Myocardial Tissue Characterization and Fibrosis by Imaging

Brief Title: Cardiovascular imaging for tissue characterization

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HIGHLIGHTS:

- Tissue composition changes such as fibrosis, edema, or infiltration are frequent features in myocardial diseases
- Cardiac imaging modalities offer the ability to characterize myocardial tissue to varying extent
- Cardiovascular magnetic resonance offers comprehensive myocardial tissue characterization providing various diagnostic and prognostic imaging biomarkers
- Advanced cardiac imaging is expected to become an integral part in risk-stratification and personalized medicine

ABSTRACT

Myocardial fibrosis, either focal or diffuse, is a common feature of many cardiac diseases and is associated with a poor prognosis for major adverse cardiovascular events. While histological analysis remains the gold standard for confirming the presence of myocardial fibrosis, endomyocardial biopsy is invasive, suffers from sampling errors, and is not practical in the routine clinical setting. Cardiac imaging modalities offer non-invasive surrogate biomarkers not only for fibrosis but also for myocardial edema and infiltration to varying degrees, and have important roles in the diagnosis and management of cardiac diseases. This review summarizes important pathophysiologic features in the development of commonly-encountered cardiac diseases, and the principles, advantages and disadvantages of various cardiac imaging modalities (echocardiography, single photon emission computer tomography, positron emission tomography, multi-detector computer tomography, and cardiovascular magnetic resonance imaging) for myocardial tissue characterization, with an emphasis on imaging focal and diffuse myocardial fibrosis.

Keywords: cardiac imaging; edema; fibrosis; late gadolinium enhancement; mapping

ABBREVIATIONS:

CMR= cardiovascular magnetic resonance
ECV= extracellular volume fraction
GBCA= gadolinium based contrast agent
LGE= late gadolinium enhancement
LV= left ventricular
MDCT= multidetector computed tomography
MRI= magnetic resonance imaging
PET= positron emission tomography
SPECT= single photon emission computed tomography

INTRODUCTION

Myocardial diseases are characterized by changes in tissue composition, such as the development of myocardial fibrosis, edema, or infiltration with fat, iron or amyloid. Modifications in the extracellular matrix may lead to diastolic and/or systolic dysfunction, increasing the risk of adverse cardiovascular events(1,2). Therefore, the early detection of structural myocardial changes is of major diagnostic and prognostic value. The gold standard technique to assess histological alterations, especially myocardial fibrosis, is endomyocardial biopsy. However, sampling errors, the invasive nature of endomyocardial biopsy, and its inability to quantify the fibrotic burden of the entire myocardium have limited its use (3). Cardiac imaging modalities (echocardiography, single photon emission computer tomography-SPECT, positron emission tomography-PET, multi-detector computer tomography-MDCT and cardiac magnetic resonance-CMR) offer the ability to detect pathophysiologic myocardial changes such as fibrosis, edema and infiltration to varying degrees, and have important roles in the diagnosis, management and prognostic assessment of cardiac diseases.

In this state-of-the-art review, we will present the role of non-invasive imaging techniques in myocardial tissue characterization, with an emphasis on fibrosis imaging, in clinical applications.

PATHOPHYSIOLOGY

Myocardial Edema

Acute myocardial injury is followed by water dispersion in the intracellular and interstitial spaces, as a consequence of ischemic acidosis, vasodilatation and increased capillary permeability (4). Edema is an important component of acute myocardial processes of varied etiologies, including myocardial infarction, myocarditis, stress cardiomyopathy and heart transplant-graft rejection, and is associated with left ventricular (LV) systolic and diastolic dysfunction(5).

Myocardial Fibrosis

Fibrosis is a common pathological feature of many cardiac diseases, resulting in increased wall stiffness, cardiac remodeling and heart failure(6). Importantly, myocardial fibrosis is a major prognostic factor of adverse cardiac events(7).

