Myocardial Fibrosis in Congenital Heart Disease

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Myocardial fibrosis is common in patients with congenital heart disease (CHD) and has been associated with arrhythmias, decreased functional status, and adverse ventricular mechanics. There are multiple types of myocardial fibrosis that occur in response to different pathophysiologic stimuli. Recent advances in imaging technology have made detection and quantification of the types of myocardial fibrosis possible. In this review, we describe the pathophysiology of myocardial fibrosis, examine the imaging techniques used to evaluate fibrosis, and discuss the relationship between myocardial fibrosis and clinical outcomes in CHD. (*Circ J* 2016; **80**: 1300–1307)

Key Words: Congenital heart disease; Extracellular volume fraction; Late gadolinium enhancement; Magnetic resonance imaging; Myocardial fibrosis

Myocardial fibrosis is a common histopathologic finding in a wide range of cardiovascular diseases and has been associated with morbidity and mortality. The mechanisms of myocardial fibrosis are variable, and include acute and chronic etiologies. Equally important, there are different types of fibrosis representing reversible and irreversible injuries to the myocardium. Recent advances in non-invasive imaging technology have made the detection of and differentiation between types of myocardial fibrosis possible. The presence of myocardial fibrosis based on noninvasive assessment has been associated with adverse outcomes and can be used to risk stratify patients in order to tailor treatment and interventions. Although most of the published literature describes the role of myocardial fibrosis in adult patients with coronary artery disease and other acquired heart diseases, there is a growing body of work investigating fibrosis in children and adult patients with congenital heart disease (CHD). In this review, we describe the pathophysiology of myocardial fibrosis, examine the imaging techniques used to evaluate myocardial fibrosis, and discuss the relationship between myocardial fibrosis and clinical outcomes in CHD.

Pathophysiology of Myocardial Fibrosis

The normal myocardium contains mostly ($\approx 75\%$) cardiac myocytes whereas the remaining partition – the interstitium – comprises fibroblasts, endothelial cells, and coronary arteries (**Figure 1**).¹ The fibroblasts are responsible for the creation and maintenance of extracellular matrix components, primarily in the form of types I and III collagen. These collagens serve as the scaffold for the myocardium and are continually being synthesized and degraded. Myocardial fibrosis occurs when the balance between collagen production and degradation is altered, favoring expansion of collagen and the extracellular matrix. This imbalance can occur from death of cardiac myocytes, from increased collagen synthesis in response to

certain stimuli, or a combination of both.

There are several types of myocardial fibrosis (**Figure 1**). *Reactive interstitial fibrosis* is a type of myocardial remodeling characterized by an increase in collagen synthesis with little or no loss of viable myocardium.² This results in an increased volume of the interstitial compartment with no change in myocyte volume. The collagen deposition is typically diffuse and occurs in response to various stimuli such as increased pressure and/or volume loads (eg, hypertension, aortic stenosis (AS), chronic regurgitation, shunt), chronic or recurrent ischemia, hyperglycemia, or aging. Reactive interstitial fibrosis typically has a progressive chronic course and may be found in patients with CHD. This type of myocardial remodeling may be reversible with elimination of the inciting stimuli or in response to targeted therapy.

Replacement fibrosis occurs in response to myocyte cell death, with subsequent increase in type I collagen deposition and expansion of the extracellular matrix.² Typically, replacement fibrosis occurs in the context of myocardial ischemia, but can also occur in response to other stimuli that disrupt the integrity of the myocyte cell membrane leading to cell death. This is associated with increased collagen synthesis, which replaces the dead myocytes. This process can be acute or chronic, and can lead to diffuse or focal fibrosis. In this type of myocardial remodeling, the affected tissue is not viable and the myocardium will not recover contractility following revascularization or removal of the causative stimulus.

Infiltrative interstitial fibrosis is third type of fibrosis, which is associated with infiltrative diseases such as amyloidosis or Anderson-Fabry disease.² These disease processes have limited relevance in CHD and are, therefore, beyond the scope of this review.

