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# Comparing the efficacy of heart-conserving measures and retransplantation for chronic rejection in the pediatric population

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By

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**Abstract**

Coronary allograft vasculopathy (CAV) is the leading cause of morbidity and mortality among pediatric heart transplant recipients and faces unsuccessful treatment for prevention and management. Post-transplant immunosuppressive therapy has been modified over the years to determine the most effective regimen for rejection. Tacrolimus has been the superior immunosuppressant used for rejection since the early 2000s. It has been shown to have substantial immunosuppressive effects, least number of adverse effects, and decreased comorbidities compared to other regimens. Despite these advantages, CAV is still prevalent. Heart retransplantation is currently the only curative treatment. Google Scholar, PubMed, ClinicalKey, ScienceDirect, Elsevier, Wiley Online Library, and National Library of Medicine were used to compare current data on heart-conserving measures and heart retransplantation for CAV in the pediatric population. New drugs have become available that bear comparison with tacrolimus, such as everolimus and sirolimus. These drugs are shown to be more effective in long-term prevention and management of CAV than tacrolimus. Incorporating widely known drugs into treatment regimens, such as statins and aspirin, have been observed to have no effect on chronic rejection. Advanced technology has produced drug-eluting stents small enough for pediatric patients for short-term use as restenosis is inevitable. Heart retransplantation is inferior to heart-conserving measures as complications decrease life expectancy significantly more.

*Keywords: cardiac allograft vasculopathy, CAV, pediatric, heart retransplantation, everolimus, sirolimus, tacrolimus, aspirin, stent*

# Introduction

## Statement of the problem

Cardiac allograft vasculopathy (CAV) is a form of chronic heart rejection that affects over 50% of pediatric heart recipients within 10-15 years after transplantation (Khoury et al., 2022 & Pighi et al., 2020). The denervated heart leaves patients with a silent killer as they typically do not feel pain from this disease. Despite CAV being the most common post-operative complication causing morbidity and mortality, present-day treatment continues to have poor prognosis. The use of maintenance immunosuppressive therapy and statins are the current regimen. The only definitive treatment for CAV is retransplantation, though, this complication can still prevail thereafter. The main focus of therapy has shifted to prevention and early detection.

The gold standard diagnostic and surveillance tool for CAV is coronary angiography annually, and intravascular ultrasound (IVUS) being highly useful as well (Pighi et al., 2020). Current maintenance immunosuppression therapy for heart transplantation consists of triple therapy using calcineurin inhibitors (CNIs), such as tacrolimus, mammalian target of rapamycin (mTOR) inhibitors, such as everolimus (EVL) and sirolimus, cell-cycle inhibitors, such as mycophenolate motefil (MMF), and steroids (Costello et al., 2013 & Kim, Y. H., 2021). mTOR inhibitors have been observed to be the most effective in preventing and managing CAV (Pighi et al., 2020).

## Pathophysiology

Chronic rejection is defined as diffuse concentric narrowing with luminal stenosis. CAV is different from typical coronary artery atherosclerosis in that it is present in both the epicardial coronary arteries and the intramyocardial microvasculature. It is caused by antigen dependent

and antigen independent immune factors, as well as autoimmune factors (Costello et al., 2013) Arterial stenosis results from repeated alloimmune attack on the transplanted organ, leading to replacement of the normal parenchyma with scar tissue (Costello et al., 2013). It has been shown that other factors can contribute to CAV, such as lack of induction therapy post-transplant, early onset rejection, CMV infection, and classic cardiovascular risks factors like diabetes, hypertension, and hyperlipidemia (Khoury et al., 2022). However, immune factors are thought to be the most important cause of disease since CAV occurs in the donor arteries and not the recipient's (Costello et al., 2013).

Independent risk factors to chronic rejection include antibody-mediated rejection (AMR) and acute cellular rejection (ACR). "AMR is defined as the histologic evidence of capillary injury caused by humoral responses, the presence of positive immunoperoxidase staining, or immunofluorescence for CD68, C4d in endomyocardial biopsies, and the detection of circulating donor-specific antibodies" (Costello et al., 2013). "ACR is defined as the histologic recognition of an inflammatory infiltrate with the presence of cardiac myocardial damage in endomyocardial biopsy samples" (Costello et al., 2013). Patients who experience AMR have a higher incidence of death from cardiovascular causes, with a 9-fold increased incidence of CAV, than do patients who experience ACR (Kfoury et al., 2006).

**Research Question**

There is deficient evidence on therapy for chronic heart rejection in the pediatric population. It is undetermined what the most effective treatment is for this disease. Research has investigated tacrolimus therapy vs EVL or sirolimus therapy for the management of CAV. Early statin and aspirin therapy intervention after heart transplantation is doubted in efficacy. Percutaneous coronary intervention, typically used for CAD, has been studied for the treatment

for CAV in pediatric recipients. Heart retransplantation is the only definite cure for this disease, nevertheless, it comes with its own complications. The following literature review discuss whether heart-conserving measures, such as drug and stent therapy, are more effective than heart retransplantation for CAV in the pediatric population.

