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DIABETES AND CARDIOVASCULAR DISEASE (S MALIK, SECTION EDITOR)

Role of Cardiac MRI in Diabetes

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Abstract Diabetes and insulin resistance have a variety of detrimental effects on cardiovascular health and outcomes. Cardiac magnetic resonance offers a non-invasive means to obtain many layers of information at a tissue level, including fibrosis, edema, intramyocardial motion, triglyceride content, and myocardial energetics. The role of cardiovascular magnetic resonance is particularly important in the evaluation of recognized and unrecognized coronary artery disease. In this review, we address the current state-of-the-art in cardiac magnetic resonance imaging – for both clinical and investigational use – as it applies to diabetic cardiovascular disease.

Keywords Diabetes mellitus · Magnetic resonance imaging · Coronary artery disease · Myocardial steatosis · Spectroscopy · Cardiac MRI

Introduction: The Need for Improved Risk Stratification in Diabetes

The global health burden of type 2 diabetes (T2D) on cardiovascular health and outcomes worldwide is immense [1–3]. Insulin resistance affects a wide spectrum of cardiovascular conditions, extending from obstructive coronary disease and calcification to left ventricular (LV) remodeling, concentric hypertrophy, and heart failure (HF), even in the absence of coronary disease or hypertension [4]. In this regard, identifying the presence, severity, and end-organ consequences of myocardial ischemia and subclinical remodeling imposed by systemic and myocardial insulin resistance on the LV is a critical goal in cardiovascular medicine. With the wide array of techniques available to the cardiovascular specialist, selecting appropriate, cost-effective modalities to investigate the origins of diabetic heart disease has become increasingly important. In this review, we address the current state-of-the-art in cardiac magnetic resonance (CMR) imaging as applicable to diabetic cardiovascular disease. Specifically, we will focus on the use of established and novel CMR techniques to interrogate pathophysiology along the spectrum of diabetic heart disease, from the detection of established myocardial ischemia to the use of CMR to quantify non-ischemic remodeling characteristic of T2D.

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Cardiac Magnetic Resonance Imaging in Diabetes: A Multi-Faceted Approach

Over the past 20 years, CMR has evolved from imaging of myocardial function and morphology to perfusion, edema, energetics, and fibrosis [5–9]. High spatial resolution (ranging from 0.5–3 mm in-plane) and high temporal resolution that rivals echocardiography can be achieved in most patients. CMR is able to quantify cardiac function and structure with relatively low restrictions from operator-dependency, echocardiographic windows, and is free from the use of ionizing radiation, thus providing important benefits in certain emerging at-risk populations, including obesity—the primary comorbid illness that drives incident T2D. Beyond volumetric ventricular function and myocardial mass, CMR "tagging" technique labels the myocardium with grids or lines to track intramyocardial motion. Such method has provided important insights into myocardial strain in diabetic cardiomyopathy [10] and the determinants of subclinical systolic and diastolic function in T2D [11].

With the advent of contrast-enhanced imaging via gadolinium chelates, CMR can measure the presence, extent, and location of fibrosis and perfusion deficits within the heart, providing prognostically important evidence on otherwise clinically unrecognized myocardial infarction (MI) or ischemia. CMR provides the ability to visualize first-pass myocardial perfusion during administration of stress vasodilator (e.g., regadenoson or adenosine) or adrenergic (e.g., dobutamine and more recently exercise) agents [12] across short- and long-axis views of the LV with high spatial resolution. Furthermore, more novel methods to acquire CMR images (e.g., spatial and radial *k*-space acquisition with parallel acceleration) offer methods to perform stress perfusion imaging with full LV coverage [13], extending the current clinical applications of CMR.

