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Non-invasive evaluation of myocardial fibrosis: implications for the clinician

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The presence and extent of myocardial fibrosis are key determinants of response to treatment and prognosis in a number of cardiac conditions. Until recently, myocardial fibrosis could only be detected ante mortem by endomyocardial biopsy, which is associated with procedural risk and sampling error. The development of novel cardiac imaging techniques and serum assays now permits the accurate detection and quantification of myocardial fibrosis. These have yielded new insights into disease progression and response to treatment.

PATHOGENESIS OF MYOCARDIAL FIBROSIS

Myocardial fibrosis develops in response to a cardiac insult, which may include ischaemia, pressure or volume overload, viral infection, or genetically mediated injury as in hypertrophic cardiomyopathy. Net collagen deposition results from an imbalance of its synthesis relative to degradation. A number of enzymes have been identified as potential mediators of myocardial extracellular matrix turnover. The matrix metalloproteinases (MMPs) are a family of at least 20 calcium dependent endopeptidases that digest interstitial constituents. The various MMPs have different substrates—MMP-1 and -13 are collagenases and MMP-2 and -9 gelatinases. Left ventricular (LV) myocardial MMP activity in idiopathic dilated cardiomyopathy and ischaemic cardiomyopathy has been shown to be greater than in normal hearts.1 Abolition of MMP-9 synthesis has been associated with reduced myocardial fibrosis and improved LV function in a rodent model of pressure overload.2,3 The tissue inhibitors of matrix metalloproteinase (TIMPs) are a family of four proteins that bind to and inhibit the effects of MMPs (figure 1). TIMP-1 expression is reduced in explanted hearts from patients with both ischaemic and non-ischaemic cardiomyopathy.2

Regardless of the aetiology and/or molecular cascade resulting in collagen deposition, the presence of myocardial fibrosis has both mechanical effects on cardiac function, mediated by increased myocardial stiffness, and electrophysiological effects, by acting as substrate for re-entry and arrhythmia.

CARDIAC MAGNETIC RESONANCE (CMR) IMAGING

CMR imaging is established as a major technique in clinical cardiology and cardiovascular research. Allied to its well recognised role in accurate and reproducible measurement of LV volumes and mass, CMR offers an unprecedented ability to detect and quantify myocardial fibrosis. It provides exquisite three dimensional images allowing concurrent assessment of myocardial structure, function, and tissue characterisation.

Late gadolinium enhancement (LGE) technique

Gadolinium-DTPA (Gd-DTPA) is a paramagnetic contrast agent that is used to delineate areas of injured myocardium. Gd-DTPA reduces hydrogen—proton T1 relaxation times in proportion to its local concentration. In T1 weighted imaging, tissues with a shorter T1 relaxation time exhibit greater signal intensity than those with longer T1 relaxation times. Gd-DTPA equilibrates rapidly between intravascular and interstitial spaces, but is excluded from the intracellular compartment by the intact cell membrane.4 Following intravenous administration, altered wash-in/wash-out kinetics and an increased volume of distribution in damaged tissue (owing to interstitial oedema and/or loss of cell membrane integrity) account for its pattern of appearance in these regions.2 Late or ‘delayed’ imaging (after at least 5 min post-contrast) with T1 weighted inversion recovery sequences identifies conditions associated with expansion of the extracellular space and hence also with fibrosis.

Ischaemic heart disease

In the clinical realm, contractile abnormalities in patients with ischaemic heart disease may occur as a consequence of stunning, hibernation and scar, with the relative importance of these factors varying both between and within myocardial segments and dynamically over time. Detecting dysfunctional and scarred myocardium (figure 2) as opposed to dysfunctional but viable myocardium is of scientific and clinical significance and there is now a reasonable body of non-randomised evidence supporting revascularisation of hibernating myocardium.5

In the setting of chronic ischaemic cardiomyopathy, to date there have been two single centre clinical studies examining the utility of the transmural extent of LGE in predicting recovery of contractile function. The first was performed by Kim et al1 in a cohort of 41 patients undergoing revascularisation by either percutaneous...
transluminal coronary angioplasty or coronary artery bypass grafting. They found that the likelihood of improvement in regional function after revascularisation decreased progressively as the transmural extent of LGE before revascularisation increased. This was subsequently confirmed in a study by Selvanayagam et al, which exclusively examined patients after surgical revascularisation. The ability of LGE-CMR to evaluate those segments that have severe dysfunction (and often the most difficult to evaluate with other imaging techniques) with high diagnostic accuracy is one of the strengths of the LGE-CMR technique. In addition, with excellent spatial resolution and contrast noise ratio, LGE-CMR has high sensitivity to detect viable myocardium and thus may provide more sensitive (albeit less specific) prediction of recovery of segmental function than inotropic contractile reserve.