## Methods

The following databases were utilized to review the literature on CAV treatment options in the pediatric population: Google Scholar, PubMed, ClinicalKey, ScienceDirect, Elsevier, Wiley Online Library, and National Library of Medicine. The following terms were used to generate a search between the years 2017 and 2023: CAV, cardiac allograft vasculopathy, pediatric, treatment, heart retransplantation, everolimus, sirolimus, tacrolimus, stent. Studies older than 2017 were reviewed regarding stents in the pediatric population due to lack of more current supporting evidence. The search process unveiled 29 articles that were used for this literature review.

## Literature Review

### Efficacy of heart-conserving measures using medications in chronic heart rejection of pediatric population

Asante-Korang et al. (2017) performed a retrospective analysis on the data of 170 pediatric heart transplant patients performed at John Hopkins All Children's Hospital from January 1995 to December 2015 to determine the effects of conversion from calcineurin inhibitors to mTOR inhibitors as primary immunosuppressive therapy. Inclusion criteria consisted of patients who were initially converted to EVL or sirolimus as the primary medication along with MMF but had to discontinue MMF and resume tacrolimus at very low doses as a secondary medication due to rejection. Of the 170 patients, 44 were identified to have been

treated with EVL or sirolimus at some point after transplantation. Of those 44 patients, 19 were converted from calcineurin inhibitors to mTOR inhibitors as the primary immunosuppressant therapy. “The target trough levels of sirolimus and EVL were 4-10 ng/mL depending on the patient's target tacrolimus or cyclosporin trough levels prior to the switch. In patients who had severe bone marrow suppression, severe exfoliative rash, or debilitating mouth ulcers, the target levels of mTOR inhibitors were decreased to 4-6” (Asante-Korang et al., 2017). Each patient acted as their own control variable for this study. The median follow up was 28 months after conversion therapy was initiated.

There were four treatment failures in which debilitating rash, bone marrow suppression, recurrent rejection, and renal transplantation resulted in discontinuation. All 19 patients maintained stable CAV, with an ejection fraction ranging between 60%-77% ($p=<0.0001$). Furthermore, no new onset of CAV or malignancies were noted. There was significant improvement in GFR following the switch, with pre-GFR ranging between 17.8-180 and post-GFR ranging between 34.9-191.3 ($p=0.0004$). The results show that conversion from a CNI to a mTOR inhibitor as the primary immunosuppressant therapy for pediatric heart transplant patients may be a safe and appropriate strategy for long-term graft and patient survival (Asante-Korang et al., 2017). A large limitation to this study was the small sample size available.

Grimm et al. (2020) conducted a retrospective, observational single-center study at Klinikum Großhadern, Ludwig-Maximilians-University, Munich with 36 heart transplanted pediatric patients to assess the efficacy of conversion to an EVL therapy from a CNI (tacrolimus plus MPA/azathioprine) therapy. The endpoints were looking at the progression of CAV, cytomegalovirus (CMV), and renal function. The main indicator for conversion therapy was the diagnosis of CAV, however, diarrhea, new onset diabetes, post-transplant lymphoproliferative

disorder, blood count changes, and colitis were other indications. Inclusion criteria for this study was a conversion date up to and including December 31, 2012. Exclusion criteria was an EVL intake of less than two weeks. Twelve out of the 36 patients were clinically pre-diagnosed with CAV using intravascular ultrasound/optical coherence tomography (IVUS/OCT) and the Stanford grading. Symptoms analysis was completed six months, 1 year, and 2 years from conversion therapy.

Twenty-nine patients were present for analysis of renal function at the two-year follow-up, and nine patients with CAV were present for analysis for the two-year follow-up. Four patients showed no progression, three showed improvements, and one a worsening of CAV. An initial CAV diagnosis under EVL occurred in one of the cases. The average Stanford grade before and after the conversion showed no change. The average CrCl showed a significant improvement at 24 months in 29 patients with a pre-conversion of 99.20 +/- 31.00 and a post-conversion of 102.75 +/- 37.53 (p=.000). No new episodes of acute rejection or CMV infection were noted during the two-year period. It is important to disclose that conversion to EVL therapy decreased overall side effects, such as infection, change in blood count, and GI symptoms, from 193 to 99 (Grimm et al., 2020). This study provides evidence that the conversion to EVL therapy from CNI plus MPA/azathioprine therapy may have beneficial effects on the progression of CAV, improved renal function, and decreased CMV infections. A substantial limitation to this study is the small sample size, and the lacking follow-up data due to patients' inability to follow through with checkups (Grimm et al., 2020)