The advent of gadolinium administration during routine CMR examinations unlocked an ability to detect and quantify areas of myocardial scar with high spatial resolution, a *sine qua non* of prior MI. Gadolinium is an extracellular contrast agent that accumulates in the myocardium specifically in areas of extracellular matrix expansion (e.g., where fibrotic collagen tissue has replaced viable cardiomyocytes after an MI). The accumulation of gadolinium in a given segment of myocardium affects the T1 relaxation property of that myocardial segment, which can be visualized as "bright" tissue on inversion recovery T1-weighted "late-gadolinium enhancement" (LGE) imaging. In essence, the amount of gadolinium in a given part of the myocardium reflects the presence and extent of scar in that territory; with a spatial resolution on the order of 2 mm, the transmural extent of a prior MI can estimate any benefit in recovering ventricular function from invasive coronary revascularization. The precise co-localization of histologic areas of MI and areas of LGE by CMR has been confirmed in canine models of MI and in human autopsy specimens [14, 15]. Using semi-automatic detection algorithms [16], areas of LGE can be quantified to the gram level. Indeed, high spatial resolution of 1-2 mm in-plane enables LGE by CMR to detect small, subendocardial MI with greater sensitivity than standard nuclear techniques [17] (Fig. 1). More recently, the application of "navigator" technology to perform LGE imaging at sub-millimeter spatial resolution without the need for breath-holding may further improve ability to detect scar [18]. Recently, these gadolinium-enhanced techniques have been extended to map cardiac extracellular matrix remodeling before LGE ("T1 mapping" techniques), a hallmark of diabetic cardiomyopathy that occurs before the onset of clinical HF or MI [19••].

Advance spectroscopic techniques to measure myocardial energetics (via phosphocreatine availability in ^{31}P-CMR spectroscopy) and myocardial lipid content (using ^{1}H-CMR spectroscopy) have emerged as research tools to investigate physiology and therapeutic effects [20, 21]. In total, CMR provides a unique comprehensive assessment of clinically validated measures of LV mass, structure and function, as well as incrementally prognostic indices of myocardial fibrosis, perfusion, and energetics. In this review, we will explore these different facets of CMR imaging to provide an overview of the current state-of-the-art in diabetic cardiac imaging with CMR. Table 1 illustrates the most common current CMR techniques and their applications for myocardial assessment in patients with diabetes.

Coronary Artery Disease in Diabetes: A Role for CMR?

Coronary artery disease (CAD) and its complications (e.g., MI, HF, and sudden cardiac death) are the commonest cause of morbidity and mortality in patients with T2D [22]. It has been long recognized that myocardial ischemia and obstructive CAD carry a significant increased hazard of death or incident MI in patients with T2D [23]. In addition, survival free of death or recurrent non-fatal MI after an index event is substantially lower in patients with T2D [24]. Importantly, in an early, seminal observation by Haffner and colleagues, rates of incident CAD and mortality from CAD in patients with T2D without any clinical evidence of prior MI were similar to non-diabetic patients who had suffered from MI [25], implicating under-recognition of risk in patients with T2D using current clinical metrics. These observations suggest that methods to comprehensively assess cardiovascular risk in both established and pre-clinical heart disease in T2D may provide benefit on survival and cost-effective delivery of medical therapies.

Current techniques to assess risk in patients with suspected CAD or myocardial ischemia rely on global measures of ventricular function (e.g., LV ejection fraction) or imaging modalities to assess degree and extent of ischemia and myocardial scar. Although current nuclear and echocardiographic are satisfactory in the wide majority of patients referred for clinical stress testing, the unique risks and physiology of the diabetic heart—including severe, multi-vessel disease ("balanced ischemia"), the prognostic implications of a small, unrecognized MI, and operator-dependence of imaging quality in obesity—suggest CMR as an alternative to current imaging techniques in the assessment of ischemic heart disease in T2D.

Coronary Artery Disease in Diabetes: LGE Imaging to Detect Clinically Unrecognized MI

The presence and extent of LGE are associated with increased hazard of death in ischemic (*HR*=1.06, 95 % confidence interval 1.0–1.12; p=0.04) and non-ischemic (*HR*=8.2, 95 % confidence interval 2.2–30.9; p=0.002) heart disease,

