Cardiac Allograft Vasculopathy
— Heart Transplantation Provides Insights Into Pathogenesis and Treatment of Arteriosclerosis —

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Last year marked the 50th anniversary of the first heart transplant (HTx) in 1967. Since then, and in particular since the introduction of cyclosporine immunosuppression in the 1970s, HTx has grown worldwide. According to data from the International Society for Heart and Lung Transplantation (ISHLT) Registry, more than 5,000 heart transplants were performed in 2015, with...
a median survival of 10.7 years in adults and 16.1 years in children.\(^1\) Causes of death during the postoperative period vary, with graft failure being most common in the first 30 days and infection prevalent later in the 1st year; with increasing time post-transplant, cardiac allograft vasculopathy (CAV), malignancy, and renal failure become progressively more important.\(^1\) In Japan, the number of HTx procedures increased to around 50 cases per year after revision of the Revised Organ Transplant Act in July 2010.\(^2\) However, few HTx procedures are performed compared with other countries, and the mean waiting period of Status I patients exceeded 1,000 days at the end of 2016 because of a rapid increase in newly registered patients on the waiting list, most of whom were using a left ventricular assist device as a bridge to transplantation.\(^2\) Because of the severe organ shortage in Japan, more marginal donor hearts are used than in other countries, but the outcomes of patients receiving these hearts have not been well studied.

### Pathophysiology of CAV

The leading cause of death between 1 and 3 years post-transplantation is CAV, an accelerated form of coronary artery disease (CAD). CAV is a diffuse concentric proliferation of the intima, often involving intramyocardial vessels, and sometimes even the coronary veins. The initial lesion comprises smooth muscle proliferation of the intima. There is rarely any calcium deposition, the internal elastic lamina is intact, and inflammation is usually present.\(^3\)

The pathophysiologic features of CAV involve components of both immune- and nonimmune-mediated endothelial inflammation and injury,\(^4\) with causative factors shown in Figure 1. This damage subsequently triggers vascular fibroproliferation of the coronary vasculature and allograft dysfunction.\(^4\) Severe CAV positively correlates with persistent inflammation and a higher degree of human leukocyte antigen (HLA) mismatch. Recent studies showed that activation and deposition of the complement degradation product C4d correlated with the presence of circulating alloantibodies specific for donor HLA molecules, which increases the risk of cardiovascular events.\(^4,5\) In particular, the combination of antibodies and complement may play an important role in the development of CAV.\(^6\) Nonimmune factors include the causes of donor brain death, ischemic reperfusion injury,\(^6\) age, obesity, dyslipidemia, hyperhomocysteinemia, diabetes mellitus, hypertension, and cytomegalovirus infection.\(^8\)

In Japan, older individuals with impaired cardiac function serve as donors because of the overall donor shortage, but their hearts often have arteriosclerotic lesions. In this issue of the Journal, Kimura et al\(^9\) study donor-transmitted coronary atherosclerosis because it is suspected that older donor age predicts recipient CAD with coronary artery calcification (CAC). Under the current circumstances in Japan, most donor procurement physicians, who cannot perform coronary angiography (CAG) alone without a hospital catheterization unit and associated staff, do not want to perform invasive examinations because they may affect hemodynamics. Also, nearly half of the procurement hospitals are relatively small and have no CAG equipment. Kimura et al screened for CAC using conventional chest computed tomography (CT) to estimate the risk of pre-existing CAD in donor hearts. They conclude that a maximal intimal thickness (MIT) \(\geq 0.5\) mm occurred more often in the CAC group than in the no-CAC group at baseline (8/8, 100% vs. 31/56, 55%, respectively; \(P=0.02\)). Additionally, the prevalence of MIT in the CAC group was higher than in the no-CAC group >1 year after HTx (Figure 2). This was the case even though everolimus, an inhibitor of m-TOR and proliferation signaling that is a potential post-HTx immunosuppressant, was administered in 7 of 8 CAC patients. There was no significant difference between the groups in the prevalence of primary graft dysfunction, duration of ICU stay, number of cardiac events, or mortality rate. An analysis of the United Network for Organ Sharing HTx database comprising data from August 1987 to May 2008 demonstrated that donors over the age of 50 years had a higher risk of CAV at 5–10 years’ follow-up.\(^12\) However, these data were obtained before the use of proliferation signal inhibitors, so further studies are needed.

### Evaluation of CAV

Intravascular ultrasonography (IVUS) studies show a significant reduction in the average increase of MIT from baseline to 1 year post-transplant in patients receiving everolimus compared with azathioprine, as well as a significantly lower incidence of CAV (defined as an increase in MIT \(\geq 0.5\) mm). These findings are highly relevant.
because MIT at both 12 and 24 months after HTx predicts subsequent major adverse cardiac events and death.\textsuperscript{13} 

Because the heart is partially denervated after HTx, patients usually show no ischemic symptoms until congestive heart failure develops or sudden death occurs because of life-threatening arrhythmia. Because CAV is often diffuse and eccentric in nature, and thus differs significantly from the focal and eccentric pattern of atherosclerotic CAD, it may be difficult to detect with conventional CAG because this modality shows only luminal changes and the arterial wall. IVUS may be the most sensitive tool for early detection of proximal CAV, and measurement of coronary flow reserve is useful for detecting lesions of the intramyocardial coronary arteries. Less invasive examination using multidetector CT has also shown high sensitivity (90.0\%) and specificity (92.2\%).\textsuperscript{14} 

In summary, the current donor shortage in Japan may require that individuals over the age of 60 years donate their hearts to recipients who have been waiting for >1,000 days. Studying the various factors that contribute to CAV, including CAC, is important to achieve good quality of life in the recipients.

References