Noninvasive Assessment of Myocardial Fibrosis

An exhaustive discussion of all the imaging modalities used

Received April 18, 2016; accepted April 18, 2016; released online May 11, 2016

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ISSN-1346-9843 doi:10.1253/circj.CJ-16-0353

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for assessment of myocardial fibrosis is beyond the scope of this review and can be found elsewhere.^{3,4} Instead, we focus on the most commonly used techniques in patients with CHD: stress echocardiography and cardiac magnetic resonance imaging (CMR). In addition, we discuss the use of positron emission tomography (PET) because it is generally considered the reference standard in the assessment of myocardial viability.

Stress Echocardiography

Echocardiography is the mainstay of cardiac imaging in patients with CHD. In those with adequate acoustic windows, exercise or pharmacologic stress echocardiography allow for the assessment of myocardial contractile reserve. Dobutamine is a commonly used agent in CHD stress echocardiography. Hibernating myocardium exhibits severe hypokinesis or akinesis at baseline, with improved wall motion and thickening with low-dose dobutamine.³ At higher doses, the affected wall segments show worsening function. This “biphasic response”

has been shown in patients with coronary artery disease to be indicative of viable myocardium capable of functional recovery after revascularization.⁵ Nonviable myocardium with replacement fibrosis does not exhibit improved function regardless of the degree of stimulation. Another form of stress echocardiography involves exercise, using either a treadmill or a stationary cycle ergometer. In the CHD population, stress echocardiography is commonly used for the evaluation of coronary ischemia in patients after the arterial switch operation or with Kawasaki disease, anomalous origin of the coronary arteries, or post-transplant coronary vasculopathy.⁶ The main limitations of stress echocardiography are that diagnostic accuracy is reduced in patients with poor acoustic windows and there is low interobserver and inter-center reproducibility.³

Positron Emission Tomography

PET is generally considered the reference standard for assessment of myocardial viability. This nuclear scintigraphy

A. Replacement fibrosis

B. Reactive interstitial fibrosis

◆ Gadolinium

Figure 2. Gadolinium-based contrast and the extracellular matrix. Patterns of increased concentration of gadolinium-based contrast in the myocardium. (A) In replacement fibrosis, there is loss of cardiac myocytes and a large expansion of the extracellular matrix, which results in a high, localized concentration of the gadolinium-based contrast agent. (B) In reactive interstitial fibrosis, the expansion of the extracellular matrix is less extensive as compared with replacement fibrosis and is typically more diffuse.

technique uses ^{13}N -labeled ammonia ($^{13}\text{N-NH}_3$) and a glucose surrogate, ^{18}F -fluorodeoxyglucose ($^{18}\text{F-FDG}$). Myocardial uptake of $^{13}\text{N-NH}_3$ is a marker of coronary perfusion. PET metabolic imaging is done after a 6–8-h fast, followed by an intravenous or oral glucose load. The administration of glucose stimulates endogenous insulin release, which results in myocardial uptake of $^{18}\text{F-FDG}$.⁷ PET viability imaging evaluates the combined uptake of $^{13}\text{N-NH}_3$ (to assess coronary perfusion) and $^{18}\text{F-FDG}$ (to demonstrate the metabolic activity of the myocardium). Normal myocardium will have normal uptake of both labeled tracers. Hibernating myocardium will have decreased $^{13}\text{N-NH}_3$ uptake with normal $^{18}\text{F-FDG}$ uptake (perfusion-metabolism mismatch).⁸ Myocardium with no $^{13}\text{N-NH}_3$ and no $^{18}\text{F-FDG}$ uptake (matched perfusion-metabolism defect) suggests nonviable tissue with replacement fibrosis. The main drawbacks of PET are its limited scanner availability, need for an on-site cyclotron, and low sensitivity for interstitial fibrosis. PET is often combined with computed tomography for high-resolution anatomic imaging, both of which result in exposure to ionizing radiation. Given that children are more vulnerable to radiation-related risk of cancer than adults and that patients with CHD are often exposed to multiple doses of ionizing radiation over their lifetime, the use of PET in this population must be carefully considered.⁹