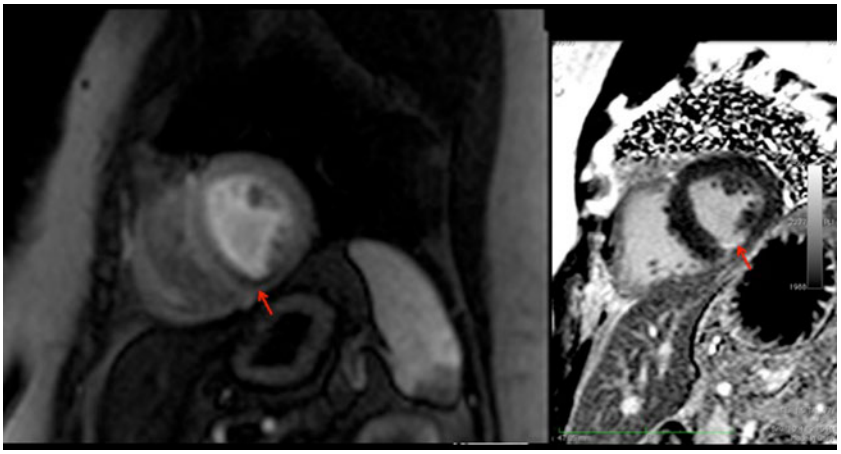


Fig. 1 A 50 year-old diabetic female with no known history of coronary artery disease underwent research imaging studies. A cardiac stress PET study did not reveal any significant perfusion defect. First-pass perfusion imaging in short axis (left panel) demonstrating an infero-septal perfusion defect. Matching short-axis late gadolinium enhancement (LGE) imaging reveals a subendocardial scar suggestive of prior infarct. Collectively these finding are consistent with unrecognized infarction with peri-infarct ischemia in the right coronary territory. A severe coronary stenosis in the mid right coronary artery was confirmed on x-ray coronary angiography

independent of traditional clinical factors and imaging markers of ventricular function [26, 27]. One of the key areas of investigation in scar detection by CMR has been in the area of unrecognized MI. This is especially relevant in T2D: (1) clinical methods (e.g., those used by Haffner and colleagues) may not actually detect all patients with prognostically important CAD and (2) the presence of T2D significantly alters subsequent post-MI course, especially important if a prior clinically silent MI is missed [25]. Our group performed an observational study of 187 patients with T2D undergoing CMR for clinical indications [28]. Of the 187 patients, 109 had no prior MI (by clinical history or electrocardiographic criteria). Of these patients, nearly one in three patients had evidence of LGE by CMR characteristic of prior MI, suggesting that silent myocardial infarction was common. At a median follow-up of 17 months, these investigators found a nearly four-fold increased hazard of major adverse cardiovascular events and over seven-fold increased hazard of all-cause mortality in patients with LGE (Fig. 2). On average, every 10 % increase in LGE was associated with a 60 % increase in hazard of major events. In a multivariable model including LV volume, age, gender, or ST-segment or T wave abnormalities, LGE was still powerfully independently associated with adverse prognosis. These results were recently extended in a prospective cohort of nearly 300 diabetics in Iceland by Schelbert et al., where clinically unrecognized MI detected by LGE was associated with an identical long-term risk of mortality as patients with clinical MI [29••]. Furthermore, these investigators found that patients with unrecognized MI were likely to be undertreated with guideline-directed therapies against CAD. Given the high morbidity and costs that accompany recurrent CAD-related events and HF in the diabetic population, these results suggest a potential consideration for CMR in the imaging of the

Table 1 CMR techniques and their applications for myocardial assessment in patients with diabetes

Pulse sequence	Physiology/myocardial characteristics being assessed	Clinical or investigational	Relevance for cardiac disease in diabetes
Steady-state free precession (SSFP)	Myocardial thickness, volume, and function	Clinical	Severity of ventricular dysfunction; left ventricular hypertrophy
Late gadolinium enhancement	Infarcted myocardium, scar, fibrosis, or infiltration	Clinical	Unrecognized myocardial infarction; myocardial fibrosis; other co-existing infiltrative cardiomyopathy
Stress perfusion	First-pass perfusion defects	Clinical	Burden of myocardial ischemia from coronary artery disease
Tagging	Wall motion abnormalities, diastolic dysfunction, and strain	Investigational	Severity of diastolic dysfunction
Spectroscopy	^{1}H: myocardial lipid content ^{31}P: myocardial energetics	Investigational	Severity of myocardial triglyceride deposition; abnormal profiles of cardiac energetics
T1-mapping	Expansion of extracellular volume, "diffuse fibrosis"	Clinical	Severity of myocardial fibrosis