The analysis of what constitutes LGE positivity in human CMR studies of ischaemic cardiomyopathy has been controversial. In earlier animal model studies performed by Kim et al, a signal intensity cut-off 2SD above normal myocardium identified accurately the extent of myocardial infarction. A recent elegant study by Amado et al in a canine model of myocardial infarction demonstrated that the full width at half-maximum technique for quantification of volume of myocardial enhancement was the most accurate. This method requires selection of a seed point within hyperenhanced myocardium. Software then identifies all pixels with signal intensity >50% of this point. The maximal signal intensity within this region is determined, and the final scar extent is defined as tissue exhibiting signal intensity >50% that of the maximal signal intensity. Quantifying scar size by tissue with signal intensity 2SD above normal myocardium, as originally described by Kim et al, was found to overestimate infarct size, whereas five and six SD thresholds were closer to histopathology.

Myocardial infarct size as quantified by the late gadolinium technique has been demonstrated to be a powerful predictor of mortality and adverse LV remodelling—more powerful than left ventricular ejection fraction (LVEF). Scar burden as quantified by CMR, or indeed single photon emissions computed tomography (SPECT) imaging, has been shown to be a powerful predictor of response to cardiac resynchronisation therapy in ischaemic cardiomyopathy patients.

Kwong et al reported a high prevalence of myocardial fibrosis among diabetic patients with clinical features suspicious of coronary heart disease, but no history of, or ECG findings consistent with, prior myocardial infarction. The presence of LGE on CMR was associated with a high risk of future adverse cardiac events, whereas its absence portended a favourable 2 year outlook.

Non-ischaemic dilated cardiomyopathy

Autopsy studies suggest that interstitial or replacement fibrosis is found in at least 57% of cases of non-ischaemic dilated cardiomyopathy (NICM) and that up to 20% of the LV myocardial mass may be scar in these cases. McCrohon et al reported the CMR findings of 90 patients with systolic LV dysfunction, all of whom underwent coronary angiography. They observed 100% prevalence of LGE in either a subendocardial or transmural distribution among those with significant coronary disease. In contrast, LGE was absent in 59% of those with NICM, had a patchy, mid-wall distribution in 28% of cases (figure 3), and displayed a subendocardial pattern indistinguishable from ischaemic cardiomyopathy in the
remaining 13%. The authors suggested that LGE-CMR might be an acceptable alternative to coronary angiography in determining the aetiology of severe cardiomyopathy because of its non-invasive nature, and because the absence of luminal coronary abnormalities on angiography does not exclude an ischaemic cause of LV dysfunction. They postulate that some of those cases without severe coronary disease may represent re-canalised myocardial infarction.

Assomull et al found mid-wall LGE in 35% of patients with established NICM recruited from a large tertiary hospital setting. They reported that fibrosis extent (using a 2SD signal intensity threshold) was a significant predictor of the development of death or hospitalisation, and was superior to LV volumes and ejection fraction. More recently, Wu et al reported that among 65 patients with NICM diagnosed a median of 4 years before, 42% exhibited LGE, involving on average 10% of myocardial mass. In contrast to the earlier study, ‘fibrosis’ was defined as signal intensity greater than the peak signal intensity of a remote normal region of myocardium. The presence of LGE has been shown to be associated with the incidence of ventricular tachycardia in HCM patients.

Valvular heart disease
Chronic valvular heart disease may impose either a volume load (in the case of mitral or aortic incompetence) or pressure load (in the case of aortic stenosis) on the left ventricle. These two

Hypertrophic cardiomyopathy
Hypertrophic cardiomyopathy (HCM) is a genetic disorder characterised by the development of cardiac muscle fibre disarray, dysplasia of small intramural coronary arterioles, and myocardial fibrosis. It must be distinguished from hypertensive LV hypertrophy and athlete’s heart, particularly in its early stages. Moon et al reported the ability of LGE-CMR to accurately identify and quantify replacement fibrosis in HCM. A cross-sectional study of 21 HCM patients demonstrated fibrosis by the LGE technique in 81% of cases. Scarring was patchy but occurred predominantly within hypertrophied segments (typically observed at the junction of the right ventricle and interventricular septum) (figure 4). Findings from another series corroborate this pattern of LGE in HCM. The presence of LGE has been shown to be associated with the incidence of ventricular tachycardia in HCM patients.

