Received: 21 November 2017 | Revised: 18 May 2018 | Accepted: 21 May 2018

DOI: 10.1111/chd.12629

ORIGINAL ARTICLE

WILEY Congenital Heart Disease

Coronary artery intimal thickening and ventricular dynamics in pediatric heart transplant recipients

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Acknowledgments
We wish to thank Lindsey Williams, Rosalie Gu, Stephanie Duncombe, and Paige Dean for their assistance in preparing the data for this manuscript.

Funding
This work was funded by a Venture Grant from the Transplant Research Foundation of British Columbia.

Abstract

Objective: Pediatric heart transplant recipients are at risk of posttransplant coronary artery disease known as cardiac allograft vasculopathy (CAV), and also may develop diastolic dysfunction. As CAV begins with a process of progressive intimal thickening, these occult diffuse changes may be detected using optical coherence tomography (OCT). We hypothesized that the development of CAV, as identified via OCT, may be a mechanism of declining ventricular function. Accordingly, the purpose of this study was to assess coronary artery intimal thickening and LV strain in children who have undergone heart transplantation.

Methods: In 17 children, we analyzed OCT images for coronary intima and media thickness, and cross-sectional area (CSA). We also performed speckle tracking imaging (STI) of the LV to determine longitudinal strain and strain rate, in addition to standard echocardiographic measures.

Results: Longitudinal diastolic strain rate was associated with maximum intima thickness ($r = -.497$, $P = .042$), intima CSA, ($r = -.489$, $P = .047$), maximum media thickness ($r = -.503$, $P = .039$), and media CSA ($r = -.614$, $P = .009$). The intima maximum thickness, intima/media, and intima/lumen ratios were associated with stroke volume index (Std. $\beta = -0.487$, $P = .023$ and Std. $\beta = -0.488$, $P = .022$, respectively).

Conclusions: These findings suggest coronary artery intimal thickening may be mechanistically linked to changes in ventricular function following cardiac transplantation.

KEYWORDS
coronary artery, heart transplantation, left ventricular strain

1 | INTRODUCTION

Heart transplantation has greatly improved life expectancy for children with critical heart disease in whom standard medical and surgical therapies have failed. Approximately 60% of pediatric heart transplant recipients now survive more than 10 years posttransplant.[1] Improvements in immunosuppressive agents have played an important role in improving the health and longevity after heart transplantation; however, they have been implicated as a contributor to the development of cardiac allograft vasculopathy (CAV).[2] Characterized by an accelerated, progressive coronary artery intimal thickening, CAV is independent of acute allograft rejection, and is considered a form of chronic rejection.[3] One in 4 pediatric heart transplant deaths are attributed to CAV, which affects approximately 50% of children by 15 years posttransplant.[4–6] Unfortunately, CAV is typically identified at an advanced stage and treatment options are limited, hence CAV is a clinical indication for retransplantation.

Conventional angiography is the accepted gold standard for evaluating pediatric heart transplant recipients for CAV.[7] Yet, angiography has poor sensitivity to detect early structural changes in

the coronary arteries because it can only identify the narrowing of the lumen.[8] Given that CAV begins with a process of progressive intimal thickening these occult diffuse changes may be missed with the current standard diagnostic approach. In an effort to improve early detection of CAV, intravascular imaging modalities have been used recently in heart transplant recipients.[9-12] For example, intravascular ultrasound (IVUS) has been used in adults to improve early identification of coronary changes and has shown prognostic utility.[9] An alternative method for intravascular imaging is optical coherence tomography (OCT). OCT has theoretical benefits in children given the small catheter size and the potential to use a smaller sheath in young children. OCT has been used to characterize intimal thickening in adult heart transplant recipients, and has shown promise to detect early changes consistent with CAV posttransplant.[11] Recently, we have demonstrated the feasibility of OCT in children, and we demonstrated that pediatric heart transplant recipients have a high prevalence of intimal thickening in the coronary arteries that is angiographically silent.[10]

The coronary vascular properties are an important determinant of cardiac performance. A reduction in coronary blood flow due to CAV may impair myocardial function as oxygen supply to myocardial cells is mainly dependent on the volume of coronary blood flow.[13] Evaluation of LV mechanics using speckle tracking imaging (STI) may provide insight into the extent of CAV development in young heart transplant recipients.[14] Resting longitudinal strain is lower in pediatric heart transplant recipients relative to control children,[15,16] and decreased left ventricular (LV) strain has been observed during acute allograft rejection.[15] More recently, retrospective analyses in pediatric patients have demonstrated greater reductions in longitudinal strain in the 2 years prior to a CAV diagnosis.[17,18] Thus, it is plausible that the early stages of CAV development (intimal thickening) may be identified in association with myocardial function identified by STI. Accordingly, the purpose of this study was to assess the association between intimal thickening and LV strain in children who have undergone heart transplantation.