There are two main types of myocardial fibrosis: 1. *Reactive interstitial fibrosis*, characterized by a diffuse microscopic distribution in the myocardium and sometimes by localized perivascular distribution, seen in arterial hypertension, valvular heart disease, diabetic cardiomyopathy, hypertrophic cardiomyopathy, idiopathic dilated cardiomyopathy and the aging heart. In contrast to replacement fibrosis, interstitial fibrosis is not induced by cell death, and is a gradual process which can be reversed, if the cause is treated promptly(8). It is considered a marker of disease severity. If the condition worsens, it is followed by myocyte apoptosis and irreversible replacement fibrosis(6). 2. *Replacement fibrosis* typically occurs after myocyte injury or death, mostly in acute ischemic conditions, where cell apoptosis triggers fibroblasts and promotes deposition of collagen fibrous tissue in the myocardium(9). It usually follows a localized macroscopic distribution. Replacement myocardial fibrosis may also occur in

myocarditis, hypertrophic cardiomyopathy, idiopathic dilated cardiomyopathy, sarcoidosis, and may demonstrate a diffuse distribution in toxic cardiomyopathies, chronic renal insufficiency, and as part of systemic inflammatory diseases(10). It is often present in the terminal stages of heart failure.

Another subtype of fibrosis is infiltrative interstitial fibrosis induced by the progressive deposition of insoluble amyloid (amyloidosis) or glycosphingolipids (Anderson-Fabry disease) in the heart(3).

Myocardial fat infiltration

Fat naturally develops around the heart, as pericoronary adipose tissue or epicardial fat, mainly adjacent to the right ventricle. Abnormal myocardial fat infiltration has been described in arrhythmogenic cardiomyopathy, cardiac lipoma, tuberous sclerosis complex, and other cardiomyopathies. Lipomatous metaplasia also occurs in some chronic scars in ischemic cardiomyopathy(11).

Myocardial iron infiltration

Myocardial iron overload is characterized by the accumulation of excess body iron in the heart. Iron initially infiltrates the ventricular myocardium and subsequently the atrium, progressively leading to iron overload cardiomyopathy(12).

Myocardial amyloid infiltration

The term “amyloid” is used to describe abnormal extracellular, insoluble, protein fibrils that resist proteolysis and infiltrate many organs(13). Cardiac amyloidosis is

characterized by extracellular amyloid infiltration throughout the heart(13). Amyloid deposits impair myocardial contractile function and electrical conduction.

IMAGING MODALITIES FOR MYOCARDIAL TISSUE CHARACTERIZATION

Echocardiography

Myocardial reflectivity to ultrasound and the analysis of backscatter signal have been used as a noninvasive method of tissue characterization and marker of collagen deposition (14). A greater calibrated integrated backscatter is indicative of greater fibrosis (Figure 1). Ultrasound elasticity imaging has been developed to measure the static stiffness of tissues. This technique can be thought of as palpating the tissues virtually using ultrasound(15). Although there is some correlation between calibrated integrated backscatter and fibrosis in patients with extensive myocardial fibrosis, this relationship is less clear in patients with milder degrees of fibrosis(16). Shear wave elasticity imaging can also detect dynamic stiffness changes during the cardiac cycle(15). Overall, ultrasonic reflection techniques have not been widely used in clinical practice for quantification of fibrosis, as they lack sensitivity and, therefore, have been surpassed by novel cardiovascular magnetic resonance (CMR) techniques.

Tissue Doppler imaging and speckle tracking echocardiography can measure myocardial strain. Regional strain is a dimensionless measurement of myocardial deformation, expressed as a fractional or percentage change from an object's original dimension. Strain rate refers to the speed at which myocardial deformation (ie, strain)

occurs. These parameters correlate inversely with systolic and diastolic dysfunction, and may reveal functional abnormalities in fibrotic processes earlier than conventional echocardiographic techniques(17)19)20). Overall, compared to late gadolinium enhancement (LGE) CMR, strain imaging using echo has moderate diagnostic capacity to detect fibrosis, because it focuses on functional measures, rather than tissue characteristics, as a surrogate marker of fibrosis.

Non-specific surrogate echocardiographic markers, such as regional increase in LV thickness and mass, have been used to suggest the presence of myocardial edema. High-frequency ultrasound techniques have been reported to indirectly characterize myocardial water content by quantification of alterations in mechanical properties of tissue(18).