Cardiac Magnetic Resonance

Most of the imaging data on the assessment of myocardial fibrosis in CHD is based on CMR. In the absence of metallic artifacts, CMR offers excellent spatial resolution and visualization of all myocardial segments. It is considered the reference standard for the quantitative assessment of ventricular size and systolic function. When combined with pharmacologic and physiologic testing, CMR can assess contractile reserve in a similar fashion to stress echocardiography. Pharmacologic stress CMR, either with dobutamine or a vasodilation agent, has been used extensively in adults with ischemic heart disease, with an excellent diagnostic profile.¹⁰ Experi-

ence in the pediatric population is more limited, but the available data are encouraging.¹¹ There are now CMR-compatible ergometers that allow for cardiac functional assessment during exercise.¹²

One of the strengths of CMR is its ability to evaluate tissue characteristics. In brief, the signal from magnetic resonance imaging comes from recovery of the tissue's longitudinal magnetization after an inversion pulse. The time when 63% of the signal intensity has recovered is known as the T1 relaxation time. The T1 relaxation times of healthy myocardium, the blood pool, and fibrotic myocardium are different. Gadolinium-based extracellular contrast agents markedly shorten the T1 relaxation time. The concentration of gadolinium-based contrast in the myocardium is determined by several factors, including the extracellular volume (ECV) of distribution of the tissue, and wash-in and wash-out kinetics. Using these concepts, there are 2 major CMR techniques used in the assessment of myocardial fibrosis: late gadolinium enhancement (LGE) imaging and T1 mapping/ECV fraction calculation.

Late Gadolinium Enhancement LGE is a CMR technique that identifies areas of discrete replacement fibrosis. Image acquisition is typically performed 10–20 min after administration of gadolinium-based contrast agent. In myocardial tissue where there has been disruption of the cell membrane, death of cardiac myocytes, and significant localized expansion of the extracellular matrix, the volume of distribution of the contrast agent is increased and the wash-out is delayed. This results in a higher concentration of the gadolinium-based contrast agent in the fibrotic tissue compared with normal myocardium, causing significant shortening of the T1 relaxation time in the fibrotic tissue (Figure 2). The LGE imaging sequence uses an inversion pulse to null the signal from the myocardium and imaging is timed so that the normal myocardium is dark (low signal intensity) and areas of increased concentration of the gadolinium-based contrast agent (ie, replacement fibrosis) are bright (high signal intensity) (Figure 3).

Studies in both animal models and human subjects have

Figure 3. Late gadolinium enhancement sequence. In the late gadolinium enhancement sequence, an inversion pulse is applied. The time from this inversion pulse to image acquisition is known as the inversion time. The graph shows the relative signal intensities vs. inversion time for normal myocardium and in areas of replacement fibrosis. Because the T1 recovery times are different, an inversion time can be selected (see highlighted image) to highlight the greatest contrast between normal myocardium and areas of replacement fibrosis. This usually corresponds to the inversion time where the normal myocardium is darkest and replacement fibrosis is brightest.

shown that the presence and extent of LGE closely correlate with myocardial histology.^{13–15} The LGE technique has high sensitivity, specificity, and reproducibility for detecting replacement fibrosis. The presence and extent of LGE have been associated with adverse clinical outcomes, including earlier time to death, heart failure, and arrhythmias in numerous adult conditions such as coronary artery disease,¹⁶ hypertrophic cardiomyopathy,¹⁷ dilated cardiomyopathy, cardiac amyloidosis,¹⁸ and AS.¹⁹

The LGE technique has some limitations. Although the reproducibility of the presence of LGE is excellent, quantification of the extent of LGE is less reliable. The “bright” signal intensity value of fibrotic myocardium is an arbitrary value, without a clear numeric cutoff between normal and abnormal tissue. The gray zone of intermittent signal intensity may reflect a transition between normal and fibrotic myocardium, but may also be confounded by partial volume effect. Furthermore, there is no consensus as to which method to use to measure LGE as a percentage of ventricular mass. Various thresholding approaches have been used, including full-width at half-maximum and using a prespecified number of standard deviations from the mean signal intensity of the normal myocardium.^{13,17} Although LGE is the best method to identify discrete replacement fibrosis, it is not sensitive for identifying reactive interstitial fibrosis.