2 | METHODS

2.1 | Study population

Ethical approval was obtained by the University of British Columbia's Clinical Research Ethics Board. We identified eligible heart transplant recipients evaluated at our clinic at British Columbia Children's Hospital (Vancouver, Canada), who had undergone both OCT imaging of the coronary arteries as part of clinical management, and standard resting echocardiography between September 2012 and September 2016. Patient demographics (age, sex, height, weight, blood pressure) were obtained from patient charts relevant to the time of OCT imaging. In addition, clinical characteristics were also noted such as time since transplantation, medications, comorbidities, episodes of acute rejection from biopsy results (defined as ISHLT ≥ 2R),[19] and diagnosis of CAV by angiography.

2.2 | Imaging

Echocardiographic assessments were performed by a clinical pediatric sonographer, using a Vivid System (GE Vingmed or Vivid Ultrasound, Horten, Norway) and 3.5-MHz transducer. M-mode images were acquired in the parasternal short axis view for the assessment of LV dimensions, and 2D images in the parasternal long-axis view and apical four-chamber views were acquired to measure the diameter of the aortic annulus and aortic Doppler flow, respectively. Peak aortic velocity (PAoV), the velocity–time integral (VTI), and ejection time (ET) were obtained and recorded. Apical two- and four-chamber views were acquired at frame rates between 50 and 70 frames per second. Three consecutive cardiac cycles were recorded.

OCT imaging (Ilumien Optis System, LightLabs, St. Jude Medical, Westford, Massachusetts) was performed in addition to selective coronary angiography, in one or more coronary arteries at the time of routine cardiac catheterization. A guide catheter is positioned in the coronary lumen and the imaging catheter is advanced over a coronary wire to image the proximal and middle segments of the vessel of interest. We have previously published the details of two modifications we have made to the usual OCT protocol used in adults, for use of this technique in children.[10] The addition of OCT imaging adds approximately 10 min to routine surveillance by angiography.

2.3 | Data analysis

Anthropometric measures were used to calculate body surface area (m^2), body mass index relative to age- and sex-specific norms (BMI z-score),[20] and systolic and diastolic blood pressure relative to age-, sex-, and stature-specific percentiles (SBP z-score; DBP z-score).[21]

2.3.1 | Echocardiography

Ventricular volumes, dimensions, and function were analyzed offline (EchoPAC, GE Healthcare, v. 110.1.1). Left ventricular mass was determined using the Devereaux formula and indexed to height $(m)^{2.7}$. Stroke volume was determined from the Doppler signal using the velocity–time integral and aortic cross-sectional area (π x aortic diameter^2/4) and indexed to BSA (SVI). Cardiac index (CI) was calculated as the product of SVI and heart rate. Fractional shortening (FS) was calculated from ventricular dimensions during systole and diastole using the parasternal long-axis window and expressed as a percent. Mean velocity of circumferential fiber shortening (MVCFc, circ/s) was calculated as the product of FS and ejection time corrected for heart rate. Figure 1 illustrates the STI analysis of LV strain, and strain rate parameters.[22]

2.3.2 | OCT imaging

OCT images were included in this analysis if ≥1cm of the coronary vessel imaged was analyzable. We identified ≥10 cross-sectional

