Review Article

My Approach to Echocardiographic Evaluation after Pediatric Heart Transplantation to Control Rejection and/or Graft Vascular Disease

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Abstract

Pediatric heart transplantation is the definitive therapeutic option for patients with heart failure refractory to optimized clinical treatment, due either to cardiomyopathies or congenital heart disease. Morbidity and mortality remain concerning factors during evolution, and primary dysfunction, rejection, and graft vascular disease (GVD) are the main causes of death in the first 5 years after transplantation. As a surveillance method, transthoracic echocardiography has significant benefits in assisting diagnosis when there is clinical suspicion of rejection or GVD. The objective of this article is to present, in a clear and objective manner, which echocardiographic data assist pediatric cardiologists in follow-up of transplanted patients. The use of echocardiography, either through conventional tools or advanced methods, carefully focusing on different early and late post-cardiac transplantation phases, with information from current and comparative examination of evolution, mainly regarding tissue Doppler and longitudinal strain, can assist pediatric cardiologists in the decision to anticipate endomyocardial biopsy and coronary angiography (gold standard) for early diagnosis and immediate intervention, allowing greater graft durability.

Introduction

Pediatric heart transplantation is the definitive therapeutic option for patients with heart failure refractory to optimized clinical treatment, due either to cardiomyopathies or congenital heart disease.[1,2] Since the first pediatric heart transplant by Dr. Adrian Kantrowitz in 1967 to the present day, when approximately 700 transplants per year are performed, there has been substantial progress in the study of the immune response to grafts, the use of medications, surgical techniques, and lifestyle changes. Therefore, survival after pediatric transplantation has progressively improved in recent years, with a median survival of 18 years for all age groups; for transplants performed in patients younger than 1 year of age, the median survival is greater than 24 years.[3]

Keywords

Echocardiography; Heart Transplantation; Heart Defects, Congenital; Coronary Disease.

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Morbidity and mortality remain concerning factors during evolution, and primary dysfunction, rejection, and graft vascular disease (GVD) are the main causes of death in the first 5 years after transplantation.[3] Other complications are associated with the use of immunosuppressive drugs, such as infections, lymphoproliferative disorders, diabetes, and target organ damage, such as kidney failure.[4]

For evaluation of graft integrity, the gold standard is the presence of direct cardiomyocyte damage on microscopy obtained through endomyocardial biopsy and the study of the coronary arteries by catheterization. However, it is an invasive procedure with risks of complications (perforation, tamponade, thrombi, arrhythmias, tricuspid valve injury) and, in the pediatric age range, the need for sedation/anesthesia. As a surveillance method, transthoracic echocardiography has significant benefits in assisting diagnosis when there is clinical suspicion of rejection or GVD. The new methods associated with myocardial deformation have shown promising results in anticipating outcomes and long-term patient survival, as untreated episodes of subclinical rejection can progress to GVD and progressive deterioration of the organ.[5] After diagnosis of GVD, survival drops significantly to 58% at 5 years and to only 40% at 10 years. These complications can lead to graft failure, and retransplantation is indicated, occurring in approximately 25% to 30% of pediatric heart transplants in the past decade.[1]

The objective of this article is to present, in a clear and objective manner, which echocardiographic data assist pediatric cardiologists in follow-up of transplanted patients, focusing on alterations that may, as early as possible, suggest graft anomalies before hemodynamic worsening, given that ventricular dysfunction due to reduced ejection fraction calculated by traditional methods is usually a late finding.[4]

Transplant timing: early versus late

Cardiac grafts present some peculiarities during the first postoperative months, requiring careful evaluation and interpretation of the data obtained by echocardiography in order to correlate and differentiate evolution suggestive of graft rejection in adaptation to the new hemodynamic state. Initially, during the period prior to implantation, the following factors may influence immediate organ function: ischemia time, donor age, presence of donor comorbidities, care in hemodynamic maintenance, and adequate preservation of the organ. After implantation, the graft may present temporary alterations due to reperfusion injury, adaptation of the right ventricle to elevated pulmonary artery pressure, and the presence of circulating inflammatory mediators.[2,3] The use of immunosuppressants, mainly cyclosporine,[6] increased circulating catecholamines, systemic arterial hypertension, and worsening lymphatic drainage lead to a progressive increase in ventricular mass, which peaks around the third postoperative month and progressively reduces until normalization in the first year after transplantation[5] (Figure 1).

