theory, can be treated for optimization and subsequent transplantation.

Improving Graft Lung Function

Cell damage secondary to lung preservation procedures and reperfusion has been extensively studied. Lung preservation, both of the vascular endothelium and alveolar epithelial cells, has been the object of numerous experimental and clinical studies.² The vascular endothelium, which regulates coagulation, vascular tone, and inflammatory response, has been experimentally treated with coagulation inhibitors such as C1-esterase and antithrombin III to prevent increased prothrombotic and antifibrinolytic factors during ischemia.³ Changes in donor and recipient type II cells and, secondarily, in the surfactant have been the object of numerous studies.⁴ Preservation solutions that are low in potassium ions have improved interstitial edema, acidosis, adenosinetriphosphatase activity, and oxygen free radical activity.

It is not yet possible to evaluate what influence these experimental studies will have on clinical practice. At present the incidence of PGF seems to have decreased, due solely to the use of low-potassium solutions.⁵ What appears certain is that the development of such solutions has deepened our knowledge of the mechanisms involved in PGF and has consequently led to new approaches destined to improve transplant outcomes.

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Non-Heart-Beating Donors

Most transplant organs at present come from donors declared dead on the basis of neurological criteria (brain-dead donors). Brain death is associated with hormone depletion, increased proinflammatory cytokine levels and, in a third of brain-dead donors, neurogenic pulmonary edema. However, some organs come from asystolic individuals, who are referred to as non-heart-beating donors.⁶ Use of lungs from such donors has been the object of much experimental study, and it has been speculated that donors whose death came from sudden cardiac arrest may provide lungs of superior quality due to the absence of mechanical ventilation, systemic inflammatory response, and neurogenic pulmonary edema.⁷ Nevertheless, the risk of PGF may be greater from non-heart-beating donors than from brain-dead donors because of a warm ischemic period—that is, the time from cardiac arrest to the start of preservation procedures. Experiments have shown that warm ischemic time in a cadaver that receives no type of resuscitation can be tolerated for as long as 60 to 90 minutes.⁸ Ventilation and insufflation of cadaver lungs retards adenine nucleotide depletion and the accumulation of hypoxanthine, a clinical picture which is a marker of brain death.

In 2001 the first such single lung transplant in a clinical setting was performed by Steen et al⁹ in Lund, Sweden. The donor was a patient in whom asystole occurred in the same hospital. Tubes were removed from the recipient 24 hours after the intervention and there were no signs of PGF. The patient felt well as of publication of a case report 5 months after transplantation. In Madrid in 2002 our group at the Hospital Puerta de Hierro began to use non-heart-beating donors from outside the hospital in collaboration with the Hospital Clínico San Carlos, the cardiac emergency center for the greater metropolitan area of Madrid.¹⁰ So far we have performed 11 double- and 2 single-lung transplants. PGF occurred in the early postoperative period in only 1 case and, in our short experience, we have observed that grafts from non-heart-beating donors have had significantly less infection than lungs transplanted from brain-dead donors over the same period of time.

Lung Function Assessment Ex Vivo

The new concept of donor lung assessment ex vivo has opened up highly promising perspectives for the future. At present, lung function assessment is performed in the donor cadaver and problems frequently arise owing to hemodynamic instability, vasoactive drugs, volume and blood infusion, changes in ventilation, etc. Ex vivo assessment involves lung explantation and reassessment in an isolated circuit that provides optimal conditions by controlled reperfusion of the organ with a special normothermic solution.¹¹

Such assessment enables not only careful examination of the organ but also evaluation of functional capacity expressed in gas exchange, and hemodynamic and ventilatory parameters. Organs previously rejected in vivo for transplantation can be assessed by ex vivo reperfusion. Steen et al⁸ have demonstrated that normothermic reperfusion is possible for several hours and does not lead to the development of edema or alterations in gas exchange. In theory, ex vivo assessment can also enable treatment of inferior quality lungs with antibiotics, inotropics, diuretics, fluids, corticosteroids, optimal ventilation procedures, bronchoalveolar lavage by bronchoscopy, and even radiologic monitoring.¹² Finally, ex vivo reperfusion offers the possibility of a longer preservation time—experimentally, longer than 24 hours—so that it might be possible to accept organs from more remote hospitals. Lung transplantation could become a scheduled intervention.⁸

Although the incidence of PGF due to lung graft ischemia-reperfusion injury has not changed significantly in recent years, techniques are being developed that will enable us to assess and improve the functional status of lungs for subsequent transplantation.

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