Fenton et al. (2018) performed a collaborative, cross-sectional study between Loma Linda University Children’s Hospital, California, USA (LLUCH) and Great Ormond Street Hospital NHS Foundation Trust, London, UK (GOSH) to investigate the clinical therapies

associated with CAV severity in the pediatric population at each institution within 2013. Inclusion and exclusion criteria were not available for this study. GOSH had a sample of 46 patients and LLUCH had a sample of 58 patients, with a total of 104 patients included for this study. Immunosuppressant therapy at GOSH consisted of basiliximab, tacrolimus, MMF, steroids, and pravastatin. At LLUCH, immunosuppressant therapy consisted of tacrolimus, MMF three months post-transplant switched to sirolimus four at months, and a statin for severe CAV disease with a Stanford Grade of III or IV. IVUS was used to detect and monitor CAV disease at both centers. This modality was performed at three months, one year after transplant, biennial thereafter at GOSH, and yearly after transplant at LLUCH. For this study, each individual patient had one IVUS imaging from the year 2013 considered for the data.

Significant differences were apparent in immunosuppressant therapy, with two patients at GOSH using sirolimus in comparison to 42 patients at LLUCH ($p=0.008$). Patients at GOSH had significantly worse CAV than patients at LLUCH ($p=<0.001$). These results indicate that with the use of sirolimus as part of immunosuppressant therapy, CAV disease is less severe than using other immunosuppressant protocols (Fenton et al., 2018). A large limitation to this study was the fact that the GOSH population had a significantly older donor age and time post-transplant than the LLUCH population (19.9+/-13.6, 3.8+/-7.8, respectively; $p=<0.001$). Emerging evidence from Fenton et al. (2018) suggests that older donor age and post-transplant time leads to inferior outcomes.

Watelle et al. (2023) conducted an international, multi-center, retrospective, observational cohort study using data from the Pediatric Heart Transplant Society to compare graft survival outcomes of monotherapy to multiple immunosuppressant therapy in the pediatric population. Frequently used drugs for monotherapy included tacrolimus, cyclosporine, sirolimus,

and EVL. The most common reason to use monotherapy in this case study was post-transplant lymphoproliferative disease. Inclusion criteria consisted of patients <18 years of age with more than one year follow-up data available between the years 1999 to 2020. The start of follow-up for the current analysis was at one-year post-transplant. A total of 3,493 patients were included for the study analysis. A total of 260 patients were already on monotherapy at the start of the analysis. There were 893 patients switched to monotherapy at least once during follow-up with the remaining 2,600 patients on more than two immunosuppressant drugs for their entire follow-up.

Monotherapy was found to be more favorable than multiple immunosuppressant therapy when looking at graft failure and CAV progression (p=0.006, HR 0.58, 95% CI: 0.45-0.74, respectively). This study showed evidence that monotherapy compared to multiple immunosuppressant therapy is significantly more protective for graft survival and CAV progression (Watelle et al., 2023). A limitation to this study was the exclusion of data of the first year after transplantation.

Rosenthal et al. (2021) conducted a retrospective analysis of all heart transplant patients <18 years of age between March 1997 and July 2020 at Charité Universitätsmedizin Berlin to evaluate the long-term efficacy and safety of CNI-free immunosuppression therapy in the pediatric population in terms of survival, graft function, and progression of CAV. Inclusion criteria consisted of patients who were >2 years after heart transplantation and had no signs of rejection or progressive CAV. Fifteen patients met inclusion criteria and underwent conversion from CNI-based to CNI-free immunosuppression therapy. CNI-free therapy was a combination of EVL (0.8-1.2 mg/$m^2$ BSA; 3-8 ng/ml trough levels) with MMF (30-50 mg/kg BW; 1.5-2.5

ng/ml trough levels). Each patient was investigated via angiography for the presence of CAV prior to CNI-free immunosuppression and at the last follow-up appointment. Patients had follow-up appointments every 1-3 months for an echocardiogram and every 1-2 years for a coronary angiogram, with increasing intervals if no rejection was detected. Three patients were transferred to another facility during the duration of the study; therefore, follow-up data were incomplete.

Fourteen out of 15 patients were alive at the time of publication (2021) with good graft function; median post-transplant age being 15 years. The one patient died from acute humoral rejection 15 years after transplantation. Angiograms and OCT were available in 12 of 15 patients showing no signs of CAV in any patient. This study suggests that a CNI-free immunosuppression regimen can be an effective and safe maintenance therapy for CAV in the pediatric population (Rosenthal et al., 2021). A limitation to this study was the small sample size, no control group, and inability to complete follow-up data for all patients.