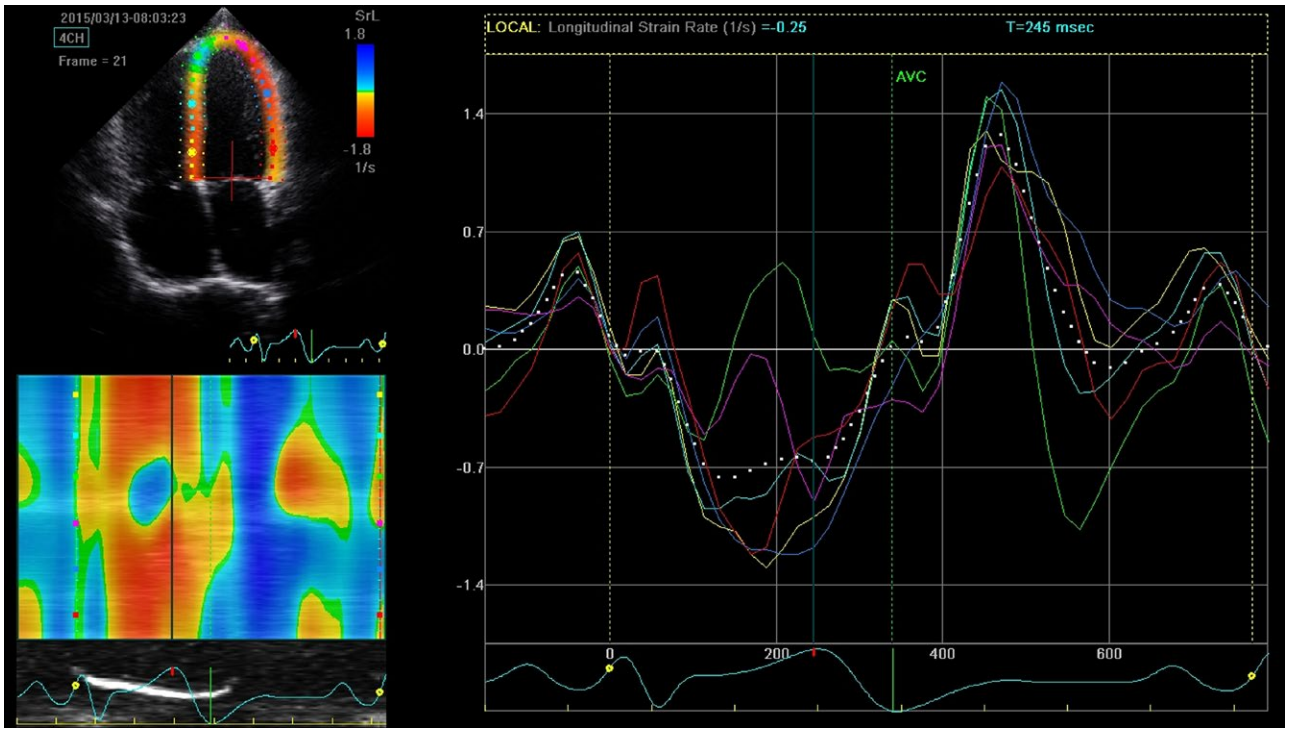

FIGURE 1 Speckle tracking of the left ventricle (left) and STI analysis (right) for one subject (male, 16 years old, 15 years since Tx) illustrating global strain rate (white dotted line) and regional strain rate (colored lines)

frames that were ≥5 frames (1 mm) apart and had no or minimal artifact or side-branches (<25%).[23] Using digital planimetry, we measured lumen, intima and media cross-sectional areas (CSA; mm^2), as well as maximal intima and media thickness (mm) for each frame (Figure 2). We calculated median values for each vessel to minimize undue influences of spurious data points. Where a vessel was imaged more than once, we calculated median values based on two image sequences. We calculated intima/media CSA ratio (I/M) and intima/lumen ration (I/L), and intima CSA to LV mass index.

2.4 | Statistical analyses

Dependent variables were assessed for normality using the Shapiro–Wilks statistic and nonparametric tests were used for those variables that were not normally distributed. Pearson (or Spearman) correlation coefficient was used to assess the effects of time since transplant on OCT and strain variables depending on normality. Linear regression models were used to determine the association between coronary and cardiac variables with adjustments for age, sex, and/or height, as appropriate for the given dependent variable (only one variable incorporated into the models at one time). Multicollinearity was assessed. The alpha level for statistical significance was set a priori at $P = .05$. Statistical analyses were conducted using SPSS software version 20.0 (IBM, Armonk, New York). Patient characteristics, cardiac, and coronary variables are presented as the median and 25th, 75th percentiles unless stated otherwise.