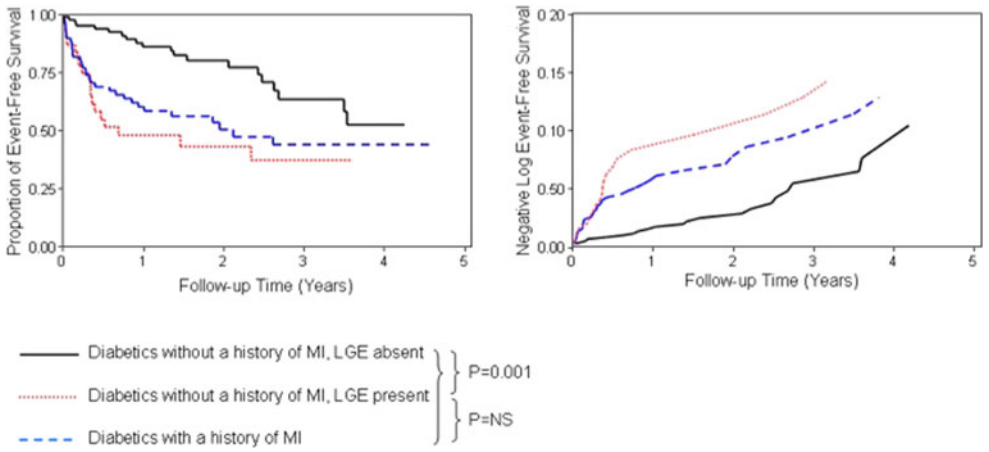


Fig. 2 Kaplan-Meier estimates of all-cause mortality in 187 patients with T2D undergoing CMR. At a median follow-up of 17 months there was a four-fold increased hazard of major adverse cardiovascular events and over a seven-fold increased hazard of all-cause mortality in patients with LGE. (From: Kwong RY, Sattar H, Wu H et al. Incidence and prognostic implication of unrecognized myocardial scar characterized by cardiac magnetic resonance in diabetic patients without clinical evidence of myocardial infarction. Circulation 2008;118:1011-20) [28]

highest-risk diabetic patients, especially as costs and availability of CMR imaging continue to decline.

Recent results have also extended these observations to other populations with dysglycemia [30•]. In a substudy of the Diabetes Control and Complications Trial, Turkbey and colleagues performed CMR imaging on 1,017 patients with type 1 diabetes, demonstrating a 4.3 % prevalence of LGE consistent with unrecognized MI in patients with type 1 diabetes without clinical evidence of cardiovascular disease [30•]. Moreover, the presence of LGE was associated with poor glycemic control diabetic nephropathy, evident by an elevated hemoglobin A1c and the presence of albuminuria, respectively, both powerful markers of cardiovascular prognosis in both type 1 and type 2 diabetic heart disease. These changes appear to be prognostic across the spectrum of dysglycemia: in a study of patients stratified by impaired fasting glucose or presence of T2D, the presence of LGE was the most powerful correlate of adverse cardiovascular prognosis in patients with pre-diabetes [31•].

Coronary Artery Disease in Diabetes: An Emerging Role for CMR in Acute MI?

Patients with T2D or even impaired glucose tolerance are at increased risk of acute MI and post-MI complications for several potential reasons: a higher burden of underlying CAD with impaired collateral vessels formation, impaired ischemic pre-conditioning, and atypical or absence of chest pain from ischemia leading to missed or delayed diagnosis and treatment. CMR quantifies the two major post-MI prognostic determinants: LV structure and function, and infarct size accurately, thus it is not surprising that CMR be a valuable tool in studying post-MI remodeling in patients with diabetes or dysglycemia. Mather and colleagues performed a longitudinal study of 93 patients (normoglycemic, dysglycemic and T2D) with CMR imaging during index hospitalization for MI and nearly 1 year thereafter. The study demonstrated that patients with dysglycemia or diabetes had a larger average LGE size at index CMR scan and a greater LGE size at follow-up [32]. These observations were independent of location of infarction, ST vs. non-ST elevation MI, and initial hemodynamic profile. In a study of 411 patients with and without T2D, Eitel et al. found that in non-diabetics, the degree of dysglycemia was associated with LGE infarct size, area of microvascular obstruction, and impairment of LV ejection fraction, whereas these relationships were not seen in patients with T2D, suggesting a different physiology in diabetics even in the acute infarct setting that may mediate differential outcomes in diabetics. These results have been confirmed by other investigators [33]. Given the importance of myocardial remodeling and risk of sudden death early in the infarct period and novel interventions (e.g., stem cell-based) therapies to limit infarct size, the use of CMR to phenotype the diabetic heart after ischemic injury is an attractive area of continued research.