Echocardiographic characteristics such as ‘sparkling’ myocardial texture, hypertrophy of the ventricles, thickening of heart valves, and restrictive LV filling pattern suggest the diagnosis of cardiac amyloidosis. In this condition, LV global longitudinal strain is significantly reduced at the basal and mid segments of the left ventricle (Figure 2), while the deformation of the apical segments may be preserved (apical sparring). In Anderson-Fabry disease, patients with myocardial fibrosis of the basal posterolateral LV wall on CMR, show more impaired LV global longitudinal strain as compared with patients without, despite having preserved LV ejection fraction. Furthermore, patients with proven cardiac sarcoidosis on CMR, have significantly more impaired global longitudinal strain as compared with controls.

Nuclear Imaging

Single Photon Emission Computed Tomography (SPECT)

SPECT myocardial perfusion imaging is well-established for the evaluation of patients with known or suspected coronary artery disease. Irreversible perfusion defects are indirect markers of fibrosis(19) whereas molecular imaging is more specific for collagen formation. Avβ3 integrin is expressed by activated cardiac myofibroblasts and endothelial cells, and represents a target for angiogenesis and scar formation post myocardial infarction. Cy5.5-RGD imaging peptide labeled with technetium-99m binds to such targets to evaluate myocardial remodeling (20). Increased uptake of radiolabeled angiotensin II receptor blocker (technetium-99m losartan) demonstrated histologically proven proliferative activity of myofibroblasts 12 weeks post myocardial infarction(21).

Bone scintigraphy (Figure 2) using 99mTc-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), 99mTc-labeled pyrophosphate (PYP), and 99mTc-labeled hydroxymethylene diphosphonate (HMDP) is highly sensitive for imaging cardiac transthyretin (ATTR) amyloidosis(22). When scintigraphy is combined with biochemical testing for a monoclonal protein in serum and urine, cardiac ATTR amyloidosis can be diagnosed in the absence of histology with >98% certainty.

Positron Emission Tomography (PET)

Perfusable tissue index has been used as an indirect marker of myocardial fibrosis. A reduction of this index has been shown to correlate with the extent of fibrosis estimated with CMR in ischemic heart disease(23). Furthermore, the index was shown to

be reduced in patients with advanced dilated cardiomyopathy indicating possible interstitial fibrosis (24).

Markedly reduced or absent 18-Fluorodeoxyglucose (18F-FDG) uptake indicates fibrosis(25), and FDG-PET is mainly used to assess myocardial viability. Molecular PET may assess mechanisms underlying fibrosis formation, but current techniques remain at an experimental stage and need to be validated in clinical studies.

Cardiac PET may be useful to detect cardiac sarcoidosis and monitor response to therapy(26). Cardiac 18F-FDG PET studies for sarcoidosis should combine both perfusion imaging and 18F-FDG imaging (Figure 3) to differentiate the patterns of disease(27). A high-fat, low-carbohydrate diet followed by prolonged fasting is needed to suppress physiologic myocardial glucose uptake.

Multidetector Computed Tomography (MDCT)

Myocardial infarction is depicted as a low density, unenhanced area in arterial-phase MDCT, and as a hyperenhanced area in late-phase MDCT. Fibrosis identification with MDCT has shown satisfactory agreement with LGE CMR, particularly in ischemic heart disease (28). A key feature of acute infarction is myocardial edema, presenting with CT values near zero, due to increased water content. Evidence from experimental models of acute infarction showed substantial correlation between unenhanced dual source CT and T2-weighted CMR to detect myocardial edema (29). The area presenting with edema in unenhanced CT, but without delayed enhancement in late-phase, is likely to correspond to the salvageable area-at-risk.

The use of MDCT to detect diffuse abnormalities of myocardial tissue is significantly more challenging than the evaluation of regional scar, due to the low contrast resolution. A small study in patients with heart failure and healthy individuals found a good correlation ($r = 0.82$, $P < 0.001$) between CMR and MDCT-derived ECV(30), but only the anterior and anterolateral myocardial segments could be reliably analyzed. Another small study in patients with aortic stenosis demonstrated that ECV, measured using an equilibrium CT technique, correlated well with histologic quantification of myocardial fibrosis and ECV measured using equilibrium CMR(31). MDCT has also been used to detect intramyocardial fibrosis in patients with hypertrophic cardiomyopathy(32), and myocardial iron overload(33).