Sirota et al. (2021) conducted a single-center, retrospective cohort study of pediatric heart transplant recipients cared for at Primary Children's Hospital (PCH) from January 1, 2002, through December 31, 2018, to understand the association between high tacrolimus variability and poor outcomes. Inclusion criteria consisted of patients <21 years of age, survived longer than one-year post-transplant, utilized tacrolimus as primary CNI, and had at least three trough levels. Exclusion criteria included patients that received a multi-organ transplant or had tacrolimus levels <3 ng/mL. Trough levels during the first-year post-transplant were not included due to goal changes to lower targets three times in the year. A total of 118 patients and 6,144 tacrolimus trough levels were included for analysis. Majority of patients were maintained with a tacrolimus goal level of 5-<9 ng/mL. Trough levels were collected every three months when post transplant was greater than one year.

Patients with increased tacrolimus variability developed CAV, required retransplant, or died (30% vs 13% in the low variability cohort). Older age at transplant was also correlated to an increased risk of CAV, retransplant, and death (p=0.021). This study showed evidence that high tacrolimus variability in pediatric heart transplant patients lead to poor outcomes when compared to low variability tacrolimus levels (Sirota et al., 2021). Limitations to this study include small sample size, change in institution tacrolimus protocol, and the decision to exclude tacrolimus levels within the first year of transplantation as this would provide valuable insight into long-term graft outcomes.

Zang et al. (2022) conducted a single-center, retrospective analysis of pediatric heart transplant patients to compare the impact of anti-thymocyte globulin (ATG) and basiliximab induction therapy against rejection, CAV, and post-transplant mortality between January 2010 and October 2017. Inclusion and exclusion criteria for this study was not available. A total of 96 patients were included for analysis of which 50 were started on ATG induction therapy (1-1.5 mg/kg/day IV for 3-6 days) and 46 started on basiliximab induction therapy (10 mg IV over 30 minutes). "The immunosuppressive maintenance regimen consisted of tacrolimus, mycophenolate mofetil/azathioprine, and/or prednisone. Serum tacrolimus trough levels were maintained at 10–15 ng/ml for the first 6 months after transplantation and then 5–10 ng/ml after that. Doses of mycophenolate mofetil (600 mg/m$^2$/day) and azathioprine (1−2 mg/kg/day) were adjusted based on total white blood cell counts" (Zang et al., 2022). A follow-up appointment occurred within one year after induction therapy.

It was found that basiliximab was correlated with increased incidence of rejection when compared to ATG (p=0.022). There was no significant difference between the two groups when analyzing the risk of CAV (p=0.275). The incidence of death did not differ significantly between

the two groups (p=0.343). This study provides supporting evidence that ATG induction therapy is associated with a lower incidence of rejection than basiliximab induction therapy. It was also observed that there is no significant difference in the overall mortality and CAV incidence when comparing ATG or basiliximab induction therapy (Zang et al., 2022). Limitations of this study include small sample size, and the lack of randomization of patient groups.

Greenway et al. (2016) conducted a retrospective review of 964 pediatric heart transplant patients ages five to 18 years of age in the multi-center Pediatric Heart Transplant Study registry from 2001 to 2012 to observe the effects of statin therapy on CAV. Inclusion criteria consisted of patients who received a statin within the first-year post-transplant (n=317). Exclusion criteria consisted of patients undergoing retransplantation, survived <1 year post transplant, or had missing data regarding statin use. The control group consisted of patients that did not receive statin therapy within the first-year post-transplant (n=647). There was no significant difference in overall survival up to 10 years post-transplant with statin therapy compared to non-statin therapy (p=0.34). There was no significant difference between statin and non-statin therapy when assessing the incidence of any degree of CAV (p=0.48). This study suggests that statin therapy is not associated with improved survival or decreased incidence of CAV in the pediatric population (Greenway et al., 2016).

D'Addese et al. (2022) performed a retrospective analysis of the pediatric heart transplant society database (1996-2019) which included 3,011 patients <17 years old that were at least 3 years post heart transplant without evidence of CAV. The objective was to determine the impact of early aspirin (ASA) use on the development of CAV and overall graft survival. Of the 3,011 patients, groups were defined based on ASA use at the time of three years post-transplant: 387 continuous ASA use, 676 intermittent ASA use, and 1,948 receiving no ASA. Across the three

groups, 451 patients developed CAV in varying severities during the study period of 10 years. The severity was defined by Grade 1, 2, 3; 1 being less severe, 3 being more severe.

The continuous ASA therapy showed worse prevention from CAV compared to other groups ($p=0.002$). However, grade 3 CAV was less common in the continuous ASA group compared to intermittent and no ASA groups ($p=0.003$ and $p=0.02$, respectively). Overall, the continuous ASA group demonstrated worse graft survival compared to the other groups ($p<0.001$). This study was unable to show a beneficial effect of early ASA use in preventing CAV or graft failure in the pediatric population. A major limitation of this study was the inability to keep a constant continuity of treatment or timing of aspirin use throughout the study (D'Addese et al., 2022).

