Current Trends in Coronary Artery Vasculopathy

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Cardiac allograft vasculopathy (CAV) is one of the leading causes of graft loss in heart transplant recipients. When I was a fellow back in the Stone Age, we were taught that the coronary disease was chronic rejection. We have learned a lot since that time. The reasons for CAV are still unclear but it is thought to be a response to an immune insult. CAV occurs readily after severe cellular rejection episodes and with frequent cellular rejection episodes. It can present in many forms, most commonly as large vessel disease. Intimal hyperplasia of the vessel occurs throughout the coronary arteries. With disease progression, luminal stenosis eventually occurs. CAV can also primarily affect the smaller coronary vessels and the microvasculature, or it can be a combination of both. In the adult population, CAV is much more common and occurs earlier than in pediatric patients. Other risk factors including age at transplant (older patient have higher risk), hypertension, donor age, hypercholesterolemia and antibody mediated rejection have all been associated with increased risk of CAV in pediatric patients. For many years, CAV has been the leading cause of death in pediatric heart transplant patients. In 2007, analysis of the pediatric report of the International Society for Heart and Lung Transplant registry showed CAV as the primary cause of death in 30-35% of the patients with graft failure a close second at 25% (1). CAV, particularly microvessel disease, likely played a role in at least some of those patients. With the advent of newer treatment regimens, the incidence has decreased. In 2015, using ISHLT registry data the cause of death from CAV and graft failure had dropped to 11% and 15%, respectively (2).

Once CAV becomes severe and compromises graft function, the only alternative is re-transplantation. 'Treatment' of CAV is most effective with early detection and prevention. The 'gold' standard for detecting CAV has always been coronary angiography. The major disadvantage of angiography is that once you diagnose vasculopathy, the disease process is too advanced with long-term survival often months. Two methods have improved early diagnosis of CAV, intravascular ultrasound (IVUS)and optical coherence tomography (OCT). In 1997, we started using IVUS at Loma Linda (3). We found that it was much more sensitive in detecting early intimal changes when compared to angiography. Vasculopathy, if present, was diffuse and found in all coronaries making it very convenient to study a single coronary, the left anterior descending. Since that time, it has become standard of care at our institution during the annual catheterization, and as needed when indicated (eg. 6 months post acute severe rejection episode). In 2017, in collaboration with Great Ormond Street, we started utilizing a better tool for assessing IVUS results (4). Using a software program, QIVUS, assessment of the vessel is done in a longitudinal fashion as compared to the old method of segmental analysis. It has proven to be more sensitive in assessing the degree of intimal hyperplasia. In conjunction, with centers in the US and Europe, the safety of IVUS was evaluated with major and minor complication rates of 0.5 % and 0.7 % respectively (5). OCT is performed similarly to IVUS. It is also very sensitive in detecting intimal changes with similar complication rates (8). Both OCT and IVUS have two limitations. First, they both evaluate the large vessels but not the microvasculature. Second, use of both techniques is limited by patient size with studies typically starting at 7-8 years of age. Coronary flow reserve (CFR) has been extensively used to evaluate the microvasculature in atherosclerotic coronary artery disease and in adult heart transplant recipients. In 2015, Denver Children's data on coronary flow reserve was presented at the annual ISHLT meeting. They found that a blunted response to adenosine challenge correlated with microvessel disease similar to findings in the adult population. The advantage of a flow wire is that it can be used at any age. The only limitation is it does not assess the larger vessels. In the adult population, fractional flow reserve and instantaneous wave-free ratio have been evaluated with a coronary flow wire. The future of diagnosing CAV early probably rests with a combination of large and microvessel analysis.

With regards to prevention of CAV, the 2015 ISHLT registry review did show a decrease compared to the 2007 assessment (11% compared to 30%). This decrease was most likely due to changes in immunosuppression management. In the 1990's, the standard immunosuppression was generally cyclosporine, azathioprine +/- steroids. By the early 2000's, tacrolimus and mycophenylate were both being used with increased frequency. In 2006, at Loma Linda, we noted a possible decrease in intimal thickening in patients who we started on sirolimus for significant CAV which was presented at the annual ISHLT meeting. By 2008, sirolimus had become part of our standard immunosuppression protocol. A larger study of the PHTS database in 2017

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showed a trend toward decreased CAV in patients on sirolimus (7). Sirolimus has also been associated with a decrease in CAV in adult heart transplant patients. Most recently, Almond, et al., developed the MATE score to assess 6 significant adverse events in pediatric heart transplant patients (8). Now, a prospective trial randomizing patients to two immunosuppressive regimens (tacrolimus + everolimus vs. tacrolimus + mycophenylate) is ongoing to evaluate the effects of immunosuppression on adverse events. This is the first prospective multi-center trial to see what effect an immunosuppression regimen could have on adverse events such as CAV.

With the advent of newer treatment regimens, I think we will continue to see a decrease in the incidence of CAV in the future. It would be good to see more collaborative prospective efforts both in immunosuppression protocols and diagnostic protocols. Although non-invasive methods of diagnosis were not discussed, in an ideal world, patients would be screened with an effective non-invasive study, and if indicated, then more invasive testing (IVUS/OCT/CFR) would be performed. It will be interesting to see how things develop in the future.

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