Cardiac magnetic resonance (CMR)

CMR is not only accurate in the assessment of cardiac anatomy and function, but is also superior in non-invasive myocardial tissue characterization, outweighing other imaging modalities in its multiparametric capabilities for a comprehensive cardiac examination. T1- and T2-weighted sequences are a basic way to perform tissue characterization. T1 relaxation time is shortened by gadolinium-based contrast agents (GBCA) and late gadolinium enhancement (LGE) images may be used to highlight areas of focal fibrosis compared to normal myocardium. Myocardial fibrosis causes significant expansion of the extracellular space, leading to a higher regional concentration of GBCA and an area of relative hyperenhanced signal(34). Mapping techniques allow direct, pixel-by-pixel quantitative myocardial tissue characterization without the need for presumed-normal reference regions of interest to highlight areas of disease. The principles of

mapping techniques are reviewed elsewhere(35). Briefly, native (pre-contrast) T1-mapping reflects a composite signal from both the intracellular (mainly myocytes) and extracellular myocardial compartments. Each tissue type exhibits a characteristic range of normal T1 relaxation times at a particular field strength, deviation from which may be indicative of disease or a change in physiology. T1 relaxation times are prolonged by increased free water content in tissues, and generally shortened by iron, fat and GBCAs. Areas of fibrosis and extracellular volume expansion are characterized by the accumulation of water, which typically prolongs native T1 time. The myocardial extracellular volume (ECV) can be quantified using pre- and post-contrast myocardial and blood T1 values, adjusting for the blood hematocrit. Pixel-wise ECV maps can also be created. Myocardial ECV may act as a surrogate marker of fibrosis when other pathologies that increase the extracellular space, such as myocardial edema/inflammation, infiltration (2) and ischemia(44), have been excluded. T2-mapping quantifies T2 myocardial relaxation times and is mainly used to detect edematous myocardium.

Acute myocardial infarction: Acute ischemic injury leads to downstream myocardial edema and eventual infarction, sometimes with complications such as microvascular obstruction and intramyocardial hemorrhage – all which can be visualized using CMR. Infarct size can be assessed on LGE imaging, although this may be over-estimated in the acute setting due to expansion of the extracellular space by edema. Conventionally, the area-at-risk is delineated using T2-weighted edema imaging. Newer mapping techniques, such as T1- and T2-mapping, correlate well with the area-at-risk measured by

microspheres in animal studies(36), and may be more sensitive for directly quantifying the area-at-risk (35). Microvascular obstruction may be seen on resting first-pass perfusion, early-gadolinium enhancement or LGE images, with good correlation to histopathology, and confers a poor prognosis(37). Intramyocardial hemorrhage associated with reperfusion injury is seen as signal voids on T2-weighted images, or shortened T2, T2* or T1 relaxation times on mapping techniques(38), caused by the breakdown products of hemoglobin and oxidized iron, which are paramagnetic (Figure 4). Mapping techniques have shown their utility in characterizing acute myocardial infarction, demonstrating increased T1, T2 and ECV in the area-at-risk, infarct zone, and even remote myocardium, offering additional insights into acutely infarcted myocardium(35). CMR imaging markers not only offer validated surrogates of pathophysiology in the assessment of acute myocardial infarction, but also confer prognosis that may be useful for risk-stratification of the individual patient(39).

Acute myocardial inflammation and edema: Inflammation results in edema and is a common feature of both acute ischemic and non-ischemic myocardial injury. The pathophysiologic changes in acute myocarditis, including edema, hyperemia/capillary leak, and myocyte necrosis, may be visualized on T2-weighted, early gadolinium enhancement and LGE imaging, respectively. The newer mapping techniques, including T1-mapping, T2-mapping and ECV, circumvent many of the known technical limitations of conventional CMR techniques in the detection of myocarditis, with promising initial results that point to their likely superiority (Figure 5) (40-47). A recent meta-analysis in patients with acute myocarditis has shown that native T1 mapping has superior diagnostic

accuracy across all CMR tissue characterization methods (52). In contrast, as T1-mapping and ECV may detect both acute and chronic changes, some reports suggest that T2-mapping may be more specific to acute myocardial edema and inflammation(48,49).