**Efficacy of heart-conserving measures using stents in chronic heart rejection of pediatric population**

Schneider et al. (2013) conducted a retrospective review of five pediatric patients who underwent percutaneous coronary intervention for CAV at the Mayo Clinic, Rochester, between 2004 to 2012 to evaluate post-procedure outcomes. The inclusion and exclusion criteria were not available. A total of eight stents, including six drug-eluting stents, were placed among the five patients. The non-drug-eluting stents were defined as bare metal stents. The drug-eluding stents were covered with sirolimus (four stents), EVL (one stent), and paclitaxel (one stent). The mean follow-up time was 2 (0.6-5.5) years post-procedure.

Angiographic evidence of restenosis was observed in two patients, occurring three- and 15-months post-procedure, which lead to retransplantation and death, respectively. The paclitaxel and bare metal stents, respectively, were used in the two patients. Restenosis occurred in each individual despite use of aspirin and clopidogrel. This study states that it is unclear whether drug-

eluting stents improve the time course between palliation efforts when compared with bare metals stents in the pediatric CAV population. Schneider et al. (2013) suggests that percutaneous coronary intervention should be used as palliative treatment in CAV to bridge to retransplantation in the pediatric population. Limitations to this study include lack of quantitative data, small sample size, and limited length of follow-up.

Alam et al. (2020) follows a case study of a 12-year-old male who underwent drug-eluting stent angioplasty five years post-transplant due to CAV. The patient's post-transplant regime included basiliximab, tacrolimus, MMF, prednisolone, aspirin, statins, and prophylactic antifungals. Despite this treatment, the patient developed grade III CAV in the left anterior descending coronary artery (LAD), right coronary artery (RCA), and left coronary artery (LCA) after five years. A stent angioplasty of the proximal and mid LAD was completed using Resolute Onyx. A six month follow up showed patent stent and mild progression in the left circumflex and right coronary artery lesions. The patient remained asymptomatic at one year follow up and doses of sirolimus and dual anti-platelet therapy was added to prevent stent thrombosis. This case study suggests that drug-eluting stent angioplasty offers a less invasive, short term treatment option for localized CAV in the pediatric population. Though, its efficacy is similar to a heart retransplantation (Alam et al., 2020).

Turner et al. (2016) conducted a retrospective chart review at the Columbia University Medical Center from January 1, 2005, to December 31, 2014, for pediatric heart transplant patients who underwent percutaneous coronary intervention for CAV treatment to evaluate post-procedural outcomes. There were 23 coronary interventions performed in 13 patients during the study. The stents used in two cases were bare metal, and the remaining cases used drug-eluting stents (type of drug was not specified). All patients had moderate to severe CAV, determined by

angiography, before intervention. The follow-up period was defined as the time from initial intervention through March 31, 2015, with an average of 10.4 months.

One patient was retransplanted post-procedure and one patient died shortly after the procedure. Nine of the remaining 11 patients had evidence of restenosis at the first follow-up. Five patients out of the 11 were retransplanted at a median time of 5.7 months after intervention. The median retransplant-free survival was determined to be 16 months. This study showed evidence that percutaneous coronary intervention for CAV in the pediatric population is only useful short-term as there is a high rate of disease progression and graft failure post-procedure (Turner et al., 2016). Limitations to this study include small sample size and the generalizability in CAV in which each patient and each lesion may be different.

Jeewa et al. (2015) conducted a multi-institutional review of the Pediatric Heart Transplant Study data to evaluate the association between percutaneous revascularization procedures and outcomes in CAV after heart transplant in the pediatric population between 1993 and 2009. The type of coronary artery intervention used within this study was either balloon angioplasty or stent placement. Patients <18 years of age who have moderate to severe CAV post-transplant were included in this study. Patient who had not gone under angiography prior to the study were excluded. Outcomes of revascularization were divided into two categories: short-term and long-term. Short-term outcomes included procedural success and complication rates. Long-term outcomes include survival after intervention and/or graft loss secondary to retransplantation or death. A total of 28 patients had a revascularization procedure performed before the age of 18, 21 of which received stent implantation and 7 undergoing balloon angioplasty.

Of the 28 patients who had the procedure done post-transplant, 13 were retransplanted and 8 died. Patients who did undergo revascularization procedures had worse early graft survival after the procedure compared with children with moderate to severe CAV who did not undergo revascularization, with more comparable graft survival beyond 6 years ($p=0.0001$). It was found that there is a significant mortality risk for pediatric patients with moderate to severe CAV with a 50% mortality within two years. This study showed that percutaneous revascularization procedures in pediatric patients with CAV have short-term success rates with negative impact on long-term graft survival among patients one year after intervention (Jeewa et al., 2015). Limitations to this study were the lack of detail on the type of stent used for intervention, a quantitative or qualitative measure on CAV before and after the procedure, and small sample size.