Non-invasive detection of acute rejection is particularly challenging in the early post-transplant period as systolic and diastolic function (relaxation disorder and restrictive physiology) undergo changes during the first few months. The denervated heart has a particular physiology, with an impact on the validation and reliability of non-invasive methods; therefore, echocardiographic evaluation must take this graft modification/adaptation into consideration during the initial months. The follow-up protocols of most large transplant centers include mandatory hemodynamic study and endomyocardial biopsy at pre-established periods during the first months, regardless of good clinical evolution[5] (Figure 2).

Conventional echocardiography measurements

Tissue Doppler imaging

Myocardial inflammation caused by graft rejection alters tissue characteristics even before the onset of systolic or diastolic dysfunction. Tissue Doppler imaging (TDI) quantifies the velocity of movement in a myocardial region in relation to the transducer. TDI is, thus, a tool that characterizes myocardial mechanics and a non-invasive imaging instrument that can monitor acute cellular rejection in adults and children.[7]

TDI values are normally lower in pediatric transplant patients without rejection in relation to the values found in healthy controls.[8] Thus, variations in TDI measurement values are more predictive for evaluation of rejection than when considered alone. The longitudinal evaluation of patients makes it possible to detect changes in graft systolic and diastolic function.

Derek et al. studied 53 transplanted children, and 8 of them evolved to terminal graft failure (death or retransplantation). The authors detected a reduction in the S′ velocity of the tricuspid valve approximately 6 months before the terminal failure. A reduction in mitral valve S′ velocity occurred only 3 months before the event, demonstrating left ventricular failure after right ventricular failure.[9]

Lunze et al. demonstrated that a reduction of up to 15% in S′ velocity and up to 5% in A′ velocity of the left ventricle was able to predict absence of rejection in pediatric transplant patients with an accuracy greater than 99%.[10]

The E/E′ ratio of the mitral and tricuspid valves is also a useful parameter in suspected humoral graft rejection, as demonstrated by Behera et al.,[11] who studied 148 pediatric heart transplant patients. Echocardiography was performed on the same day as endomyocardial biopsy. The mitral and tricuspid E/E′ ratio was significantly lower in patients with rejection compared to patients without alterations on biopsy.

The myocardial performance index (MPI) derived from TDI is a useful parameter in suspected graft rejection in transplant patients. The MPI can increase by an average of 98% during the period of rejection compared to the baseline value and return to pretreatment index levels after resolution of myocardial inflammation.[6]

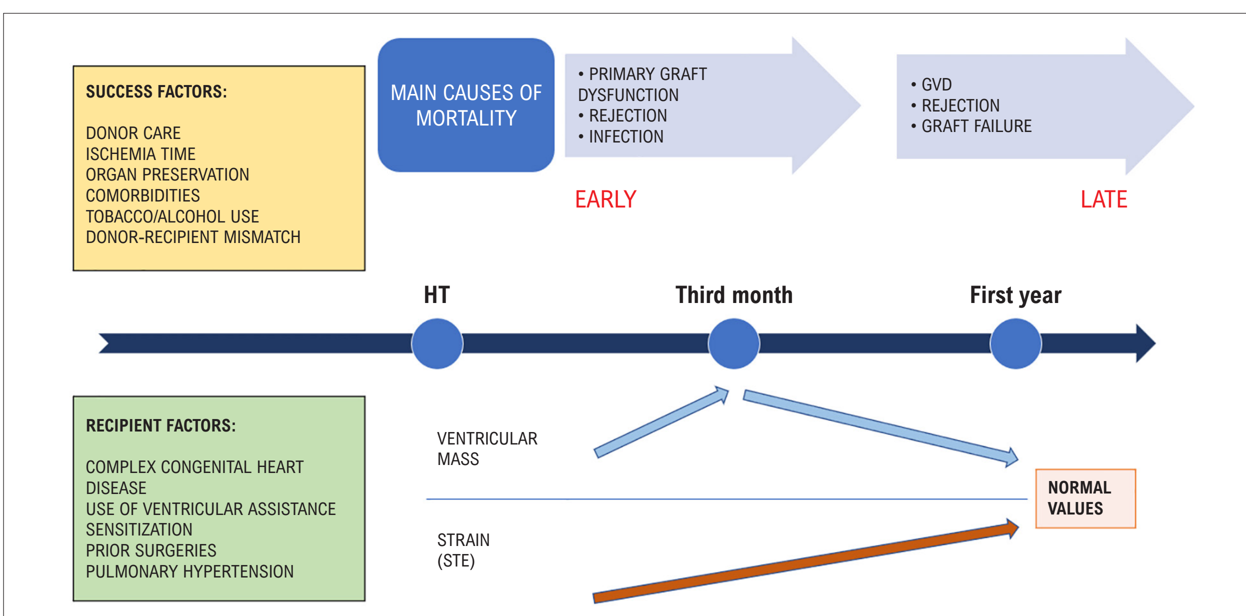

Figure 1 – *Main factors associated with success in early and late transplantation that influence graft function and echocardiographic findings, showing the evolution of ventricular mass and ventricular strain (STE). HT: heart transplantation; STE: speckle-tracking echocardiography; GVD: graft vascular disease.*