Myocardial fibrosis detection using LGE: LGE is still considered the clinical gold-standard for identifying areas of myocardial infarction with high spatial resolution, including small subendocardial scars which may be missed by SPECT(50). Multiple studies have demonstrated excellent spatial correlation between areas of myocardial scarring identified on LGE imaging and histopathology, both in the acute and chronic phases of infarction(51). Importantly, the transmural extent of infarction on LGE inversely predicts the likelihood of regional contractile recovery after revascularization(52) and is the current CMR standard for myocardial viability assessment.

LGE in a predominantly non-ischemic (non-subendocardial) pattern is also present in a significant proportion of patients with non-ischemic myocardial injury and cardiomyopathies(10). Its presence is strongly associated with poor prognosis, including increased risk of all-cause mortality, heart failure hospitalization and sudden cardiac death(53). Depending on the LGE pattern and distribution, CMR may, together with functional and morphological imaging, be used to diagnose specific cardiomyopathies [detailed review elsewhere (10)]. Areas with LGE in non-ischemic cardiomyopathies often correlate to (although are not specific for) areas of focal fibrosis on histopathology. For instance, the areas of midwall and subepicardial LGE typically seen in myocarditis (Figure 5) correlate to areas of inflammation, myocyte necrosis and fibrosis (54). In

dilated cardiomyopathy, mid-wall enhancement often seen in the interventricular septum (and sometimes in the inferolateral walls) corresponds to areas of macroscopic fibrosis and microscopic collagen deposition admixed with myocytes on histopathology(55). In hypertrophic cardiomyopathy, the histologic basis of LGE is complex and non-specific, which includes different types of fibrosis, such as replacement fibrosis, plexiform fibrosis associated with myofibril disarray (e.g. at the RV-LV insertion points), perivascular fibrosis and microscopic replacement scars, as well as different extent of interstitial expansion(56). Dilated lymphatic channels may also appear as areas of LGE in hypertrophic cardiomyopathy(57). The presence and extent of LGE in hypertrophic cardiomyopathy appears to be a powerful risk marker for sudden cardiac death(58). In arrhythmogenic cardiomyopathy, areas of mid-wall or subepicardial LGE may be seen in the LV, and transmural LGE in the RV. LGE in arrhythmogenic cardiomyopathy is associated with a greater risk for ventricular arrhythmias, and correlates well with the detection of fibrofatty replacement on endomyocardial biopsy (59). In aortic stenosis, fibrosis on LGE imaging is a useful biomarker of LV remodeling, and its presence is associated with worse long-term outcome after aortic valve intervention(60).

Limitations of LGE in detecting diffuse fibrosis: LGE imaging, whilst powerful in detecting areas of focal fibrosis, has limitations in detecting diffuse myocardial fibrosis. It requires regions of presumed normal myocardium, to provide the necessary contrast between affected and unaffected tissue, which may not be available in diffuse pathology. The development of T1-mapping enabled the identification and quantification of not only focal, but also diffuse myocardial fibrosis(61).

T1-mapping and ECV quantification in focal fibrosis: In general, focal replacement fibrosis in chronic myocardial infarction, as identified by LGE, exhibit high native T1 and ECV values(62-64). Native T1-mapping may provide a contrast-free method for myocardial infarction detection, especially in patients with severely impaired renal function in whom GBCAs are contraindicated(65). However, lipomatous metaplasia may occur in some chronic myocardial scars leading to lowered, pseudo-normalized or even paradoxically elevated T1 values due to fat bias(35). Furthermore, apparently-unaffected remote myocardium on LGE imaging in acute and chronic myocardial infarction exhibit abnormal T1 and ECV values(63,66), and may identify myocardium prone to adverse cardiac remodeling, worsening of contractile function and poorer prognosis(66). In non-ischemic heart disease, such as myocarditis, sarcoidosis, dilated cardiomyopathy, and hypertrophic cardiomyopathy, areas of focal fibrosis seen on LGE generally demonstrate high T1 and ECV values(2).