3 | RESULTS

Seventeen patients (6F; 7-17 y) were included in this study. The clinical characteristics for the patients are provided in Table 1. All patients were asymptomatic at the time of assessment, and no episodes of rejection had occurred in the year prior to testing. None of the patients were diagnosed with CAV based on angiography. Renal dysfunction (35%) and hypertension (24%) were the most common comorbidities.

Two hundred seventeen OCT images were analyzed. Echocardiographic variables are shown in Table 2. The standard echocardiographic measures of systolic function were normal, while the longitudinal strain values were lower than normal values published for children and youth.[22] Only 4 patients displayed longitudinal strain values within these norms. Coronary artery dimensions for the group are shown in Table 3. Figure 2 represents two sample OCT images, illustrating the variation in thickening that may be observed in patients with normal selective coronary angiography. Correlational analysis revealed diastolic strain rate was associated with LV mass ($r = -.491$, $P = .045$), and LV mass was positively associated with age ($r = .590$, $P = .013$). Since age and height were highly correlated ($r = .878$, $P < .001$), only one of these covariates could be applied to the linear regression models at one time. Only systolic strain rate was associated with heart rate ($r = -.534$, $P = .027$). As shown in Figure 3, linear regression analysis revealed associations for diastolic strain rate and maximum intima thickness ($r = -.497$,

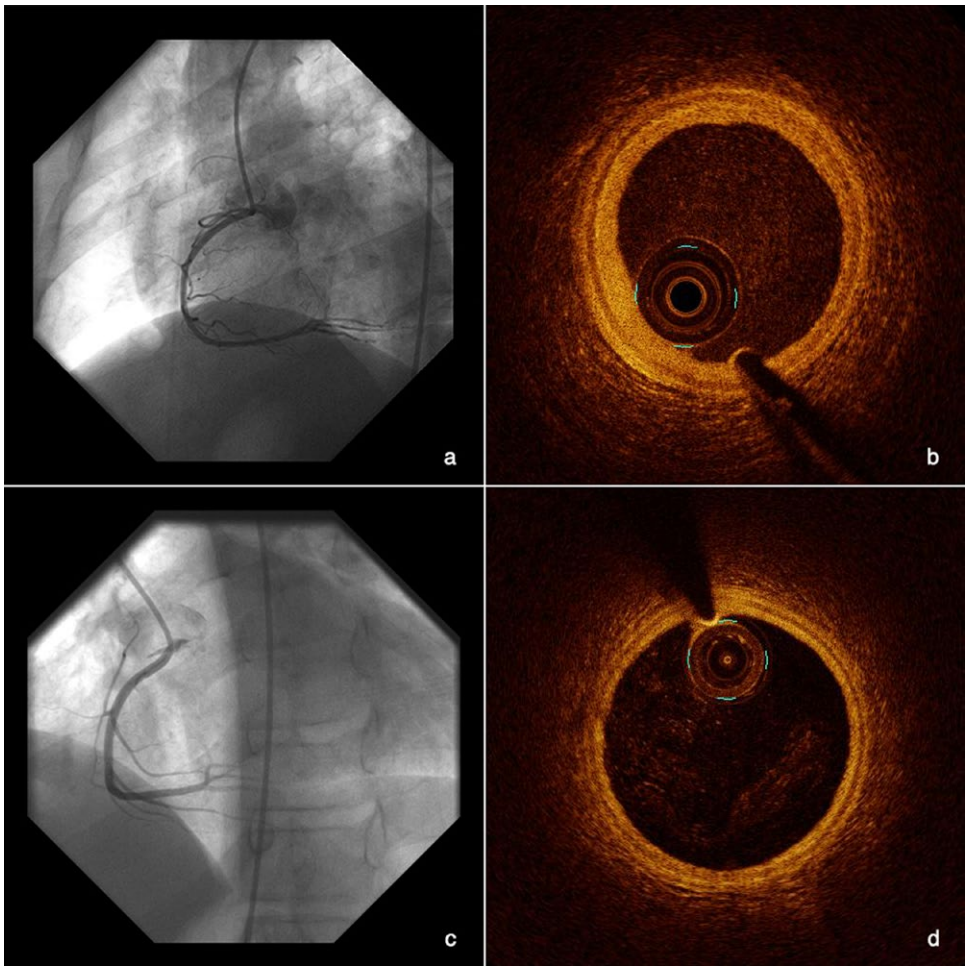

FIGURE 2 Selective coronary angiography of the RCA in a patient with intimal thickening (A and B), and in a patient with normal intimal thickness (C and D)