Figure 3  Short axis late gadolinium cardiac magnetic resonance image demonstrating hyperenhancement typical of fibrosis in a patient with non-ischaemic dilated cardiomyopathy (arrow). Fibrosis may be seen mid-wall.

Figure 4  (A) Short axis late gadolinium cardiac magnetic resonance (CMR) image demonstrating hyperenhancement typical of fibrosis in a patient with hypertrophic cardiomyopathy (arrow). Fibrosis is typically seen within hypertrophied segments, particularly at the junction of the right ventricle with the interventricular septum. (B) Corresponding short-axis cine CMR image of the left ventricle.
pathophysiological processes result in different patterns of chamber remodelling: volume overload results in eccentric remodelling, in which wall thickness is reduced relative to chamber volume; pressure overload causes concentric remodelling, where wall thickness is maintained or increased relative to chamber size. Myocardial fibrosis is a feature of longstanding valvular heart disease irrespective of the mechanism. CMR has demonstrated sensitivity of 74% and specificity of 81% for detection of myocardial fibrosis in patients with severe aortic valve disease. Fibrosis quantity was associated negatively with LVEF. Rudolph et al reported a 62% prevalence of LGE in patients with aortic stenosis and LV hypertrophy. Weidemann et al confirmed that myocardial fibrosis is common in patients with severe, symptomatic aortic stenosis, and could be detected accurately by CMR. Not surprisingly, they found that myocardial fibrosis was not reversible following aortic valve replacement.

Other conditions
Myocardial fibrosis may also be seen in a number of other cardiac conditions, such as sarcoidosis and arrhythmogenic right ventricular cardiomyopathy. The ability of CMR to identify fibrofatty replacement and/or infiltration, as well as to provide images of high spatial resolution in any plane, permit it a role in their diagnosis.

T1 mapping
The major limitation of late gadolinium enhancement CMR in the detection of myocardial fibrosis is its reliance on differences in signal intensity between scarred regions and adjacent normal myocardium. It thus has reduced sensitivity for the detection of diffuse myocardial fibrosis, which is the pathological hallmark of NICM and volume overloaded conditions. T1 mapping, the calculation of a post-contrast myocardial T1 time by imaging a given plane with sequentially increasing inversion times, has been validated in animal studies as showing a good correlation with ex vivo fibrosis content. Reproducibility has been defined, and more recently this technique has been used to discriminate heart failure patients from healthy controls even after excluding myocardial segments displaying late gadolinium enhancement. In this study, Iles et al performed CMR on 25 patients with heterogeneous causes of heart failure, and 20 healthy controls. The mid-chamber short axis slice was imaged at a range of inversion times 15 min following the administration of 0.2 mmol/kg gadolinium-DTPA. The average T1 in regions of interest was measured using specialised software (figure 5). They found a significant difference in T1 time between LGE positive and negative myocardium among heart failure patients (380±30 ms vs 429±22 ms, respectively, p<0.02) and a significant difference in T1 time between the LGE negative myocardium of heart failure patients and healthy controls (429±22 ms vs 564±25 ms, respectively, p<0.001). Although more work needs to be done on the robustness of the technique, especially with respect to multicentre, multi-vendor application, this technique shows promise in the quantitative evaluation of diffuse myocardial fibrosis, and hence may have a potentially wide array of applications in heart failure, cardiomyopathy, and valvular heart disease.

ECHOCARDIOGRAPHY
Myocardial composition influences its acoustic properties. Collagen is an important cause of ultrasound scattering and attenuation. The measurement of peak integrated backscatter and cyclic variation in integrated backscatter may thus reflect a degree of myocardial fibrosis (figure 6). Hoyt et al demonstrated a linear relationship between myocardial hydroxyproline content as a marker of fibrosis and magnitude of echocardiographic integrated backscatter in autopsy specimens from victims of myocardial infarction. Among a cohort of hypertensive patients, integrated backscatter decreased and cyclic variation in integrated backscatter increased following treatment with blood pressure lowering agents. Myocardial scar, as defined by two dimensional echocardiographic wall thickness <6 mm, was associated with increased acoustic reflectance, and predicted response to cardiac resynchronisation therapy among patients with ischaemic cardiomyopathy. This technique has a limited role in the assessment of fibrosis in non-ischaemic cardiomyopathies.