Hirose et al. (2023) follows a case study of a two-year-old pediatric patient who underwent heart transplantation due to cardiomyopathy. This patient developed severe CAV (90% blockage) in the LAD nine years post transplantation despite the use of tacrolimus and EVL treatment. Dual anti-platelet therapy consisting of aspirin 100 mg and clopidogrel 75 mg were initiated daily prior to intervention. A paclitaxel coated balloon was selected for minimizing blockage of the LAD. A seven month follow up revealed no restenosis of the previously blocked artery, low risk for emboli, and dual anti-platelet therapy was discontinued. This case study shows supporting evidence of drug-coated balloons versus drug-eluting stents for treatment of CAV in the pediatric population. Preference of drug-coated over drug-eluting is due to the major problem of restenosis after drug-eluting procedures. These findings indicate that drug-coated balloons may be an effective treatment option for localized CAV in the pediatric population (Hirose et al., 2023).

Shaddy et al. (2000) followed three pediatric patients who underwent coronary artery intervention as palliative treatment for CAV as they awaited heart retransplantation. Initial transplant occurred at age 5, 12, and 16, and the time post-transplant to develop severe CAV was 7, 6, and 2 years, respectively. A Cook Gianturco-Rubin 2 stent for larger vessels and AVE Micro stents for smaller vessels were placed via catheterization. Patient 1 had a stent placed in the left anterior descending coronary artery and is currently awaiting retransplantation. Patient 2 had a stent placed in the left anterior descending coronary artery, the left circumflex coronary artery, and second diagonal artery of which all demonstrated restenosis, as well as new stenosis lesions. Patient 2 eventually underwent retransplantation. Patient 3 had a stent placed in the right coronary artery and truncation of the left coronary artery leading to retransplantation four months after coronary intervention. The two patients that underwent retransplantation demonstrated severe luminal narrowing with intimacy thickening in the coronary arteries in the explanted hearts. This report shows evidence that pediatric heart transplant patients can undergo coronary interventional procedures for palliative treatment for CAV while awaiting retransplantation. Short-term outcomes are valuable; however, long-term outcomes are not favorable (Shaddy et al., 2000). Limitations to this study include lack of quantitative data and small sample size.

Desai et al. (2021) follows a case study of an eight-year-old female that used the first Flash ostial system for managing CAV in the pediatric population. This catheter is designed to conform to the ostium during stent post-dilatation and angioplasty, allowing for apposition and stability. The medical history and post-transplant regime for the patient was not discussed within the case study. This patient was diagnosed using IVUS with severe ostial left main coronary artery stenosis after an acute graft rejection episode. It was decided to use the Flash ostial system

to place a stent for intervention. A Xience 4.5 X 15 mm stent was deployed using the Flash into the ostial left main coronary artery.

Graft function improved after the procedure, and the patient was discharged on dual anti-platelet therapy with aspirin and clopidogrel. The patient continues to do well and follows up in outpatient clinic. It is noted that restenosis is inevitable in this case, and management will be technical and highly dependent on the patient's presentation (Desai et al., 2021). While this case provides supporting evidence for treatment of CAV using the Flash ostial system, it lacks in pre- and post-operative data. The past medical history and treatment leading up to the procedure was not available. Specific data on the outcome and follow up of the patient was not provided.

**Efficacy of retransplantation in chronic heart rejection of pediatric population**

Barghash and Pinney (2019) reviewed candidacy, outcomes, and management of heart retransplantation in the pediatric population using data from the International Society for Heart and Lung Transplantation and the Organ Procurement and Transplantation Network. It was found that the median age of retransplantation is at 14 years with a mean interval of 6.8 +/- 5.1 years after primary transplant, with the majority of indications for retransplantation being CAV. Pediatric retransplant patients were more likely to develop hypertension, hyperlipidemia, renal dysfunction, increased graft failure, graft rejection, and CAV compared to primary pediatric transplant patients. It was determined that early survival rates were similar between primary transplant and retransplant patients (1-year survival 84% primary transplant, 81% retransplant; 5-year survival 72% vs 63%), however, late mortality risk was higher with retransplant patients versus primary transplant patients (10-year median survival 60% vs 46%, 20- year survival 42% vs 26%) with a median survival of 15 years in primary transplant patients versus 7.3 years in retransplant patients. The rates of malignancy were shown to be comparable between primary

transplant and retransplant. While rates of infection, rejection, and malignancy are similar between the two groups, heart retransplantation remains an inferior long-term option for CAV pediatric patients who are not in critical condition requiring ICU, ventilator, or ECMO (Barghash & Pinney, 2019).

Zhu et al. (2022) conducted a retrospective analysis at Stanford University and Lucile Packard Children's Hospital from January 6, 1968, to June 2019 to evaluate the outcomes of pediatric heart retransplantation. This study included both adult and pediatric patients who received primary and secondary transplantation. Inclusion and exclusion criteria were not available. Eleven pediatric patients were included in the retransplantation group. It was not stated how many pediatric patients were in the primary transplantation group. The indications for heart retransplantation were CAV (75%) and graft dysfunction (25%). The average length of follow-up was 4.8 +/- 5.7 years reflected by the median survival of 4.6 years after retransplantation.