T1-mapping and ECV quantification in diffuse myocardial fibrosis: The measurement of T1 and ECV has known dependencies on age and sex(67). As discussed earlier, elevated T1 or ECV values may not necessarily reflect the development of diffuse myocardial fibrosis, must be interpreted within the clinical context after exclusion of confounders, and typically including the use of age- and sex-matched controls. Native T1 and ECV quantification generally show good correlation to collagen volume fraction and diffuse myocardial fibrosis on histopathology in animal models of hypertension(68) and clinical

cohorts of heart failure, valvular heart disease, and heart transplant patients with ischemic and non-ischemic cardiomyopathies(69-72).

In dilated and hypertrophic cardiomyopathy, both T1 and ECV can detect abnormalities in apparently normal myocardium on LGE-CMR. Studies have shown that, in patients with dilated or hypertrophic cardiomyopathy, even segments with normal wall thickness and no LGE show increased T1 values(73), potentially due to the presence of diffuse myocardial fibrosis and/or other causes of increased free water content not readily detected by LGE. Hypertrophic cardiomyopathy patients, including asymptomatic relatives with are genotype-positive but without LV hypertrophy, also demonstrate elevated ECV(74). In dilated cardiomyopathy patients, elevated T1 values predict a higher risk for cardiovascular events and heart failure, and there is a strong correlation between elevated ECV and collagen volume fraction within the spectrum of dilated cardiomyopathy patients(75). Patients with heart failure with preserved ejection fraction were shown to have elevated ECV compared to normal controls(76). Both T1 and ECV appear to have added value in detecting abnormalities and predicting prognosis in patients with heart failure and cardiomyopathies(77-80). The ability to detect diffuse myocardial fibrosis early may identify novel therapeutic targets and opportunities for early intervention before irreversible myocardial pathology and dysfunction develops.

Aortic stenosis is a condition characterized by a number of pathophysiologic changes in the heart as the disease progresses, including LV hypertrophy, resting coronary vasodilatation and the development of diffuse and focal fibrosis. T1 and ECV have generally been observed to be elevated in moderate-severe aortic stenosis, and correlate

to histological interstitial fibrosis and collagen volume fraction(81). It is important to keep in mind that expansion of the intravascular compartment, such as that seen in coronary vasodilatation, also contributes to elevation of T1 and thus ECV. In fact, the stress/rest T1 response has been shown to normalize after aortic valve replacement in some aortic stenosis patients(81). Thus, elevation of T1 and ECV in aortic stenosis is multifactorial. Myocardial ECV has been shown to be a stronger predictor of adverse cardiovascular outcomes than the extent of LV hypertrophy in aortic stenosis, demonstrating prognostic value(35). In the future, T1 and ECV may even play a role in the optimal timing of valve replacement in AS. Systemic arterial hypertension is another condition that subjects the LV to an increased afterload, potentially leading to hypertrophy, diastolic and systolic dysfunction. Native T1 and ECV are mildly elevated in patients with hypertension and LV hypertrophy compared to those without, which may reflect diffuse myocardial fibrosis(82). The degree of T1 or ECV elevation may help differentiate hypertensive heart disease from other LV hypertrophy phenotypes, such as hypertrophic cardiomyopathy, cardiac amyloidosis or athlete's heart.

T1/ECV in Athlete's Heart: Recent studies using CMR showing normal or decreased ECV in athlete's hearts support the notion that the physiological LV hypertrophy is due to myocyte enlargement rather than increased extracellular matrix(83). These were in contrast to findings of hypertrophic cardiomyopathy, in which the pathological LV hypertrophy has been shown to correlate directly with ECV, suggesting that a significant proportion of the LV mass is due to an increase in extracellular matrix and that mapping may potentially be useful in differentiating athlete's hearts from other forms of

cardiomyopathy(83). Focal areas of fibrosis have been demonstrated in up to 13% of elite and veteran athletes, both in histopathology and on CMR LGE, with an apparent dose-response of focal fibrosis to exercise(84). It is less clear whether high-intensity exercise first induces diffuse myocardial fibrosis which then progress to focal fibrosis, or whether there is a dose-response threshold of developing either focal or diffuse fibrosis in response to exercise in this setting(85). Longitudinal characterization of the cardiac phenotype in athletes would provide further insights.