Acute MI is known to trigger a profound innate inflammatory response crucial for cardiac repair. In a humanized mouse model of type 1 diabetes (T1D), our group recently reported that this same pathway may trigger a destructive autoimmune lymphocytic response in the myocardium leading to impaired myocardial healing and adverse myocardial remodeling. Extending these findings to humans, Gottumukkala et al. developed immunoassays and reported detection of autoantibody positivity in as high as 83 % of post-MI T1D patients [34]. Given CMR's ability to characterize myocardial edema, along with infarct sizing and tissue perfusion status, it is plausible that clinical application of CMR may shed novel

insights in post-MI remodeling in autoimmune-prone diabetic patients.

Coronary Artery Disease in Diabetes: Detecting Myocardial Ischemia with Stress-perfusion CMR

The prognostic importance of myocardial ischemia in patients with T2D is well established [35], and the ability to quantify the area of jeopardized ischemic myocardium for revascularization may improve clinical outcomes [36]. Although current modes of imaging myocardial ischemia have been well-validated both diagnostically and prognostically, there are important limitations specific to standard nuclear or echocardiographic methods to an emerging category of patients with T2D, characterized by obesity and multi-vessel coronary disease, including suboptimal imaging windows, increased doses of ionizing radiation, and the challenges from balanced ischemia.

In this regard, stress-perfusion CMR methods imaging the myocardium after application of vasodilatory or beta-adrenergic stress during first-pass gadolinium transit have emerged as a potential alternative to other stress modalities. By providing a comprehensive look at myocardial function, scar, and perfusion, stress-perfusion CMR is an attractive single modality to capture a variety of prognostically important myocardial indices (Fig. 3). The diagnostic sensitivity of stress-perfusion CMR has been validated against gold-standard invasive coronary angiography [37–39]. In the largest prospective study evaluating CMR to date, the sensitivity of CMR to detect angiographically significant coronary stenosis (>50 % left main coronary artery or >70 % branch disease), CMR had an 86.5 % sensitivity and 83.4 % specificity, when stress-perfusion, wall motion, LGE, and CMR coronary angiography were considered [39].

Although published work on stress-perfusion CMR has not specifically addressed patients with T2D, there is substantial evidence that stress-induced wall motion abnormalities and perfusion defects are highly prognostic regardless of background risk. In 513 patients (19 % diabetic), both dobutamine-induced wall motion abnormalities and an adenosine-induced perfusion defect carried an over five-fold risk of adverse cardiac prognosis, with a three-year event-free survival of 99.2 % for a negative CMR scan [40]. In a recent report from Buckert and colleagues of 1,152 patients (21 % diabetic) undergoing adenosine stress-perfusion CMR, a reversible perfusion defect by CMR was associated with an over three-fold higher risk of a cardiac event, even after adjustment for age, diabetes, and resting wall motion abnormality [41]. Indeed, stress perfusion defects and stress-induced wall motion abnormalities appear to contribute independently to risk of MACE [42–44]. Based on a comparable diagnostic accuracy to current methods and an emerging wealth of longer-term prognostic data, stress-perfusion CMR has currently achieved a class IIa recommendation by the American College of Cardiology Foundation/American Heart Association guidelines for the diagnosis and management of stable ischemic heart disease [45]. Further work on prognostication within a group of patients with diabetes is warranted.

Non-ischemic Cardiac Remodeling in Diabetic Heart Disease: Population-based Studies

It well known that diabetics experience a higher risk of HF, adjusted to coronary disease, hypertension, or obesity, a product of non-ischemic, organ- and tissue-level remodeling fundamental to insulin resistance and dysglycemia [46]. The integration of CMR imaging methods into community-based, longitudinal studies has clarified a diabetic cardiac