P = .042), intima CSA, (*r* = −.489, *P* = .047), media thickness (*r* = −.503, *P* = .039), and media CSA (*r* = −.614, *P* = .009). Inclusion of covariates of age, height, sex, or heart rate, did not affect these relationships. The maximum intima thickness, I/M, and intima/lumen ratios were associated with stroke volume index (Std. β = −0.487, *P* = .023 and Std. β = −0.488, *P* = .022, respectively) with a significant effect for sex in each model (*P* = .013, *P* = .027, and *P* = .030, respectively). As a means to control for body size (ie, relative growth) the intima CSA relative to LV mass was assessed using a linear regression model controlling for height and time since transplant. This model explained 47% of the variance in SVI (Std. β = 0.603, *P* = .017). Reductions in longitudinal strain and diastolic strain rate were associated with increasing age (Figure 4).

4 | DISCUSSION

This study presents novel findings of an association between coronary vascular structure and ventricular function in pediatric heart transplant recipients. Evidence of intimal thickening in association with early indicators of impaired cardiac function supports our hypothesis that changes in coronary structure may be mechanistically linked to diastolic dysfunction often reported in heart transplant recipients,[24] although these results do not imply causality. The pediatric transplant population is well suited to study the evolution of CAV due to a lower prevalence of confounders that may be present in adults such as advancing age, pretransplant coronary artery disease,[7] or poor lifestyle habits in the recipients (ie, smoking, diet, sedentary behavior).

Earlier studies have assessed the utility of tissue Doppler imaging (TDI) and STI as indicators of acute and chronic rejection in pediatric heart transplant recipients.[15,25,26] In the most recent of these studies, longitudinal strain, and strain rates may serve as an indicator of those children who would go on to develop CAV.[17,18] Early decrements in myocardial mechanics may be due to microvascular disease.[17] Longitudinal strain and strain rate are known to be sensitive to changes in myocardial contractility across a wide range of ischemic syndromes,[27] and appear to be independent of maturation.[28] Peak longitudinal strain rate has been shown to closely correlate with invasive markers of LV contractility, and is considered a robust measure of regional myocardial dysfunction.[27] The validity of 2D-strain imaging for identification and quantification of myocardial

TABLE 1 Clinical characteristics of patients

Characteristic	(*n* = 17)
Age, years	14.0 (9.0, 16.5)
Male/female, *n*	11/6
Age at Tx, years	2.7 (0.6, 7.6)
Time since Tx, years	9.0 (5.0, 15.5)
Height, cm	157.6 (131.4, 167.5)
Weight, kg	45.4 (26.9, 54.4)
SBP z-score	0.10 (−0.25, 0.85)
DBP z-score	0.50 (−0.20, 1.20)
BMI z-score	−0.64 (−1.07, 0.10)
Medications	
Pravastatin, *n* (%)	13 (77)
Tacrolimus, *n* (%)	12 (71)
Sicrolimus, *n* (%)	5 (29)
Cyclosporine, *n* (%)	1 (6)
Mycophenolate mofetil, *n* (%)	7 (41)
Antihypertensives, *n* (%)	5 (29)
Acetylsalicylic acid, *n* (%)	4 (24)
ACE inhibitor, *n* (%)	3 (18)
Predisone, *n* (%)	3 (18)

Abbreviations: Tx, transplant; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.
Data presented as median (25th, 75th percentiles) unless otherwise indicated.