Myocardial strain refers to its degree of deformation through the cardiac cycle. Strain may be measured by either tissue Doppler imaging or speckle tracking. The latter technique relies upon echocardiographic software recognition of myocardial echo-contrasts points by their acoustic characteristics, and measurement of their displacement over the cardiac cycle (figure 7). Given the effect of collagen deposition on myocardial deformation, strain measurement may be well suited to indirect evaluation of myocardial fibrosis. Gjesdal et al and Roes et al have both demonstrated a high sensitivity and specificity for longitudinal strain scores to predict extent of myocardial scar among patients with ischaemic LV dysfunction as compared with contrast enhanced CMR. Weidemann et al quantified myocardial fibrosis histologically in biopsies from the LV outflow tract in 58 aortic valve prosthesis recipients for severe, symptomatic aortic stenosis. Patients underwent comprehensive echocardiographic evaluation (including radial and longitudinal strain and strain rate imaging using tissue Doppler) preoperatively and 9 months postoperatively. The authors demonstrated uniform improvement in these parameters only among subjects with no or mild fibrosis. Baseline radial LV function and LVEF were similar irrespective of myocardial fibrosis burden, whereas longitudinal indices of LV function were significantly reduced in those with more extensive fibrosis. This study suggests that quantitative evaluation of longitudinal LV function may be a sensitive tool for detection of the mechanical effects of myocardial fibrosis.
NUCLEAR IMAGING
Cardiac nuclear imaging encompasses the techniques of positron emission tomography (PET) and SPECT, and with these techniques there is now a wealth of evidence in the assessment of myocardial viability and therefore indirectly of scarred and fibrotic myocardium. The basic principles of PET are similar to those of SPECT (both form images by way of intravenous radioisotopes concentrating in viable myocardium, giving off $\gamma$-radiation which is detected by an external $\gamma$-camera); however, for scar detection, PET systems are generally more sensitive than SPECT systems, having better spatial resolution, and providing more accurate attenuation correction.

In patients with ischaemic cardiomyopathy, scar tissue as detected by PET is a good predictor of lack of recovery of LV systolic function after coronary artery bypass surgery, though precise individual prognostication is difficult.16 17 Also, as expected, PET provides information on outcome. In a meta-analysis of 10 such studies (1046 patients), annualised mortality rates were 4% for those with viable myocardium who underwent revascularisation versus 17% for those with viability who did not.18 17 If no viability was demonstrated with PET, revascularisation was not associated with changes in mortality rates (annual mortality rates of 6–8%). Such evidence has encouraged studies in which treatment is based on PET findings, but so far the studies have only been partly successful. In the PARR-2 trial, treatment based on $^{18}$F-FDG PET findings was equivalent to standard care after 1 year of follow-up.18 In a post-hoc analysis of the PARR-2 trial data, however, the patients with ischaemic cardiomyopathy with larger amounts of perfusion–metabolism mismatch (>7%) did have improved outcome with revascularisation,18 and PET may find a place to assess outcome in patients with critical ischaemic cardiomyopathy in whom surgery is of risk.

The water perfusable tissue index has emerged as a candidate for in vivo detection of myocardial fibrosis by PET.19 Briefly, the ratio of the water perfusable tissue fraction to the anatomic tissue fraction is determined using the tracers $H_2^{15}$O and $C^{15}$O. In normal individuals, the perfusable tissue index should be 1.0, but fibrotic tissue is unable to exchange water rapidly and hence the tissue index decreases in fibrotic myocardium. In dogs a reduction of the perfusable tissue index correlates well with the extent of fibrosis after infarction. In humans, comparisons have been made to LGE-CMR in different patient populations. In patients

Figure 5  T1 mapping. (A) Regions of interest are drawn around the left ventricular myocardium at different inversion times. (B) Signal intensities for each region of interest are fitted to an exponential recovery curve to obtain the myocardial T1 time. Reproduced with permission from Illes et al.13

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with scarring due to myocardial infarction, late gadolinium enhancement was indeed negatively correlated \((r=-0.65)\) with the perfusable tissue index, but the water perfusable tissue index systematically underestimates the amount of scar tissue if the latter becomes extensive. With respect to replacement fibrosis in patients with HCM where Gd late enhancement was seen, the perfusable tissue index was essentially unaffected. The perfusable tissue index was slightly lowered in the LV free wall of patients with HCM, but not at all in the septum where myocardial disarray, oedema, and later fibrosis predominantly take place (figure 8). The authors suggest that hyper-enhancement by LGE-CMR may not be solely governed by fibrosis but also (especially so early in the natural history of HCM) by oedema; however, in light of missing histology, the finding may equally well be attributed to a lack of sensitivity by the perfusable tissue index technique.