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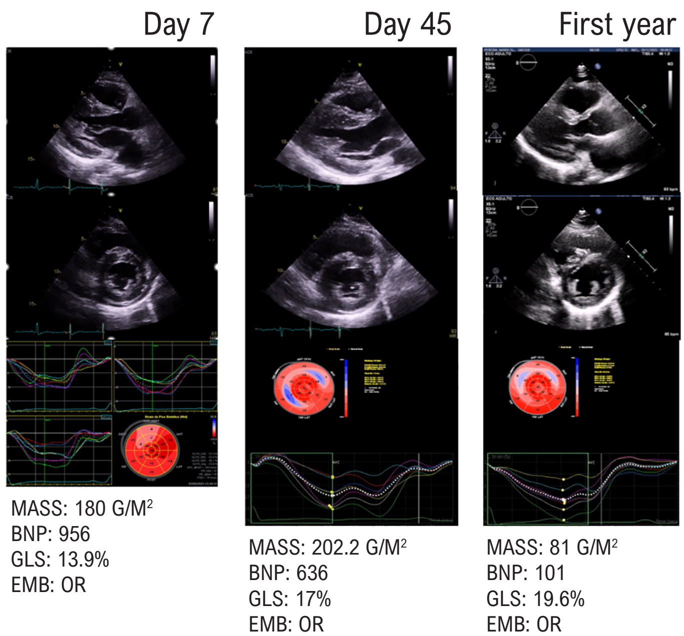

Figure 2 – *Temporal follow-up of evolution after cardiac transplantation in parasternal longitudinal and short-axis echocardiographic views, showing 2-dimensional imaging, global longitudinal strain, ventricular mass, biomarkers, and paired endomyocardial biopsy results. BNP: B-type natriuretic peptide; EMB: endomyocardial biopsy; GLS: global longitudinal strain.*

Flanagan et al. studied 40 children with heart transplant (60 days after the procedure) with endomyocardial biopsy-proven acute cellular rejection and compared them with 40 children with transplantation, but without rejection. The authors identified a significant increase in left ventricular MPI during the rejection period in relation to the same patient's baseline value (0.59 +/− 017 versus 0.41 +/− 0.11; $p < 0.001$) and similar values of left ventricular MPI after resolution of inflammation compared to the baseline value without rejection (0.41 +/− 0.11 versus 0.42 +/− 0.11; $p = 0.65$). Thus, the authors concluded that an increase of ≥ 0.47 in the baseline value of left ventricular MPI had a sensitivity of 82.5% and specificity of 85% in the detection of acute cellular rejection and that an increase of ≥ 20.4% in left ventricular MPI in relation to the patient's baseline value has a sensitivity of 90% and specificity of 100% in the detection of acute cellular rejection. Their study illustrates the importance of longitudinal evaluation of left ventricular MPI in patients with heart transplantation.[12]

Tricuspid annular plane systolic excursion (TAPSE)

Echocardiographic markers are essential for diagnosis and monitoring of the graft in cases of rejection. Initially, this evaluation focused mainly on the left ventricle. More recently, parameters for evaluating right ventricular function have been studied in this scenario.

TAPSE is a measure that evaluates right ventricular longitudinal function. Using the M mode, with the cursor positioned on the lateral wall of the tricuspid annulus, it is possible to measure the displacement distance of this annulus, a parameter that evaluates right ventricular longitudinal function. Heart transplantation alters the geometry of the heart and thus modifies the longitudinal movement of the right ventricle. Changes in TAPSE soon after heart transplantation may correspond to changes in the mechanism of right ventricular contractility rather than solely systolic dysfunction in this chamber.[12] Hence, longitudinal follow-up of patients is important in order to detect variations in graft performance.