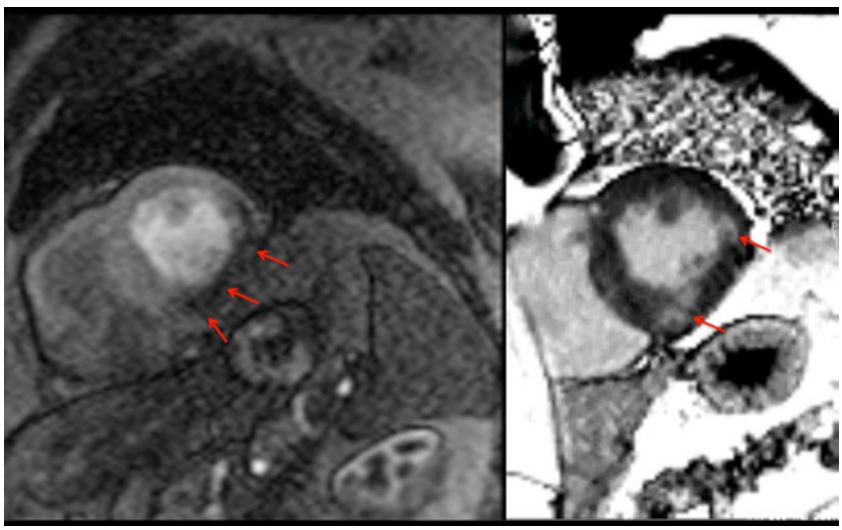


Fig. 3 Adenosine stress perfusion imaging (left) reveals a defect in the basal and mid inferior, inferoseptal and inferolateral walls. Phase-sensitive late gadolinium enhancement (LGE) imaging shows accumulation of gadolinium in the basal inferolateral and basal inferior segment to suggest prior infarct

pathophysiology occurring before coronary heart disease. In 4,869 asymptomatic patients without clinical cardiovascular disease in the Multi-Ethnic Study of Atherosclerosis (MESA), Heckbert and colleagues reported an increase in 3.5 grams in LV mass, a decrease of 4.5 ml in stroke volume, and a 0.8 % lower LV ejection fraction in diabetics [47]. Studies within MESA have demonstrated that the association between diabetes and these measures of subclinical LV remodeling may be modified by race: for example, White, Black, and Hispanic participants in MESA had a higher LV mass, while Chinese participants did not [48]. In a study within MESA utilizing CMR to quantify myocardial perfusion reserve with adenosine-induced hyperemia, hyperemic myocardial blood flow was associated with higher fasting glucose [49]. These associations were independent of coronary heart disease, suggesting the existence of a separate "diabetic cardiomyopathy" entity that defines subclinical ventricular remodeling in T2D. Indeed, these observations have been translated into an early, pre-diabetic stage of cardiac remodeling: in both the Framingham Heart Study and MESA, markers of insulin resistance are tightly associated with concentric LV remodeling by CMR (LV end-diastolic mass to volume ratio), suggesting that CMR-defined phenotypes of subclinical myocardial disease exist on a spectrum of dysglycemia even before T2D [50, 51].

Non-ischemic Cardiac Remodeling in Diabetic Heart Disease: Myocardial Energetics and Lipid Overload

Beyond tissue characterization in diabetes, CMR provides a unique view into two other aspects of subclinical myocardial remodeling seen in the diabetic heart: lipid overload and energetics [52].

Myocardial Steatosis: Impact on Ventricular Function and Effects of Therapy by CMR

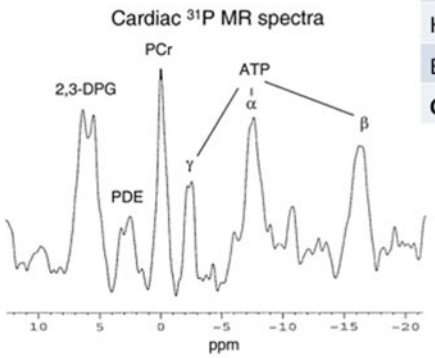
Investigations on myocardial steatosis using CMR have been both descriptive and therapeutic in nature. Studies using CMR have established an association between myocardial lipid overload and LV diastolic dysfunction independent of age, blood pressure, and obesity in T2D [21] and improvements with anti-diabetic intervention track with diastolic function [53, 54]. In a study of 42 men with T2D, Ng and colleagues describe an association between myocardial triglyceride content by CMR and both left and right ventricular longitudinal strain by echocardiography, suggesting a subclinical effect of steatosis as detected by CMR on myocardial function [10]. In another study of 42 patients with T2D, Korosoglou and coworkers performed strain-encoded CMR, ^{1}H-CMR spectroscopy (for measurement of triglyceride content) and adenosine stress-perfusion (for assessment of quantitative perfusion reserve). These investigators found myocardial triglyceride content (but not perfusion reserve) was associated with LV diastolic dysfunction in T2D, even after adjustment for age, gender, duration of T2D, blood pressure, or fasting blood glucose [55]. This has been recapitulated by other investigators in T2D using CMR-based techniques [21].