Patients who underwent retransplantation within one year after primary transplantation demonstrated worse long-term survival than those who underwent retransplantation between one, five, or greater than 5 years after primary transplantation ($p=<0.0001$). This study suggests that pediatric heart retransplantation within the first year after primary retransplantation should only be considered for select patients as it demonstrates poor graft survival outcomes (Zhu et al., 2022). Limitations to this study include lack of inclusion and exclusion criteria for population analysis, lack of immunosuppressant regimen before and after transplant, and small sample size.

Kennedy et al. (2022) conducted an analysis of the United Network for Organ Sharing database to identify pediatric patients who are more likely to benefit from heart retransplantation. Inclusion criteria consisted of patients who were <18 years of age and underwent retransplantation between 1987 and 2020. A total of 9,993 patients were included in the primary

transplantation group and 782 patients in the retransplantation group. The most common reason for retransplantation was CAV.

The median graft survival was longer for primary transplant patients than it was for retransplant patients (p=0.0083). The median graft survival was no longer significant if the interval between primary and secondary transplantation was greater than 12 months (p=0.0602). If secondary transplantation took place within 12 months of primary transplantation, the median graft survival dropped to 15 months (HR = 2.32; 1.7-3.2). This analysis showed that graft survival is significantly shorter following retransplantation when compared to primary transplantation in the pediatric population. However, there are multiple patient cohorts in which retransplantation survival is equivalent to primary transplantation survival, such as being one year out from primary transplant (Kennedy et al., 2022).

Alvarez et al. (2022) conducted a multivariate analysis of the Pediatric Heart Transplant Society database to determine if there has been an era effect on outcomes of heart retransplantation in the pediatric population. The eras were determined as such: Era 1 (1993-2001), Era 2 (2002-2010), and Era 3 (2011-2018). Inclusion criteria for this analysis consisted of patients who received a primary and secondary transplant <18 years of age between January 1993 to December 2018 from 32 centers in four countries. Secondary transplantation was due to CAV (62%), non-specific graft failure (21%), and rejection (12%). A total of 6,779 patients were included of which 6,548 were primary transplants and 222 were secondary transplants. Of the secondary transplant recipients, 30 were in Era 1, 90 in Era 2, and 102 in Era 3.

> Graft survival was 84%, 64%, 44%, and 40% at 1, 5, 10, and 15 years, lower compared to primary transplants (90%, 79%, 68%, and 57%; p< .0001). The median survival was 9.3 years compared with 20.2 years for primary transplant. There was an increase in graft

> survival at 1, 5, 10, and 15 years from Era 1 (67%, 43%, 18%, and 12%) to Era 2 (90%, 68%, 51% and 51%; $p < .0001$). There was no significant change from Era 2 to Era 3 with a survival of 85% and 68% at 1 and 5 years post-retransplant ($p = .95$). Freedom from CAV in the retransplant cohort was 99%, 80%, 61%, and 39% at 1, 5, 10, and 15 years which was worse compared to primary transplants ($p< .0001$) but showed no significant differences between eras. Freedom from infection in the retransplant cohort was 70%, 49%, 28%, and 24% at 1, 5, 10, and 15 years which was worse compared to primary transplants ($p = .04$). (Alvarez et al., 2022)

This analysis shows that overall graft survival after pediatric heart retransplantation has improved over time, however, post-transplant morbidities have not improved. It was also found that post-transplant morbidities are more common after retransplantation than after primary transplantation. Retransplantation should be offered to appropriately selected patients in the setting of early graft failure (Alvarez et al., 2022). A limitation to this study was the loss of follow up due to transfer to another institution.

Azeka et al. (2020) conducted a retrospective cohort study to compare the outcomes in pediatric patients who have undergone both primary heart transplantation (PTx) and a subsequent retransplantation (RTx) indicated by CAV at the Heart Institute University of São Paulo Medical School between 1992 and 2018. Inclusion criteria for this study were those who had been diagnosed with CAV and also underwent RTx. Exclusion criteria was not available. The immunosuppressant therapy of these patient pre-RTx was cyclosporine and tacrolimus. It was found that 200 children underwent PTx, with seven RTx performed due to CAV progression.

Four of the seven patients suffered a rejection episode within the first year of RTx. Of these seven patients, three died within 5 years of RTx due to either infection, multiple organ

failure, or sudden death. Median survival post-RTx was determined to be 3.3 years, with a survival rate at one month 85.7%, three years 71.5%, and 5 years 47.6%. With the data of the 200 PTx patients, it was concluded that the probability of freedom from relisting for RTx at 3-, 5-, 10-, 15-, 20-, and 25- years was as follows: 99.0%, 96.8%, 90.6%, 68.5%, 59.9%, and 48%. Azeka et al. (2020) believes the freedom from RTx was influenced by the institution's change in immunosuppression regimen to sirolimus over the course of the study. This research found that rejection episodes were more common after RTx than PTx, but the difference was insignificant. Cardiac RTx can be a management option for CAV in the pediatric population, however long-term complications of RTx need to be analyzed further with a larger sample size (Azeka et al., 2020). A limitation to this study was the lack of qualitative data provided, such as p-values.