CMR for myocardial infiltration: CMR has a major role in the diagnosis and prognostication of infiltrative myocardial pathology. Amyloid light-chain (AL) and cardiac transthyretin amyloidosis can be detected by a circumferential pattern of LGE in combination with a dark blood pool, initially affecting the subendocardium but expanding transmurally as disease progresses (Figure 2)(86). T1-mapping techniques have high diagnostic accuracy for detecting cardiac amyloidosis (Figure 6) and probably greater sensitivity for detecting early disease compared to LGE-CMR (86,87). The degree of ECV expansion in established cardiac amyloidosis is beyond that of any other myocardial disease, making it almost pathognomonic, especially when combined with structural, functional and clinical features. Myocardial native T1-mapping and ECV predict mortality in patients with systemic amyloidosis(80).

Myocardial fat can be easily detected with T1-or T2-weighted CMR as areas of bright signal. Native T1-mapping is also a good way to identify fat, with low T1 values in

general, with the caveat of paradoxically high T1 values in voxels partially occupied by fat (88).

Anderson-Fabry disease, characterized by accumulation of intramyocardial sphingolipids, has a characteristic CMR phenotype, with LV hypertrophy accompanied by small areas of diffuse LGE pattern (corresponding to areas with abnormal lipid accumulation), with a broad band of midwall enhancement localized to the basal inferolateral wall (corresponding to regions of dense collagen on histopathology)(87) (Figure 7). Native T1-mapping can distinguish these two populations of abnormal myocardial pixels, offering incremental value to LGE(89,90) and may also detect RV involvement(91). T1-mapping may identify the Anderson-Fabry phenotype early as LV hypertrophy with low T1 values, differentiating from other diseases with hypertrophy(89).

Myocardial iron overload has been shown to shorten T1, T2, and T2* values. The standard CMR technique for the detection of cardiac iron accumulation is T2* mapping, validated in animal and human studies(92), while T1 and T2 mapping show excellent quantitative agreement, with both showing good correlation to T2*(35,93)

Conclusions

Often, cardiac diseases result in common pathophysiologic processes, including myocardial edema, and the development of diffuse and focal fibrosis which portend a poor prognosis. In this regard, non-invasive imaging modalities provide important information on cardiac structure, function and tissue changes to varying degrees. With the

advancement of quantative, pixel-wise CMR mapping technology, it is now feasible to detect changes in acute myocardial injury, as well as focal and diffuse myocardial fibrosis, with high spatial resolution. The effective use of these sophisticated imaging biomarkers for medical decision-making, prognostication and development of therapeutic targets will maximize clinical utility. Advanced cardiac imaging is expected to become an integral part in risk-stratification and personalized medicine for the greatest clinical impact.

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FIGURE LEGENDS

Figure 1. Calculation of Calibrated Integrated Backscatter
Measurements of tissue intensity are obtained from sample volumes placed within the pericardium (yellow), posterior wall (blue), and anteroseptum (green) in a parasternal long-axis view. A resultant integrated backscatter curve is derived with standard commercial software (Echopac, General Electric Medical Systems, Milwaukee, Wisconsin) and enables calibrated integrated backscatter to be calculated by subtracting mean pericardial integrated backscatter intensity from mean integrated backscatter intensity of the posterior wall or anteroseptum at end diastole. (As originally published in Jellis. et al. (94); reproduced with permission)

Figure 2. Multimodality workup of a patient with cardiac transthyretin amyloidosis This multidisciplinary workup of a patient with cardiac transthyretin amyloidosis with an Se77Tyr variant displayed (A) a strain pattern characteristic of an infiltrative process; (B) a 4-chamber cine steady-state free precession image and corresponding LGE image showing transmural LGE; and (C) whole-body anterior 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy and hybrid single-photon emission computed tomography-computed tomography showing Perugini grade 1 abnormal uptake. As published in Martinez-Naharro A et al(86), reproduced with permission.