T1 Mapping and ECV Calculation Several CMR techniques have been developed to measure myocardial T1. The most commonly used approaches include Look-Locker, modified Look-Locker inversion recovery (MOLLI), shortened MOLLI (ShMOLLI), saturation recovery single-shot acquisition

(SASHA), and saturation pulse prepared heart rate-independent inversion recovery (SAPHIRE). A technical review of the strengths and weaknesses of these techniques can be found elsewhere.²⁰ The Look-Locker technique and its modifications have higher reproducibility and precision, whereas SASHA and SAPHIRE have improved accuracy.²⁰ In most of the published studies in CHD either the Look-Locker or MOLLI approach has been used.^{21–24}

Native T1 time refers to the T1 relaxation time without the administration of a gadolinium-based contrast agent. With increased interstitial or replacement fibrosis, native T1 relaxation times increase. The specificity of using native T1 assessment alone is limited because other conditions, including myocardial edema and amyloidosis, lengthen the T1 relaxation time, while Anderson-Fabry disease shortens it.²³ To our knowledge, there are no published data on the prognostic value of native T1 in CHD lesions.

ECV is the ratio of interstitial volume to the total myocardial volume. It is the most widely used imaging biomarker for interstitial fibrosis.²⁵ ECV is derived by comparing the native (precontrast) and postcontrast T1 times in the myocardium and in the blood pool, and accounting for the hematocrit. Expansion of the extracellular space allows for an increase in the gadolinium-based contrast agent concentration, thus shortening the postcontrast T1 relaxation time (Figures 2,4). ECV measurements have been shown to correlate closely with collagen volume fraction evaluated by quantitative histology.^{26–28} In adult patients, elevated ECV has been associated with systemic hypertension,^{29,30} ventricular arrhythmias,³¹ ischemic injury,³² myopathies,³³ and increased mortality rates.³⁴

An important limitation of ECV measurements is the lack of vendor agnostic standards for both acquisition and postprocessing. Native and postcontrast T1 times are influenced by magnetic field strength (1.5 vs. 3 T) and, to a lesser degree, by the type and dose of gadolinium-based contrast agents.³⁵ As mentioned, there are several T1 mapping techniques, with different strengths and weaknesses,²⁰ including different postprocessing approaches that can also affect T1 values.³⁶ Areas of LGE are usually excluded from the region of interest for ECV calculation, as doing so will artificially increase the ECV value. Given the lack of consensus regarding a vendor-neutral standard approach to image acquisition and postprocessing, individual centers are encouraged to generate their own normative data.²⁵

Myocardial Fibrosis in CHD

Most of the published work evaluating myocardial fibrosis in CHD uses the CMR techniques of LGE and ECV. In the following section we review the current knowledge about myocardial fibrosis in CHD lesions and discuss its association with ventricular function and clinical outcomes.

Tetralogy of Fallot (TOF)