## Discussion

A limited amount of data comparing the efficacy of heart-conserving measures and retransplantation for chronic rejection in the pediatric population has emerged in the past decade. It has been observed that mTOR inhibitors, such as EVL and sirolimus, as the primary immunosuppressant agent may have more beneficial effects in CAV management than calcineurin inhibitors, such as tacrolimus (Asante-Korang et al., 2017). EVL and sirolimus as the primary agent showed less severe disease, improved renal function, and fewer rejection episodes than tacrolimus in the long term (Grimm et al., 2020 and Fenton et al., 2018). Patients converted from tacrolimus to EVL showed significant improvement in CAV severity as well. High trough levels of tacrolimus have been shown to not be preventative in CAV development and manifest worsening of disease (Sirota et al., 2021). Low trough levels of tacrolimus are preferred, however, mTOR inhibitors still prevail as primary immunosuppressive agent. Monotherapy as a

whole was shown to be more protective against graft failure and CAV than multiple immunosuppressant therapy (Watelle et al., 2023).

Other heart-conserving regimens studied to prevent and manage CAV show that ATG induction therapy is no more effective for treatment of CAV than basiliximab induction therapy (Zang et al., 2022). Both therapies revealed similar CAV incidence and overall mortality rates. It is important to note that basiliximab did show higher rates of rejection that ATG. Statin therapy was not effective in the prevention or management of CAV as non-statin therapy seemed to have similar effects (Greenway et al., 2016). Early use of ASA was also shown to not be effective when compared to no ASA therapy (D'Addese et al., 2022).

Drug-eluting stents implanted by percutaneous coronary intervention were observed to be useful as a short-term, palliative treatment in pediatric CAV management (Alam et al., 2020, Desai et al., 2021, Hirose et al., 2023 Jeewa et al., 2015, Schneider et al., 2013, Shaddy et al., 2000, and Turner et al., 2016,). It is undetermined if drug-eluting stents are more effective than bare metal stents. However, this method is typically used as a bridge to transplant as the long-term effects are not favorable with restenosis being inevitable.

Heart retransplantation was observed to be an inferior long-term option for the treatment of CAV in the pediatric population. Patients that had undergone retransplantation were more likely to develop morbidities, increased graft failure/rejection, and develop CAV once again when compared to primary transplant patients (Barghash and Pinney, 2019 and Alvarez et al., 2022). Graft survival is significantly shorter for retransplantation than it is for primary transplantation, especially if retransplantation occurs within the first 12 months after the primary transplantation (Kennedy et al., 2022). It is possible that the post-retransplant immunosuppression regimen could affect graft survival duration, however, primary

transplantation still proves to be superior. Heart retransplantation should only be recommended as treatment for CAV in the pediatric population for patients in critical condition requiring ICU support, such as a ventilator or ECMO.

These recent findings have begun to provide insight into an updated protocol for chronic rejection in the pediatric population. Limitations to past studies include small populations, short trial duration, and limited follow-up availability. This suggests researchers know relatively little about the effects of heart-conserving measures and retransplantation in the long term. To produce the most effective treatment for CAV, more pediatric patients must be properly followed for a longer duration. While the current data suggest heart conserving measures are superior to retransplantation, it would be beneficial to see the impact throughout the patient's lifetime. Future research could potentially focus on these interventions on a larger group of individuals for an extended period of time, preferably longer than five years. Such data could put into greater perspective how heart-conserving measures and retransplantation prevent and manage chronic heart rejection in the pediatric population.

## Conclusion

Chronic rejection is the leading cause of morbidity and mortality among the pediatric population following heart transplantation. Current regimens using immunosuppressants and statins are insufficient in treating CAV long-term. The only definitive treatment is heart retransplantation. Research suggests that the use of heart-conserving measures is more effective in treating CAV than heart retransplantation in the pediatric population. mTOR inhibitors have been shown to prevent and manage chronic rejection more successfully than calcineurin inhibitors. Statin and ASA therapy seem to have no effect on CAV severity. Drug-eluting stents are an adequate short-term option for CAV, with restenosis being inevitable. Heart

retransplantation is curative by nature, though, it comes with its own complications. Comorbidities and graft failure/rejection are more common in retransplantation, as well as the concern for CAV returning in the new organ. Heart-conserving measures should be investigated further with larger populations for extended periods of time to measure the efficacy of prevention and management of CAV in pediatrics.

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