Figure 3. PET in cardiac sarcoidosis.
Cardiac PET short-axis views. (A) Severely decreased 13N-ammonia uptake in most of the apex, mid left ventricle and basal inferolateral segment of the left ventricle. There is corresponding 18F-FDG uptake in most of these regions consistent with cardiac sarcoidosis with active inflammation. Scattered areas of scar in the mid left ventricle are also present. (B) After treatment with immunosuppressive medications, the patient improved clinically. There is severely decreased inferolateral 13N-ammonia uptake, with no myocardial 18F-FDG uptake, consistent with advanced cardiac sarcoidosis with scar but without active inflammation. As originally published in by Aggarwal et al(27) reproduced with permission.

Figure 4. CMR tissue characterization of an inferior myocardial infarction
Basal left ventricular (LV) short axis of a patient with an acute inferior myocardial infarction (MI) depicting microvascular obstruction (MVO) on late gadolinium enhancement (LGE) scans with corresponding hypointense cores (red arrows) on the basal LV short axis T1, T2, and T2* maps and the follow-up scan with corresponding maps and areas of residual myocardial iron on the T2* map. (as originally published by Wolters Kluwer Health, Inc. in Bulluck H. et al. (95) and shared under the "Creative Commons Attribution Noncommercial License"

Figure 5. CMR images (1.5 Tesla) of a patient who presented with severe acute viral myocarditis.

(A) Dark-blood T2-weighted imaging showed global and focal increased myocardial T2 signal intensity, with a T2 SI ratio compared to skeletal muscle (not shown) of > 3.0, consistent with severe acute edema. (B) T2-mapping showed global increase in myocardial T2 values of 89 ± 7 ms, consistent with edema. (C) Late gadolinium enhancement (LGE) imaging showed multiple areas of midwall, subepicardial and

patchy enhancement in a non-coronary distribution. (D) Native T1-mapping using the ShMOLLI method showed significantly increased global myocardial T1 values (1048 ± 79 ms; normal 962 ± 25 ms), and up to 1240 ms in focal areas of injury. (E) Post-gadolinium contrast T1-mapping (at 15 min) showed areas of very low T1 in areas of LGE. (F) Extracellular (ECV) mapping showed significantly expanded ECV of 43% (normal 27 ± 3 %). (Ferreira VM, J de Lara Fernandes, C Basso, Friedrich MG. Myocarditis. In: *The EACVI Textbook of Cardiovascular Magnetic Resonance* M. Lombardi, V. Ferrari, C. Bucciarelli-Ducci, S. Petersen, and S. Plein, Eds.Oxford, UK: Oxford University Press; (in press); reproduced with permission).

Figure 6. CMR techniques for tissue characterization in cardiac amyloidosis
Images shown include 4-chamber cine, corresponding LGE image with phase-sensitive reconstruction, native T1 maps, and extracellular volume (ECV) maps in 3 patients with cardiac transthyretin amyloidosis. The patient with no LGE has normal native T1 and ECV maps; the patient with subendocardial LGE had borderline T1 values and high ECV values; and in the patient with transmural LGE, very high native T1 values and very high ECV values were seen. (As originally published in Martinez-Naharro A et al.(86) reproduced with permission

Figure 7. Native T1 mapping in Anderson-Fabry disease
Native T1-maps (basal short-axis) from a healthy volunteer (**A**) and a patient with Anderson-Fabry disease (AFD; **B**). Blue areas (T_1 lowering) are seen diffusely in the AFD left ventricular myocardium and red (T_1 increasing) in the inferolateral wall, correlating with the area of late gadolinium enhancement in the same patient (**C**, arrow). (As originally published in Sado D. et al.;(89) reproduced with permission).

Central Illustration: CMR techniques for myocardial tissue characterization
CMR allows comprehensive myocardial tissue characterization offering superior and well-validated biomarkers of important pathophysiological processes encountered in cardiac diseases, i.e. fibrosis, edema, iron or amyloid infiltration etc. ECV map image originally published in Messroghli DR, et al (35) and shared under the “Creative Commons Attribution Noncommercial License”.