Coronary Microvasculopathy After Heart Transplantation
A New Marker to Guide Future Trials?

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A unique form of coronary artery disease remains the major limitation to long-term survival in heart transplant recipients, playing a major role in the current half-life of the graft of ∼10 years. Our understanding of the pathogenesis of cardiac transplantation coronary artery disease (TCAD) has evolved from the initial paradigm that it was due entirely to the host immune response or an antigen-dependent process. This belief was based on observations such as circumferential involvement of the allograft vessels throughout their length, the limitation of this process to the allograft vascular bed, and its appearance in recipients of all ages, including adolescents. However, unlike with kidney transplantsations, the expected correlation between the number of HLA antigens matched between donor and recipient and the number or severity of rejection episodes and the development of TCAD has not been very consistent.1

This inconsistency led to examination of antigen-independent factors.2 An abundance of data now demonstrates that an equally significant number of antigen-independent factors contribute to the pathogenesis of TCAD. These include the damage to the conduit arteries (of all organs) by the large catecholamine surge that often accompanies brain death in the donor that results in not only contraction band necrosis in the myocardium but also severe injury to the intima and media of the conduit vessels.1 The importance of this catechol-mediated injury was subsequently confirmed in a large clinical series in which the presence of contraction band necrosis, the hallmark of catecholamine injury, on early routine endomyocardial biopsies was the highest risk factor correlating with subsequent development of TCAD, greater than the number or severity of rejection episodes.2 This high risk is due in part to the significant upregulation of myosin heavy chain antigen expression on the vascular endothelium by catechol surge, which can be mimicked by ischemia-reperfusion injury,3 thereby making the graft more “immunogenic.” The detection of early injury to the endothelium as manifested by abnormal vasoreactivity to provocative testing as early as 1 month after transplantation also has been shown to predict TCAD at 1 year.4 Other antigen-independent risk factors include infection with Cytomegalovirus5 and traditional risk factors for nontransplantation CAD such as elevated lipids and markers of the metabolic syndrome.6 Another interesting observation consistent with the vascular biology of atherosclerosis is the finding of a correlation between the age of the heart donor and the duration of cold ischemia and the development of TCAD.7 This finding suggests a progressive decline in the repair mechanisms in response to the multiple sources of endothelial injury. The rate of progression of developing TCAD may reflect all of the potential mechanisms of endothelial injury that occur early after transplantation. Kobashigawa et al8 have shown that the greatest increase in intimal thickening occurs during the first year after transplantation.

The ability to diagnose TCAD by demonstration of intimal and medial thickening of allograft microvessels on routine histological examination of endocardial biopsies after transplantation was first reported by Palmer et al,9 who noted that the biopsy finding of microvasculopathy was associated with a fatal cardiac event not long afterward. This disease in third- or fourth-order branch vessels typically was concentric and was consistent with a uniform process throughout the length of the allograft vessels. However, the predictive power and frequency of finding significant microvascular thickening that not only leads to luminal reduction but also might predict disease progression have never been studied in a large cohort of patients.

In this issue of Circulation, Hiemann et al10 report the results of a detailed retrospective analysis of >9700 endomyocardial biopsies obtained during the first year after transplantation from 873 heart transplant recipients. The goal of the study was to examine the correlation between stenosis of the coronary microvasculature (vasculopathy) as detected by light microscopy on routine histological staining of the biopsies and freedom from cardiac death. The study also included coronary angiography at 1 year after transplantation to examine the correlation between epicardial and microvascular disease. The study revealed that significant epicardial disease (>75% luminal stenosis) was found in 19% of patients at 1 year after transplantation, whereas microvascular stenosis was present in 43% of patients, involving predominantly the media (91%) rather than the endothelium. The key finding was that neither endothelial disease nor nonstenotic disease of the media was associated with a worse prognosis, whereas stenotic microvasculopathy of the media was associated with a significant reduction in overall survival (P=0.037) and freedom from fatal cardiac events (P=0.0001), which was independent of the presence of significant epicardial disease. Importantly, this process was evident as early as the first 3 months after transplantation.
Unlike previous reports, this study suggested paradoxically that microvasculopathy correlated with younger rather than older donors. The authors provide a new classification system for grading the type and extent of microvasculopathy. Unfortunately, although this process seems specific, it is not that sensitive, nor can a single vessel be used as a primary end point of a study because of the inability to reproducibly follow the progression in the same vessel over time as a result of the random location of biopsy samples.

The authors used the definition of wall thickness that included the entire wall except the endothelial layer. This is not in conflict with the concept of primarily an expanded intima. These findings are still consistent with the prevailing concept of host immune and inflammatory cells crossing the endothelium as a result of a variety of stimuli and secreting a number of growth factors and mitogens that lead to the expansion of the intima and vessel wall by proliferating smooth muscle cells. By this paradigm, smaller microvessels would logically be affected earlier than larger-diameter epicardial vessels if the progression of disease were uniform throughout the length of the vessel, regardless of the type(s) of injury.

What does all of this mean? It suggests that we now may have a sensitive marker for the risk of developing TCAD, which may be detectable as early as 3 months after transplantation, before angiographic stenosis is evident. What this study provides is a testable hypothesis, namely that aggressive intervention in the early months after transplantation could potentially alter the development of TCAD and reduce fatal cardiac events in the future. Although most centers have moved to using statins from the time of transplantation, it may well be that our efforts have been inadequate. Studies in nontransplantation CAD have shown the added benefit of higher doses of statins, and the recent results of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial suggest that aggressive treatment of all risk factors, including better diabetes control, can have a powerful impact on outcomes. The other treatment arm for such a study would be intensification of immunosuppression by using new assays to test donor-specific alloreactivity as markers of adequate immunosuppression and correlation with future fatal events. This arm of the study could potentially help address the contribution of the immune response to the pathogenesis.

The final arm of the study could test the use of novel antiinflammatory agents such as a serine proteinase inhibitor that was shown to nearly block the expected intimal proliferation seen in control subjects in a Lewis-to-Fischer rat model of TCAD using only a single dose at the time of reperfusion of the heart after transplantation. Only by conducting new trials with better end points and disease markers can we reduce the adverse impact of TCAD on survival of heart transplant recipients.

Disclosures
None.

References

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