Outcomes of patients with TOF have improved dramatically in the past half-century. Despite excellent results in the first 2 decades of life, morbidity and mortality rates increase as these patients reach adulthood.³⁷ Pulmonary regurgitation, right ventricular (RV) volume and/or pressure overload, ventricular dysfunction, and arrhythmias are some of the abnormalities commonly seen in these patients. The currently available risk stratification models in this disease do not fully explain the observed adverse clinical outcomes.³⁸ This observation has sparked an interest in exploring a possible relationship between

myocardial fibrosis and clinical outcomes. Babu-Narayan et al³⁹ published one of the earliest studies evaluating LGE in patients after TOF repair. In their cohort of adult patients (n=92, mean age 32 years), LGE in the RV was universal, seen at almost all surgical sites in the RV outflow tract (RVOT) and at the ventricular septal defect patch. Most patients also had LGE at the septal-free wall insertion sites. Half of the patients also had left ventricular (LV) LGE. The authors devised an LGE score by segmenting the RV and LV and assigning a point for each segment with LGE. On univariable analysis, patients with a higher RV or LV LGE score were more likely to be older at the time of CMR, older at the time of TOF repair, have more frequent clinical arrhythmias, and have a decreased duration of exercise on stress testing. Increased RV and LV LGE scores were also associated with decreased RV and LV ejection fraction (EF), respectively. In a multivariable model, RV LGE score remained a predictor of arrhythmia, after adjustment for age and exercise duration.

Wald et al⁴⁰ devised a novel 3-dimensional RV endocardial surface model in 62 patients with repaired TOF (median age at CMR 20 years). Using end-diastolic and endsystolic surface maps, the RV was divided into an average of 550 triangles allowing segmental analysis of RV function, displacement, and LGE. There was good agreement between segmental RV dyskinesia and the presence of LGE. Unlike the findings of Babu-Narayan et al, in this younger cohort there was no LGE in the LV and most of the RV LGE was in the RVOT. Furthermore, the extent of the RVOT dyskinesia was associated with decreased exercise capacity. As with the study from Babu-Narayan et al, a higher RV LGE score also correlated with a lower global RVEF. Since then, several other reports on LGE in TOF have noted similar findings.^{41–43}

There have been 2 recent reports evaluating ECV using a Look-Locker technique and clinical outcomes in patients with

repaired TOF. Chen et al²¹ measured both RV and LV ECV in 84 patients (median age 23 years) and compared them with 20 normal control subjects. ECV values were 2 standard deviations above control values in the LV in 13% of patients and in the RV in 11% of patients. There was a significant positive correlation between LV and RV ECV ($r=0.54$), suggesting an adverse ventricular-ventricular interaction at the tissue level. By univariable analysis, both LV and RV ECV were associated with female sex, lower RV mass-to-volume ratio, and increased pulmonary regurgitation. In a multivariable model, LV ECV was the strongest predictor of arrhythmias. Using a similar technique, Broberg et al²² calculated the LV ECV in 52 patients. Compared with the study of Chen and colleagues, their patients were older (mean age 39 years) and an elevated ECV was more common, seen in 29% of TOF patients. By univariable analysis, elevated LV ECV was associated with female sex, older age, decreased 6-min walk distance, and higher prevalence of atrial arrhythmias.

The results of these studies suggest an important association between RV and LV myocardial fibrosis and adverse outcomes in patients with repaired TOF. In the larger, multicenter INDICATOR study, one of the independent risk factors for adverse outcomes was an increased mass-to-volume ratio (LGE was not evaluated).³⁸ Using quantitative histology, Pradegan et al⁴⁴ measured the degree of myocyte hypertrophy and diffuse fibrosis in 8 heart specimens of patients who died late after TOF repair and compared them with 11 controls. They found that increasing age at death correlated with a higher percentage of RV fibrosis and with increasing myocyte diameter. These data support the CMR findings of Chen et al²¹ and Broberg et al²² and suggest a possible link between RV hypertrophy, reactive fibrosis, and adverse clinical outcomes.

