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Comparison of cardiac allograft vasculopathy in heart and heart–lung transplantations: A 15-year retrospective study

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KEYWORDS:
cardiac allograft vasculopathy;
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long-term outcomes

BACKGROUND: Cardiac allograft vasculopathy (CAV) is a major factor limiting long-term survival after heart transplantation (HTx). Specific determinants of CAV and long-term outcome after CAV occurrence have been poorly investigated after heart–lung transplantation (HLTx).

METHODS: Between January 1996 and December 2006, 79 patients underwent HLTx (36.3 ± 12.2 years old; 47% men) and 141 patients underwent HTx (49.2 ± 12.3 years old; 77% men) at two different institutions. CAV grading was reviewed in both groups according to the 2010 standardized nomenclature of the International Society for Heart and Lung Transplantation. The mean post-transplant follow-up was 94 (1 to 181) months.

RESULTS: Overall 10-year survival rate was 58% after HTx and 43% after HLTx ($p = 0.11$). The Grade 1 (or higher) CAV-free survival rate was 95% at 4 years and 69% at 10 years after HLTx, and 77% and 39%, respectively, after HTx ($p < 0.01$). Mean cyclosporine blood levels were similar between the groups at 3, 6, 12, 24 and 36 months. The main causes of mortality beyond 5 years after HTx and HLTx were malignancies and bronchiolitis obliterans, respectively. By multivariate analysis, recipients who developed >3 acute myocardial rejections during the first year post-transplant were exposed to a higher risk of CAV (95% CI 1.065 to 2.33, $p = 0.02$). Episodes of acute pulmonary rejection and bronchiolitis obliterans were not associated with an increased risk of CAV ($p = 0.52$ and $p = 0.30$).

CONCLUSION: HLTx recipients appeared protected from CAV compared with HTx patients in this retrospective study. Repeated acute cardiac rejections were independent predictors of CAV. Unlike bronchiolitis obliterans, CAV had a very low impact on long-term survival after HLTx.

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Heart–lung transplantation (HLTx) remains the only treatment for end-stage cardiopulmonary disease. Transplants for refractory congenital heart disease or pulmonary arterial hypertension currently account for the majority of HLTxs.[1]

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The 1-year survival rate after HLTx has progressively improved to 70% in recent years, compared with 64% in the previous era, whereas the 10-year survival rate remained stable around 40% over the last 3 decades.[2–4] Malignancies, non-cytomegalovirus infections and chronic allograft dysfunction are the main causes of morbidity and mortality beyond 5 years in HLTx recipients.[4] Among these, late allograft failure may not be the consequence of long-term exposure to immunosuppressive therapies, but instead may be considered a manifestation of chronic allograft rejection.

Bronchiolitis obliterans syndrome (BOS) is the most frequent form of chronic rejection, affecting 59% of HLTx recipients by 5 years, with nearly 90% free of coronary allograft vasculopathy (CAV), the other manifestation of chronic rejection after HLTx.[4] After experimental findings showing a progressive fibrous remodeling of the transplanted vessels in animal models, CAV was first described in human heart transplants in 1970 by investigators at Stanford University.[5] This accelerated form of neointimal hyperplasia results in significant narrowing of the coronary vessels beyond 1 year after heart transplantation (HTx) and is responsible for chronic allograft dysfunction due to myocardial ischemia.[6] Potential causes of CAV after HTx have included both immunologic determinants, such as acute rejection and human leukocyte antigen mismatches, and non-immunologic factors, such as metabolic disorders, ischemia–reperfusion injury and cytomegalovirus (CMV) infection.[6]

When compared with HTx recipients, HLTx recipients appear to be relatively spared from CAV, although BOS develops at a rate similar to that seen in double-lung transplant recipients.[2,4,7] Specific determinants of CAV after HLTx and the mechanisms of its lower frequency compared with BOS remain unclear in this population. Therefore, we sought to compare our experience in HLTx to a series of HTxs over the same period to determine whether lung allografts could provide protection from CAV development. We also aimed to investigate risk factors and the impact of CAV on long-term outcomes after combined HLTx.