TABLE 2 Echocardiographic measures of left ventricular size and function

Variable	*n* = 17
LV mass, g	89.7 (80.3, 115.6)
LV mass, g/m$^{2.7}$	36.8 (32.2, 49.7)
Stroke volume index, mL/BSA	35.5 (27.5, 41.5)
Heart rate, bpm	89.0 (82.5, 96.0)
Cardiac index, L/min/BSA	3.10 (2.55, 3.70)
Shortening fraction, %	37.0 (35.0, 42.5)
Wall stress, g/cm^2	52.1 (35.7, 62.2)
MVCFc, circ/s	1.2 (1.0, 1.3)
Mitral valve E/A	2.30 (1.95, 3.35)
Longitudinal strain, %	−16.6 (−18.0, −14.9)
Longitudinal systolic strain rate, s^{-1}	−1.00 (−1.09, −0.85)
Longitudinal diastolic strain rate, s^{-1}	1.63 (1.44, 1.91)

Abbreviations: BSA, body surface area; MVCFc, heart rate corrected mean velocity of circumferential fiber shortening; E/A, ratio of early to late diastolic filling.
Data presented as median (25th, 75th percentiles).

TABLE 3 OCT-derived indices of coronary structure

Variable	*n* = 17
Lumen CSA, mm^2	6.52 (4.99, 7.44)
Lumen diameter, mm	2.88 (2.51, 3.08)
Maximum intima thickness, mm	0.10 (0.08, 0.15)
Maximum media thickness, mm	0.08 (0.07, 0.11)
Intima CSA, mm^2	0.58 (0.46, 0.92)
Media CSA, mm^2	0.55 (0.40, 0.78)
I/M ratio	1.13 (1.00, 1.41)
I/L ratio	0.11 (0.08, 0.16)

Abbreviations: CSA, cross-sectional area; I/M, ratio of intima CSA to media CSA; I/L, ratio of intima CSA to lumen CSA.
Data presented as median (25th, 75th percentiles).

ischemia was proven to be valid in pigs with occlusion of the left anterior descending artery (LAD)[29] and in rat ischemia-reperfusion models with temporary LAD occlusion.[30] In the present study, many of the children displayed longitudinal strain and strain rate values below published normal values, similar to other reports of diastolic dysfunction in pediatric heart transplant recipients.[15,22] In addition, in our cohort, lower SVI was also associated with increased coronary dimensions. As such, longitudinal diastolic strain rate, a measure of ventricular relaxation, may be a marker of intimal thickening well in advance of it progressing to overt CAV. Further study is needed to understand the relationship between intimal thickening and myocardial function.

Maximum intima thickness is a predictor of outcomes in adults. A change in intima thickness of greater than 0.5 mm in the first year after transplant has been reported to be associated with all-cause mortality, cardiovascular events, and angiographic abnormalities at follow-up in adult heart transplant recipients.[9] Unlike lesions distinctive of atherosclerosis in coronary artery disease, the progression of CAV is often diffuse in pediatric heart transplants, and progression may be so uniform so that it could go undetected until it becomes more severe.[31] During the initial stages of CAV development, there is no initial decrease in luminal diameter due to vascular remodeling.[32] Only when the process is more advanced does the lumen narrow, and at this stage angiographic detection is possible.[33] Thus, through the routine use of OCT imaging we may be able to detect coronary changes predictive of CAV at an earlier stage, and enhance our understanding of the ventricular consequences of the early intimal thickening.

The mechanisms underlying the development of CAV, particularly in children, remain poorly understood. Innate and adaptive immune responses, as well as ischemia-reperfusion injury, viral infections and metabolic disorders (ie, dyslipidemia) are thought to play a role in the pathology of CAV ultimately resulting in endothelial injury.[3,9,11] Cardiac myocyte function may be impaired through alterations in vascular permeability leading to ischemia or by altered release of nitric oxide, influenced by chronic exposure to cytokines.[34,35] Indeed Inducible nitric oxide synthase mRNA expression has been shown to be associated with systolic and diastolic left ventricular contractile dysfunction measured by echocardiography.[36] In adult heart transplant recipients, coronary artery vasoconstriction

