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The Utility of Early Aspirin Use and the Development of Pediatric Cardiac Allograft Vasculopathy

Despite numerous advancements in all other aspects of pediatric heart transplant (HT) medicine, cardiac allograft vasculopathy (CAV) remains a hurdle to long-term allograft longevity. Immunosuppression medications, de-sensitization therapies, non-invasive monitoring of rejection, and treatment for rejection have all improved. The diagnosis and treatment of CAV, however, has not followed the same trajectory, thus maintaining its position as a leading cause of graft failure and need for retransplantation. Adult studies suggest that early aspirin (ASA) initiation can decrease the risk of CAV. In early 2020, I was a newly minted junior attending reading one of these studies and I wondered if this potential benefit held true in pediatric HT recipients. I submitted a proposal to the PHTS Scientific Committee who thought it was a good question and allowed me and my esteemed co-authors to utilize the PHTS database to try and answer it. The results of that study, "Early aspirin use and the development of cardiac allograft vasculopathy in pediatric heart transplant recipients: A pediatric heart transplant society analysis" and are discussed here, as well as a call for future research.1

Understanding the Challenge: Pathogenesis and Treatment Limitations
The etiology of cardiac allograft vasculopathy is not fully understood. Histologically, it is characterized by progressive, concentric intimal smooth muscle cell proliferation and lipid deposition leading to diffuse luminal stenosis. Risk factors for CAV are well documented and include immunologic and non-immunologic factors that cause endothelial damage and platelet dysregulation, culminating in diastolic dysfunction and graft failure.

The gold standard for diagnosing CAV is coronary angiography. Unlike the focal lesions seen in coronary artery disease, however, the diffuse, concentric nature of CAV makes early detection challenging. While Intravascular ultrasound (IVUS) is more sensitive than angiography at detecting CAV, percutaneous interventions are often not feasible and freedom from graft failure after revascularization is low.2

The Role of Aspirin: Mechanisms and Potential Benefits
Aspirin exerts its effects by irreversibly inhibiting enzyme cyclooxygenase, which is responsible for the production of thromboxane A2, thus reducing platelet aggregation and mitigating the risk of thrombosis. ASA also has anti-inflammatory properties that decrease the production of other inflammatory mediators that contribute to endothelial dysfunction. Adult HTx recipients have more dysregulated platelet aggregation compared to healthy controls, and this dysregulation appears most pronounced in patient with CAV.4 Thus, ASA is an appealing therapeutic target for attenuating CAV. Peled and colleagues demonstrated that early ASA use (defined as ASA initiation within 1-month post-HTx) was independently associated with a reduced risk of CAV and separate studies by Kim et al and Bergmark et al suggested that early ASA use (defined as ≥ 6 months use in the first year) reduced the risk of moderate to severe CAV.4-6

Study Design
This was a 10-year (January 1, 1996 – December 31, 2016) retrospective analysis of the PHTS database. Subjects <17 years of age at the time of primary HTx who survived ≥ 3 years and had at least one annual surveillance cardiac catheterization with coronary angiography and/or IVUS within that period without evidence of CAV were included. Given the known incidence of CAV with time, this age cut-off was chosen to optimize the number of subjects with at least 3 years of follow-up in the database. Patients with a positive crossmatch or undergoing multi-organ or cardiac retransplantation were excluded. Post-HTx surveillance data is submitted to PHTS on an annual basis. Therefore, for the purposes of this study, **"early ASA use"** was defined as ASA initiation within the first 3 years post-HTx and was classified into three categories:

1. **Continuous ASA** present on all annual follow-up forms.
2. **Intermittent ASA** present on at least one annual follow-up form.
3. **No ASA** no documented use during the first 3 years post-transplant.

Key Findings
Of the 9,755 transplants performed during the study period, less than one-third (i.e. 3,011) met the inclusion criteria. ASA use varied from 0% to 100% across centers and 65% of patients received no ASA. The overall incidence of CAV was only 15%, of which two-thirds of patients had only mild (ie ISHLT grade 1) CAV. Contrary to what has been described in adult studies, patients who received continuous ASA had worse freedom from CAV compared to the other groups ($p=0.002$), but with less severe CAV ($p=0.05$). Continuous ASA use was also associated with higher graft loss compared to the other groups ($p<0.001$). There were several differences in baseline characteristics between the continuous ASA continuous ASA and other groups, including older age, higher incidence of myocarditis, lower rate of induction therapy, and higher incidence of rejection. Multiphase parametric hazard modeling did not reveal that ASA use was independently associated with CAV, though it did show that continuous ASA use was independently associated with inferior graft survival compared to the other groups ($p=0.002$). To further adjudicate this finding, we performed propensity score matching after which no significant difference remained between the groups.

Implications, Limitations, and Future Directions
This PHTS study did not demonstrate a protective effect of early ASA use in preventing CAV or graft failure. Disappointing? Sure. Discouraging? Not at all! In fact, the findings in this study could very well hold the key to better delineating the relationship between ASA and CAV in our patients.

First and foremost, the definition of early ASA initiation in this PHTS study differed significantly from that used in the adult literature. This could suggest the presence of beneficial ASA-related effects that are lost if not "activated" at the appropriate time. Second the nature of the PHTS surveillance forms required us to make rather large assumptions about the accuracy of group classifications. For example, patients in the continuous ASA group may have been started on ASA just days before data submission occurred. Conversely, patients may have been on ASA for most of the year, but had it discontinued just prior to data entry into the registry and, therefore, been identified as not receiving ASA. Third, only 15% of participants developed CAV, so the study may have been underpowered to show a protective effect. Nearly two-thirds of the study population never received ASA, which could have further underwhelmed the results.

The wide variability in ASA utilization across PHTS centers was interesting. Given the differences in baseline characteristics, and the fact that continuous ASA remained independently associated with inferior graft survival in multiphase parametric hazard modeling, an underlying selection bias is likely. It is reasonable to imagine that some centers

are fully “proactive” while others are entirely “reactive” in their ASA prescribing practices, leading to higher ASA use in higher risk patients. The small proportion of patients receiving concomitant statins may also have been in this higher risk group, but the potential synergistic effect of combined ASA-statin therapy may have been underrepresented as only 35% of participants were taking statins. Finally, we did not stratify the groups by age, which may have shown a beneficial effect of ASA in older recipients.

Ultimately, this study highlights the need for a standardized approach to patient selection and initiation and maintenance of ASA therapy in pediatric HTx recipients. A prospective, randomized control trial in which ASA is started early (i.e. first 6 months) post HTx is needed to determine its true effect on CAV and graft survival. The PHTS database and network of pediatric HTx centers globally affords the perfect infrastructure for such a venture, and I welcome collaboration from interested centers.

References

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