Methods

Data collection

Patients who underwent HLTx at Marie Lannelongue Hospital or isolated HTx at Rennes University Hospital between January 1996 and December 2006 were analyzed retrospectively. Donor characteristics were reviewed from the national transplant database of the "Agence de la Biomédecine" (La Plaine Saint-Denis, France) with regard to age, gender and cardiovascular comorbidity. Patients <18 years old at time of transplantation and those who received repeat transplantations were excluded. A total of 220 patients were analyzed according to type of transplant (heart–lung vs isolated heart) with respect to survival, acute rejection, CMV infection, BOS and CAV rates. The mean post-transplant follow-up was 94 (range 1 to 181) months. A third group of double-lung transplant (LTx) recipients from Marie Lannelongue Hospital (transplanted from 1996 to 2006, $n = 92$) was compared with HTx and HLTx groups in analyses of overall survival, causes of death, and events related to level of prolonged immunosuppression.

The institutional review boards of the University Hospital of Rennes and Marie Lannelongue Hospital approved the study and waived the need for informed consent.

Heart and heart–lung procurement and implantation

Donor assessment included arterial blood gas measurement, transthoracic echocardiography, chest radiography and visual inspection of heart and lungs. Myocardial preservation consisted of a 1-liter infusion of conventional ice-cold hyperkalemic crystalloid cardioplegia solution into the ascending aorta to achieve complete diastolic arrest. The heart was then placed in sterile cold Ringer's solution for transport. For heart–lung procurement, cardiac preservation was associated with lung preservation, including an initial injection of 500 μg of prostaglandin E1 into the pulmonary artery, followed by infusion of 4 liters of modified Papworth solution using leukocyte-depleted blood until December 2005, after which low-potassium dextran (50 ml/kg; Perfadex; Vitrolife, Goteborg, Sweden) was used for lung preservation. A patent foramen ovale was systematically closed when present. The heart–lung block was then placed in cold saline for transport.

The surgical approach was mid-line sternotomy for all HTxs and in most of HLTxs. All allografts were implanted under cardiopulmonary bypass with mild hypothermia (32°C). The HTx and HLTx techniques have been described previously and were modified toward bicaval anastomosis since 2005.[8,9]

Immunosuppressive regimen

HTx and HLTx recipients received the same immunosuppressive regimen following the Stanford protocol.[3] Details are reported in the Supplementary Material (available online at www.jhltonline.org). Briefly, induction therapy was based on rabbit anti-thymocyte globulin at a dose of 1.5 mg/kg intravenously until Day 6 post-transplant.[2] Methylprednisolone (1 g) was started between 1 and 2 hours before transplantation and the daily dose was progressively decreased thereafter to reach the level of 0.5 mg/kg. Maintenance immunosuppression consisted of cyclosporine (3 mg/kg) and azathioprine (2 mg/kg). Starting in 2002, mycophenolate mofetil replaced azathioprine, with a target blood level of between 3 and 8 ng/ml. Acute rejections were treated by infusion of methylprednisolone, which was combined with thymoglobulin in cases of severe allograft dysfunction. Thereafter, the maintenance immunosuppression regimen was transiently increased. In patients with repeated acute rejections, tacrolimus and mycophenolate mofetil replaced cyclosporine and azathioprine.

Long-term follow-up and CAV definition

Patients were closely followed by the post-transplant teams. Acute rejection of the pulmonary allografts was defined as any episode of Grade ≥ 2 rejection on transbronchial biopsy. Endomyocardial biopsies were performed weekly at the beginning (first 6 weeks) and then regularly spaced. Additional biopsies were performed when clinically indicated. BOS was defined as a $>20\%$ decline in forced expiratory volume in 1 second or in forced expiratory flow, mid-expiratory phase, in the absence of acute rejection or infection on bronchoscopy. Because most patients in this study did not benefit from recent technologies to detect post-transplant