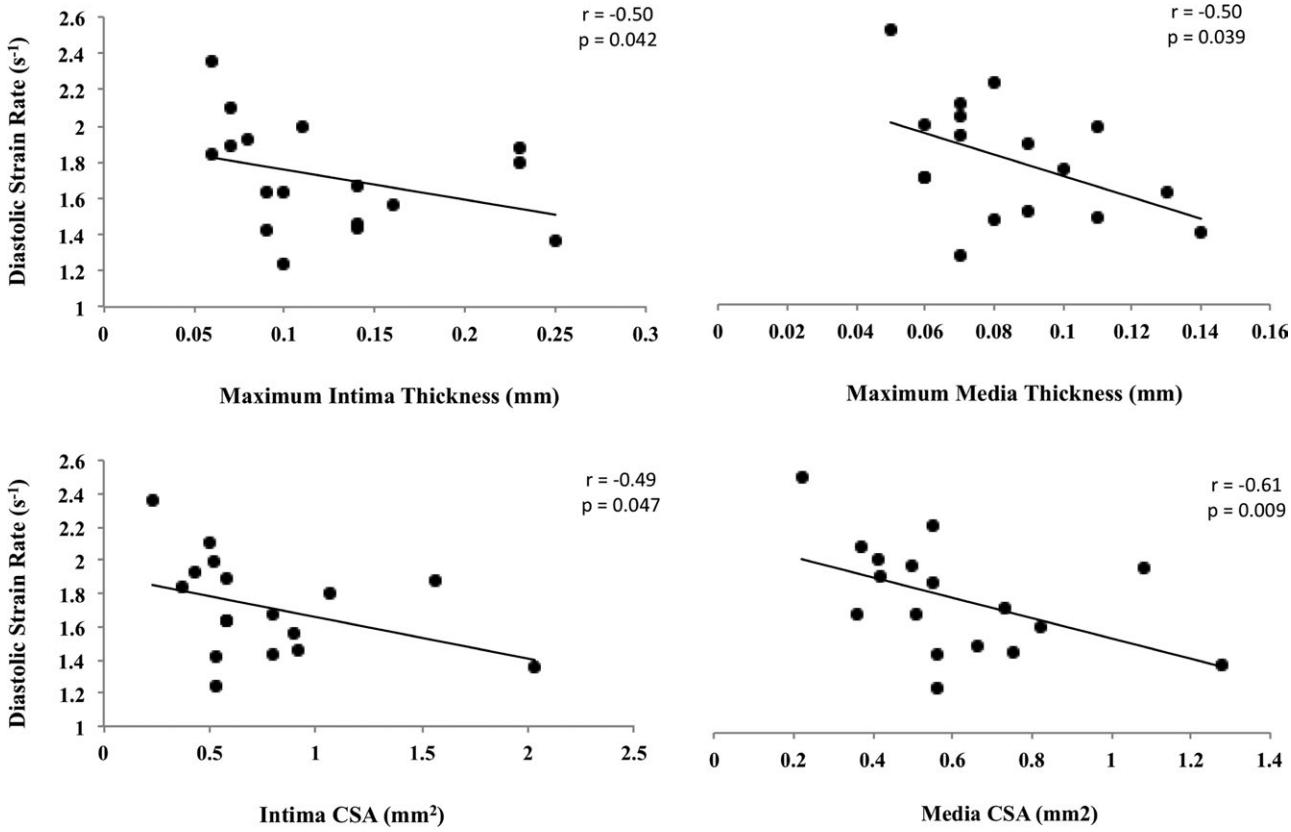

FIGURE 3 Coronary dimensions found significantly associated with diastolic strain rate (unadjusted). Associations were found for diastolic strain rate and maximum intima thickness ($r = -.497$, $P = .042$), intima CSA, ($r = -.489$, $P = .047$), media thickness ($r = -.503$, $P = .039$), and media CSA ($r = -.614$, $P = .009$)

occurred following an acetylcholine challenge early after transplant, in those individuals who later developed CAV as opposed to those who did not have future CAV, presented with vasodilation.[37] As time from transplant increases, coronary artery remodeling may ensue involving intimal hyperplasia and increased medial tone, which eventually results in luminal narrowing affecting coronary perfusion and may contribute to myocardial ischemia.[38–40] Hypertrophy of cardiac myocytes and interstitial fibrosis that occurs with cardiac remodeling following heart transplantation, is thought to further drive oxygen demand and may impair myocardial relaxation and reduce ventricular compliance.[41,42] Isolating cardiac remodeling from CAV in the sequela of posttransplant ventricular dysfunction will require longitudinal studies.