Brian et al. studied 127 stable pediatric heart transplant patients and compared them with 380 age-matched healthy children. The authors demonstrated a reduction in TAPSE values in transplant patients compared to healthy controls (mean Z score: −3.38).[13] Michalski et al. retrospectively studied 52 patients (pediatric and adult) with heart transplantation and observed a reduction in TAPSE immediately after transplantation, with progressive improvement over time. They also demonstrated an association between a reduction in TAPSE and an increase in mean pulmonary artery pressure calculated by cardiac catheterization 10 years after transplantation.[14]

Pediatric patients show a decrease in TAPSE during an episode of rejection, and the values improve after resolution of the condition, as demonstrated in a retrospective study carried out by Arthur et al., which evaluated 44 pediatric heart transplant patients.[15]

Mitral annular plane systolic excursion (MAPSE)

MAPSE is a parameter for evaluating left ventricular systolic function, measured using the M mode of the lateral portion of the mitral annulus in 4-chamber view. This index may also be reduced in pediatric patients who have undergone heart transplantation.

Chinalli et al. studied 60 children who underwent heart transplantation and compared them with 60 healthy controls.

All patients had normal ejection fraction by Simpson's method. The transplanted patients had lower MAPSE values than patients in the control group (13 mm +/− 2.6 versus 18 mm +/− 2.3; $p < 0.0001$).[16]

New technologies: applications in the pediatric range?

Echocardiography is commonly the primary non-invasive technique for surveillance of the transplanted heart; however, the traditionally used parameters are affected by heart rate, pre- and after-load conditions, and paradoxical movement of the graft septum, leading to calculations of ventricular function with low sensitivity and specificity to detect asymptomatic episodes of rejection.[17,18] The greatest advantage in cardiac graft evaluation is the method's ability to distinguish between passive and active myocardial movement.

The use of speckle tracking in 2-dimensional echocardiography is relatively new, non-invasive, and reliable, with adequate sensitivity, and it is not angle-dependent for measuring ventricular systolic and diastolic function.[17,19] Two-dimensional strain and strain rate analyze myocardial deformity by tracking natural acoustic markers (speckles) during the cardiac cycle.[20]

The ability of myocardial strain to detect subclinical abnormalities, including subtle changes in regional mobilities, has led to its being explored as an early predictor of rejection. Longitudinal peak systolic strain has been shown to be more sensitive in the evaluation of lesions and reliable in relation to myocardial maturity in the pediatric population.[17]

A gradual increase occurs in longitudinal peak systolic strain values during the first 2 years after heart transplantation, and many patients continue with values below the normality of control groups, even in the absence of rejection or GVD, constituting the "new normal" for stable transplant patients, with absolute values between 16% and 18%.[16,19]

Chanana et al., simultaneously comparing data obtained by catheterization and echocardiography, obtained a cut-off value of 14% for longitudinal strain as a predictor of acute rejection in pediatric recipients, reaching sensitivity greater than 85% and specificity greater than 80%.[17]

Engelhardt et al., using global longitudinal strain comparatively during stable phase and episodes of rejection in transplanted children, observed that a 33% reduction in values from the baseline result was associated with the presence of rejection.[21]

Regardless of the presence or absence of focal coronary stenosis, GVD may be associated with low global longitudinal strain and strain rate values. The use of the method for evaluating left ventricular synchrony and synergy allows the detection of regional differences in the left ventricle and may even indicate the relationship with coronary perfusion and the area it encompasses (Figure 3).

GVD typically manifests loss of the distal coronary vasculature by proliferation of the intima and media layer, and it occurs diffusely, affecting the entire microvasculature, resulting in diastolic dysfunction and graft loss. Zoller et al. have described a reduction in left ventricular global longitudinal strain in patients with coronary vasculopathy, preceding diagnosis via cardiac catheterization by approximately 2 years.[17]

It is important to remember that it is very difficult to establish cut-off values in the pediatric age group, as the samples are numerically small for generalization, and the available data are from single-center studies; consequently, other echocardiographic measurements such as circumferential strain, radial strain, and twist present conflicting data. Due to the already mentioned aspects of the transplanted heart, stress echocardiography, whether induced by exercise or by the infusion of dobutamine, has limitations in the pediatric range. The use of the 3-dimensional method and right atrial and left atrial strain, with numerous studies carried out in adults, still require better validation in the pediatric range.

How can these data help?

