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Non-invasive detection of myocardial fibrosis in pediatric heart transplant recipients: the role of cardiovascular magnetic resonance

Jonathan H. Soslow, MD, MSCI¹ and Justin Godown, MD¹

¹Thomas P. Graham, Jr. Division of Pediatric Cardiology, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN

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The use of cardiac magnetic resonance imaging (CMR) in pediatric cardiology has increased significantly over the past 20 years. While there are multiple advantages to CMR, tissue characterization is perhaps the most intriguing. Standard tissue characterization usually involves a combination of T2-weighted imaging and late gadolinium enhancement (LGE). These methods are particularly useful for identifying areas of infarct after myocardial infarction or detection of edema/inflammation in the setting of myocarditis. However, these semi-quantitative techniques have limitations, particularly the need to null “normal” myocardium to demonstrate areas of LGE. This can be quite difficult in patients with diffuse cardiovascular disease and no “normal” myocardium. This had led to significant interest in alternative and more quantitative methods of tissue characterization, particularly T1 and extracellular volume fraction (ECV) mapping.

Using various CMR sequences, most commonly a modified Look-Locker inversion recovery (MOLLI), a parametric map of the longitudinal relaxation constant (T1) can be created.[1] In general, the native T1 (pre-contrast T1) of myocardium increases with edema and fibrosis. A pre-contrast and post-contrast T1 map can be used to determine the change in T1 in the myocardium and blood pool after contrast administration. When corrected for hematocrit, an ECV map can be calculated. The ECV is a non-invasive measure of the extracellular matrix, and increases in ECV result from both edema and fibrosis. T1 and ECV mapping have demonstrated potential utility in many disease processes. Given the common association of fibrosis and graft failure,[2] it seems natural to apply these methods to heart transplantation.

In this issue, Feingold et al. present their pilot data evaluating myocardial fibrosis by ECV mapping compared with concurrent endomyocardial biopsies (EMB) [3]. Their correlation with collagen volume fraction (CVF) was relatively modest at only 0.47, which is lower than that found in many adult validation studies.[4, 5] However, as discussed by the authors, this

Corresponding Author: Jonathan H. Soslow, MD, MSCI, Assistant Professor, Pediatrics, Division of Pediatric Cardiology, Vanderbilt University Medical Center, 2200 Children's Way, Suite 5230 DOT, Nashville, TN 37232, (615) 322-7447, jonathan.h.soslow@vanderbilt.edu.

result is likely partially related to the methods used. The EMB in this study only sampled tissue from the right ventricular endocardium, while the authors, “traced the middle third of the myocardium to avoid partial volume effects,” meaning the regions of interest they traced were not the same as the regions that were biopsied. It also must be noted that the ECV represents the average ECV of a relatively large region of interest while the CVF was from a small, focal area. In addition, EMBs tend to come from the same area of the endocardial surface; in patients who have had multiple EMBs, there can be fibrosis related to the prior biopsies. The authors point out that the majority of adult studies used more invasive methods to obtain larger samples for CVF, likely contributing to the improved correlation between ECV and CVF in these studies.

It is interesting that patients in this study did not have significantly increased ECV compared to controls, though 5 patients were above the normal range. It is notable however that the native T1 in controls were relatively high with a mean of 1015ms, though the ECV of controls was comparable to that of other studies. These data contrast somewhat with the study by Ide et al, which demonstrated increased native T1 and ECV in transplants compared with controls. These differences may be accounted for by the small sample sizes of both studies. Additionally, patients enrolled by Ide et al were closer to transplantation, which may have impacted tissue characterization. The lack of association with the number of rejection episodes, allograft age, or cardiac allograft vasculopathy is surprising, but could be impacted by the relatively “healthy” heart transplant population included in this study.

The long-term implications of ECV in pediatric heart transplant recipients remain unclear. Will elevated native T1 or ECV predict earlier graft failure? If so, the correlation with EMB may be less relevant. In fact, the ability of CMR to evaluate the entire myocardium, and not just areas accessible to EMB, may someday allow CMR or other imaging modalities to surpass EMB. While tantalizing, we are not yet near that point, and larger cohorts with longitudinal follow up are necessary to answer these questions. Perhaps more importantly, methods to reverse, or at least delay, the progression of graft fibrosis must be evaluated. Without an adequate intervention, the ability to detect early fibrosis becomes less valuable.

Parametric mapping also has potential to detect rejection. The native T1, ECV, and T2 should increase with inflammation. A non-invasive method to detect rejection would be of huge benefit to patients, potentially decreasing the number of cardiac catheterizations.[6] However, both inflammation and fibrosis lead to extracellular matrix expansion, which may complicate assessment of increased T1 and ECV. Studies also suggest a period of myocardial remodeling during the first 6–12 months after heart transplantation; this remodeling may decrease the utility of non-invasive measures early after transplant, the period when patients are at the highest risk for developing rejection.[7, 8]

Enthusiasm for these methods must be tempered as there are important limitations. ECV can only be measured after administration of gadolinium contrast agents, which are contraindicated in patients with renal dysfunction due to the risk of nephrogenic systemic fibrosis. Renal dysfunction is not uncommon in patients following heart transplantation, and therefore may limit access to these techniques. Moreover, CMRs are expensive and require patients to remain still and perform breath-holds during certain sequences. This limits the

ability to perform CMRs without sedation or anesthesia in children under 8 years old or in children with developmental delays. While newer sequences should help improve free-breathing acquisitions, these limitations remain significant.

There are also specific limitations of T1 and ECV mapping; chief among these is the difficulty in standardizing native T1 values. There are multiple types of sequences provided by multiple different vendors, each with advantages and disadvantages, and all with slightly different T1 values. The same sequence performed on the same type of magnet at different sites can result in different T1 values. The calculation of ECV diminishes many of the problems with generalizability, but the issues with native T1 remain. Some of these issues may be addressable using phantoms, and an ongoing project assessing mass-produced phantoms provides hope of improved standardization.[9] However, until the field settles on standard sequence parameters, translation of results will be difficult.

Diffuse graft fibrosis is a complex process that is likely multifactorial. While only pilot data, the study presented by Feingold, *et al.* is promising and we applaud their efforts. Non-invasive assessment of graft fibrosis may prove to be an invaluable tool for graft assessment; however, further research is needed to determine the optimal role of CMR in the care of pediatric heart transplant recipients. This can only be determined with larger numbers and longer follow up, and limitations in generalizability must be addressed.

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Abbreviations

CMR	cardiac magnetic resonance
CVF	collagen volume fraction
ECV	extracellular volume fraction
EMB	endomyocardial biopsy
LGE	late gadolinium enhancement
MOLLI	modified Look-Locker inversion recovery
T1	Longitudinal relaxation constant

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