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EDITORIAL COMMENT

Cardiac Allograft Vasculopathy

It Really Has Changed Over Time*

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Development of cardiac allograft vasculopathy (CAV) in the transplanted human heart was not an anticipated consequence of transplantation. Early investigators in this field simply supposed that healthy young donor hearts with initially normal coronary arteries could be subject to other complications such as rejection and infection, but their coronary arteries would live out their normal life span, unless risk factors supervened. This supposition quickly proved false. This obliterative and diffuse form of vasculopathy was identified in early heart transplantation survivors and has proven to be a most difficult clinical problem. It was first noted in autopsies of patients who died early post-operatively of other causes (1) and later recognized as leading to clinical events (2). There were early suggestions that preventing cytomegalovirus (CMV) infection could decrease the prevalence of CAV (3), and subsequently, other measures such as the use of statins and introduction of newer immunosuppressive agents have targeted that disease.

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The paper in this issue of *JACC: Heart Failure* by Tremblay-Gravel et al. (4) analyzes longitudinal data from a single, highly respected heart transplantation center to track changes in patient and donor demographics and changes in patient treatments of the prevalence, severity of disease, progression of disease, and outcomes of CAV in their program. They arbitrarily subdivided their experience into early (1983 to 1998) and late (1999 to 2011) cohorts. They found, not surprisingly, that patients in the early cohort were younger and had more rejection and more coronary artery disease risk factors and very little statin use. CAV in this population is more prevalent and more progressive and is associated with increased mortality and major adverse cardiac events. The big question is why these things changed over the years. There is, of course, most likely no single answer, but a number of possibilities do come to mind. The new and routine use of statins in the recent cohort of patients is an obvious one, as is the introduction of the newer immunosuppressive agent mycophenolate mofetil (MMF). The clinical trial which validated the use of MMF (5) had as 1 target the surrogate marker for CAV in the form of intravascular ultrasonographic measurements of coronary intimal thickness and showed significant attenuation of such thickness and slower progression of thickness in patients treated with MMF. That agent has been in routine use since that trial.

The other factors which may be influencing the prevalence, progression, and outcomes of CAV in more recent years include the more routine use of CMV prophylaxis regimens and the new recognition of the existence of antibody-mediated cardiac allograft rejection (AMR) and an aggressive approach to its treatment (6). AMR has become well known as a factor leading to CAV and often to its rapid progression. None of these factors are accounted for, or can be accounted for, in the retrospective database used in this study.

The article by Tremblay-Gravel et al. (4) is a major contribution to understanding the clinical impact of CAV and its changing impact over time. Although the number of patients involved is relatively small (n = <300) and huge databases such as those from International Society for Heart and Lung

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Transplantation and United Network for Organ Sharing can track much larger numbers of patients, the advantage of data from a single center with uniform data collection over time cannot be ignored. The decrease observed in the rate of progression of CAV over the years is a unique observation that could likely not be gleaned from the larger databases.

Future areas of development in this field will hopefully include prospective databases that track things such as the incidence and severity of AMR, the incidence of CMV infection, and the use of specific immunosuppressive agents (now including mammalian target of rapamycin [mTOR] inhibitors as well as the previous ones) and correlating these clinical factors with the prevalence of CAV and its progression and clinical consequences. The eventual achievement of the "holy grail" of immunosuppression development in the form of inducing immune tolerance may well bring an end to the need for such data, but even that remains to be seen.

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