The main objective of a multidisciplinary team is to provide quality of life to patients with heart transplant, limiting damage to the graft, by means of strict monitoring for early diagnosis of rejection and GVD, which are associated with significant morbidity and mortality. The use of echocardiography, either through conventional tools or advanced methods, carefully focusing on different early and late post-cardiac transplantation phases, with information from current and comparative examination of evolution, mainly regarding TDI and longitudinal strain, can assist pediatric cardiologists in the decision to anticipate endomyocardial biopsy and coronary angiography (gold standard) for early diagnosis and immediate intervention, allowing greater graft durability. In recent decades, the progressive increase in the survival of children who undergo heart transplantation has shown evidence of this continuous effort to adapt technological innovations without losing the human relationship (Figure 4).

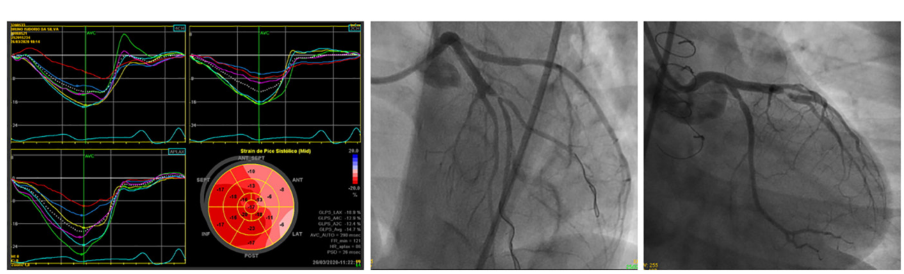

Figure 3 – *Regional alterations demonstrated by segments in global longitudinal strain correlated with diffuse focal lesions in the left coronary artery visualized in coronary angiography.*

Author Contributions

Conception and design of the research and critical revision of the manuscript for intellectual content: Siqueira AWS; acquisition of data and writing of the manuscript: Siqueira AWS, Almeida MF.

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No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

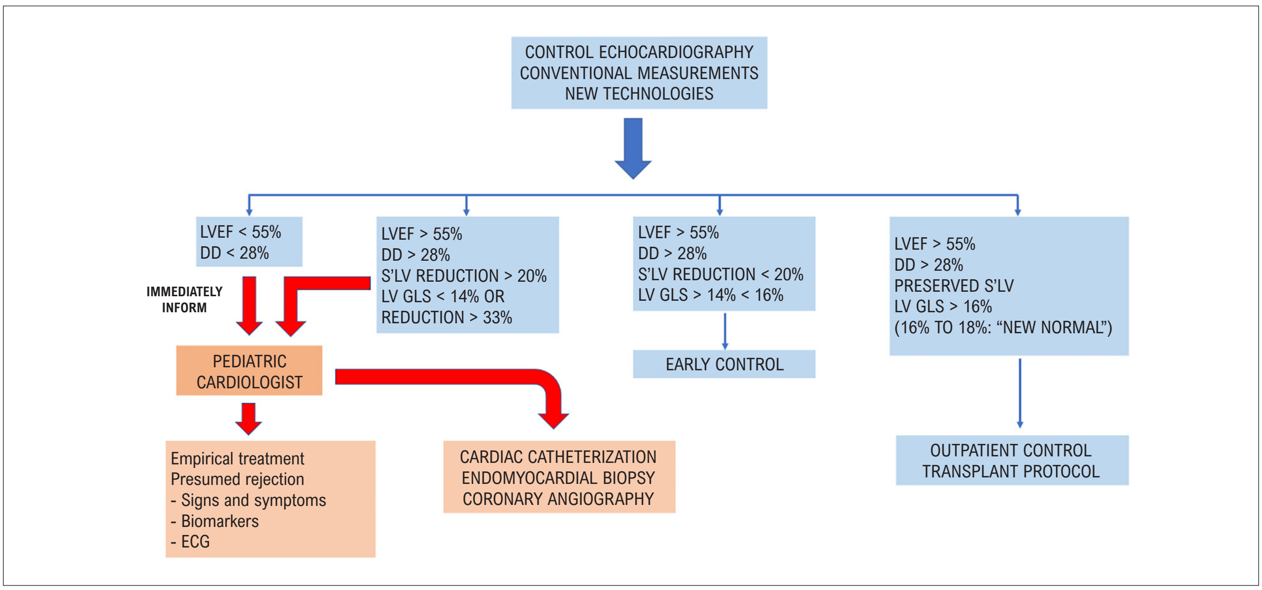

Figure 4 – *Diagram of echocardiography findings directly associated with suspected alteration of the cardiac graft, highlighting the main data for pediatric cardiologists to intervene. DD: delta D or shortening fraction; ECG: electrocardiogram; GLS: global longitudinal strain; LVEF: left ventricular ejection fraction; s'LV: s' of the left ventricular lateral wall.*

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