In clinical practice, SPECT is still the more robust and more often applied technique and a wealth of evidence testifies to its ability to demonstrate (larger) viability defects and provide for important prognostic information. In comparison with PET, SPECT has more limited spatial resolution.

**Figure 6** Segmental curves representing regional integrated backscatter in the parasternal short axis view by speckle tracking echocardiography.

**Figure 7** Segmental curves representing regional longitudinal left ventricular strain in the apical four chamber view as determined by speckle tracking echocardiography.
Biomarkers of myocardial fibrosis

In comparison with cardiac imaging, serum biomarkers of myocardial fibrosis have yet to achieve general acceptance in clinical practice. This may relate to the semi-quantitative nature of measurement techniques, and to inferior specificity in a general population, in whom collagen turnover may be increased due to comorbid conditions. Nonetheless, serum biomarkers of myocardial fibrosis are conceptually appealing as they allow measurement of diffuse fibrosis, the quantification of which remains elusive using current imaging techniques.

Martos et al found higher concentrations of serum carboxy-terminal telopeptide of procollagen type I, amino-terminal propeptide of procollagen type III, MMP-1, -2, and -9, and TIMP-1 in patients with diastolic heart failure compared with those without. Serum TIMP-1 concentration has been associated with echocardiographic indices of diastolic dysfunction in hypertensive patients. This study demonstrated that serum MMP-2 concentration was the most sensitive and specific biomarker of heart failure with preserved ejection fraction, superior to B-type natriuretic peptide (BNP). Based on this finding, the authors propose an adjunctive role for MMP-2 in the diagnosis of this condition, although this is yet to gain widespread clinical acceptance.

In a cross-sectional study of 1069 subjects from the Framingham Heart Study, serum TIMP-1 concentration was positively related to LV mass, end-systolic diameter, and left atrial diameter after adjustment for age, sex and height. Although adjustment for further clinical covariates attenuated the strength of association between TIMP-1 concentration and echocardiographic measures, the authors concluded that this evidence supports the hypothesis that cardiovascular risk factors promote LV remodelling by influencing turnover of the extracellular matrix.

In a study by Yan et al of systolic heart failure patients, serum MMP-9 concentration was demonstrated to have a positive linear relationship with LV end-systolic volume and a negative association with LVEF. Over 43 weeks follow-up, there was a negative relationship between change in serum MMP-9 concentration and change in LVEF. In contrast, Vorovich et al have recently shown that serum MMP-9 concentration is a poor marker of LV remodelling and clinical outcome compared with BNP.

At the present time, although associations between serum fibrosis biomarker concentration and indices of myocardial disease have been demonstrated, the clinical role of serological testing remains to be defined. Moreover, the robustness of these assays outside of research laboratories is unknown.

Future directions

Novel imaging techniques

There is preliminary research to suggest a potential role for molecular imaging in fibrosis detection and quantification. Collagen targeting molecules have
LGE-CMR technique, and can be inferred through its functional consequences in terms of echocardiographic measures of LV strain or PET metabolic imaging. In contrast, diffuse myocardial fibrosis remains difficult to identify using currently available imaging modalities, although T1 mapping by CMR holds promise. There is preliminary evidence to support the ability of serum markers of collagen turnover to identify myocardial fibrosis. The utility and clinical benefit of these assays in ‘real world’ practice remains to be demonstrated.

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► Recent key paper on the use of T1 mapping CMR technique to quantify diffuse myocardial fibrosis in dilated cardiomyopathy.


► Paper illustrating the potential for ultrasonic tissue characterisation by backscatter analysis in hypertensive patients.


► Study demonstrating the ability of strain as measured by speckle tracking echocardiography to identify regions of myocardial infarction.


► Comprehensive serological study of hypertensive patients with varying degrees of diastolic dysfunction.

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