Single Ventricle

Despite significant advances in diagnosis and management, patients with functional single ventricles have high morbidity and mortality rates, with only two-thirds of patients surviving beyond the first 3 years of life.⁴⁵ These patients typically undergo several surgical and transcatheter procedures, culminating in one of the modifications of the Fontan operation. Adverse outcomes become more frequent as these patients age and enter adulthood.⁴⁶ Rathod et al⁴⁷ analyzed 90 patients (mean age 23 years) who had a CMR with LGE after the Fontan procedure. LGE was seen in 28% of patients. Compared with patients who did not have LGE, those who did had a lower EF, increased end-diastolic volumes, increased ventricular mass, higher frequency of regional wall motion abnormalities, and a higher frequency of nonsustained ventricular tachycardia. LGE lesions that were associated with regional wall motion abnormalities were also correspondingly more likely to have dyskinesia. Multivariable analysis showed that more extensive LGE, expressed as percent LGE of total myocardial mass, was associated with a lower EF, increased end-diastolic volume, increased ventricular mass, and a higher frequency of nonsustained ventricular tachycardia. In another study ($n=132$) from our center, which focused on clinical outcomes in patients with Fontan circulation, the presence of LGE was not associated with shorter time to death or need for transplant.⁴⁸ Further studies with larger numbers of patients and longer follow-up may demonstrate the prognostic value of LGE and ECV measurements in this patient population.

Aortic Stenosis

Studies evaluating LGE and ECV in adults with AS have reported LGE in 27–66% of patients.^{49,50} Dweck et al reported

on 143 patients with AS (mean age 68 years) who had a mid-wall or an infarct pattern of LGE and had a significantly higher risk of death.⁵¹ LGE has also been shown to have a good correlation ($r=0.69$) with histopathology on intraoperative biopsies during aortic valve replacement.¹⁹

There are limited data on myocardial fibrosis in young patients with AS. A small case series showed that patients could have minimal residual AS or regurgitation, but then present in teenage years with severe diastolic dysfunction and confluent subendocardial LGE.⁵² Dusenbery et al²⁴ measured LV LGE and ECV in 35 patients with AS (median age 16 years) compared with 27 control subjects. LGE was seen in 24% of patients and ECV was elevated in 33% of subjects with AS. Both LGE and ECV correlated with echocardiographic parameters of diastolic dysfunction, including a lower septal E' z-score and a higher E/septal E' z-score. In a subset of patients ($n=21$) who had contemporaneous catheterization data, LV LGE and ECV did not correlate with LV end-diastolic or pulmonary capillary wedge pressures. ECV was also not associated with the degree of AS, LV mass, mass-to-volume ratio, or EF.

Systemic Right Ventricle

Before the advent of the arterial switch operation, the atrial switch operation was the primary palliation for patients with transposition of the great arteries. This procedure has been associated with numerous late morbidities, often related to the long-term consequences of a RV supporting the systemic circulation. Rydman et al⁵³ studied 55 patients (mean age 27 years) and found RV LGE in 56% of patients. They were followed prospectively for a median of 7.8 years for a composite endpoint of new-onset sustained atrial or ventricular arrhythmia, decompensated heart failure admission, transplantation, or death. A total of 22 patients reached the endpoint, most as a result of new atrial arrhythmias ($n=19$). In a multivariable model, the presence of RV LGE and predicted peak $\dot{V}O_2$ were independently associated with the endpoint. RV ECV was not evaluated in that study.

Future Work

Additional studies are needed to expand our understanding of myocardial fibrosis in CHD and its clinical implications. Future work should focus on development of noninvasive imaging biomarkers of fibrosis validated against histopathology. Although assessment of LGE is a common standard of care, assessment of discrete replacement fibrosis should not be limited just to the presence or absence of LGE. We recommend studies quantify the scar burden as a percentage of myocardial volume, while investigating the optimal cutoffs between normal and abnormal myocardium. ECV has significant promise as a novel imaging biomarker of reactive interstitial fibrosis, but it is still a technique in evolution. Standardization of acquisition techniques (eg, MOLLI vs. SHASHA) and optimization of postprocessing methods for ECV measurements are critical for acceptance in clinical practice. Future studies will require larger numbers of patients, likely possible only through multicenter trials and registries. These studies will hopefully identify reproducible imaging biomarkers of myocardial fibrosis that can be used to design intervention trials to reverse myocardial fibrosis.

Acknowledgments

The authors thank Emily Harris for the artwork.

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