4.1 | Limitations

The adaptation of the donor heart to the recipient circulation following transplantation is a dynamic process, and myocardial growth seemingly occurs despite immunosuppression and denervation.[43] However, various factors unique to the individual patient (ie, donor–recipient mismatch) and the absence of pediatric normative (OCT) coronary dimensions provide challenges for evaluating coronary structure in these children. In addition, in some cases only one vessel is examined by OCT during catheterization, due to individual anatomic factors and the current absence of pediatric appropriate curves in coronary guide catheters.[10] As a result, we cannot exclude the possibility that intima thickening was present in another branch of the coronary tree; however, given the diffuse nature of CAV,[31] we speculate that early coronary changes would not be preferentially observed in one coronary branch compared with others. Furthermore, given the relatively recent application of IVUS and OCT imaging in children, the optimal metrics for assessing intimal changes in growing children are not yet definitively known. Longitudinal studies are needed to determine which OCT measures will have the greatest prognostic value in predicting CAV in children, and how changes in coronary structure relate to changes in functional outcomes. Additionally OCT cannot be performed in small children (we typically have performed this in children > 20 kg) due to the need for a 5 Fr sheath in the femoral artery.

In summary, we have demonstrated that structural coronary changes are associated with abnormal ventricular strain in pediatric transplant recipients. Our findings suggest that there may be important mechanistic ventricular–vascular links in this population. Longitudinal studies will better inform the evolution of these changes over time. Further, while OCT is an evolving technology that needs validation in children, advanced imaging techniques including OCT demonstrate promise as a means of early detection of coronary vascular changes.

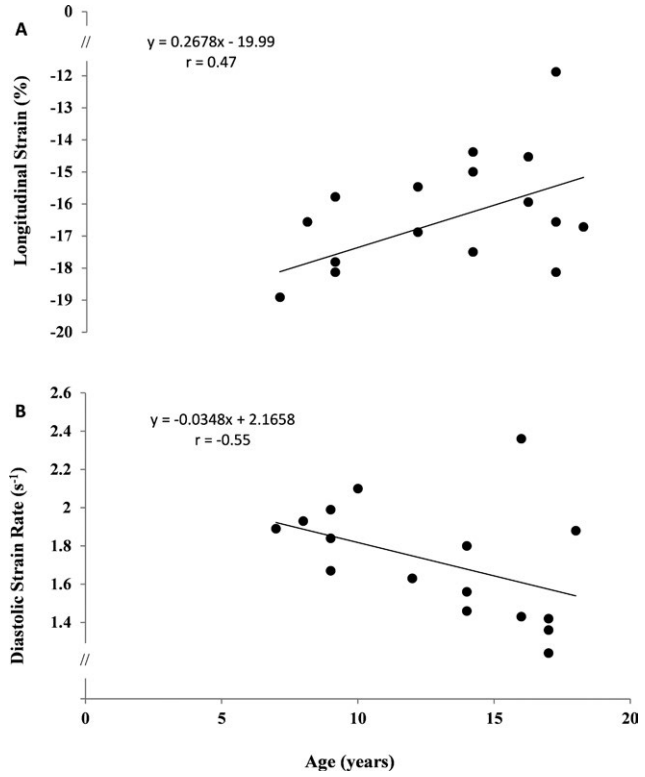

FIGURE 4 Impaired longitudinal strain (A) and diastolic strain rate (B) associated with increasing age

CONFLICT OF INTEREST

Dr Harris holds an unrestricted research grant from St Jude Medical. Dr Harris is a consultant for St Jude Medical. None of the other authors have any interests to disclose.

AUTHOR CONTRIBUTIONS

AC, DH, and KH conception and design of research
MH and KH performed OCT imaging
DH and GS directed echocardiography
AC performed all strain analysis
CV performed the OCT analysis
AC and CV analyzed data
AC, MH, CV, DH, GS, and KH interpreted imaging findings
AC prepared figures
AC and KH drafted manuscript
AC, MH, CV, DH, GS and KH edited and revised manuscript
AC, MH, CV, DH, GS and KH approved final version of manuscript

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How to cite this article: Cote AT, Hosking M, Voss C, Human DG, Sandor GGS, Harris KC. Coronary artery intimal thickening and ventricular dynamics in pediatric heart transplant recipients. *Congenital Heart Disease*. 2018;13:663–670. https://doi.org/10.1111/chd.12629