In a therapeutic context, CMR has been used to interrogate on-therapy effects. In a study of 78 men with T2D without any cardiovascular disease randomized to pioglitazone, metformin or placebo for 24 weeks, there were no therapy-related effects on lipid content or energetics by ^{1}H and ^{31}P CMR spectroscopy despite changes in diastolic function [56•]. Similar results describing a null effect of rosiglitazone on alterations of lipid content within the heart by ^{1}H-CMR spectroscopy have been reported [57•]. Interestingly, prolonged caloric restriction in T2D appears to decrease myocardial triglyceride content alongside coordinate improvements in diastolic LV function [53].

Finally, myocardial steatosis is present in the prediabetic period: in a large study of ^{1}H-CMR spectroscopy in patients with impaired glucose tolerance with normal LV systolic function, McGavock and colleagues demonstrated a 2.3-fold higher myocardial triglyceride content in patients with impaired glucose tolerance relative to those without, indistinguishable from those with established T2D [58].

Phosphate Energetics: An Abnormal Phenotype in Diabetic Heart Disease by CMR

Alongside the widespread use of ^{1}H-CMR spectroscopy to assess lipid content, ^{31}P-CMR spectroscopy has been utilized in the diabetic heart to address the implications of abnormal high-energy phosphate handling on myocardial function. The complexity of these techniques has limited their use to an investigational context within several centers of CMR excellence worldwide. However, the published literature utilizing CMR to examine energetics has provided fundamental insights into diabetic myocardial biology. Most of the work in this field has used a multi-modality approach, with the simultaneous use of nuclear techniques to assess metabolism alongside ^{31}P-CMR. In a study of 21 patients with T2D, cardiac phosphocreatine-to-ATP ratio (an index of high-energy phosphate availability) was lower in T2D than in healthy volunteers [59] (Fig. 4). Furthermore, the phosphocreatine-to-ATP ratio was associated with parameters of diastolic LV function [60], suggesting an intimate link between energetics and myocardial function. In a study of 61 patients with T2D undergoing positron emission tomography with metabolic tracers and CMR, Rijzewijk and colleagues reported an association between hepatic triglyceride content (by ^{1}H-MRI) and impaired cardiac perfusion, function, and high-energy phosphate



	Controls (15)	Type 2 DM (21)
Age, years	52 ± 3	57 ± 2
HgbA1c, %	5.7 ± 0.1	9.5 ± 0.6
Echo E/A	1.29 ± 0.05	0.98 ± 0.12
Cardiac PCr:ATP	**2.30 ± 0.12**	**1.50 ± 0.11**

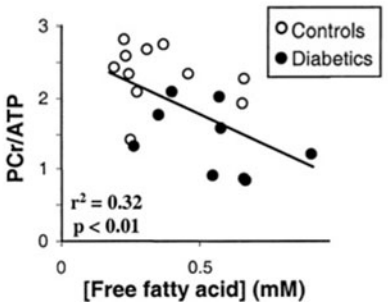


Fig. 4 ^{31}P-spectroscopy allows for the study of myocardial energetics by identifying the spectra that represent high-energy phosphate availability. In a study of 21 patients with T2D, cardiac phosphocreatine-to-ATP ratio was lower in T2D than in healthy volunteers

metabolism [61], suggesting a central cardiometabolic regulation of myocardial function. ^{31}P-CMR studies in type 1 diabetes have demonstrated abnormal high-energy phosphate metabolism within the heart exists independent of perfusion and duration of diabetes [62, 63]. Notwithstanding the technical accessibility of these methods to assess cellular phosphate metabolism, the ability to quantify myocardial phosphate turnover with high accuracy may prove important in evaluation of novel therapies in diabetic heart disease.

Non-ischemic Cardiac Remodeling in Diabetic Heart Disease: Extracellular Matrix Expansion

One of the most exciting areas of ongoing research has revolved around the use of CMR to phenotype the extracellular matrix in diabetic heart disease. Despite ongoing controversy around the existence of a "diabetic cardiomyopathy," animal studies, small physiologic studies in humans, and large community-based studies of patients with T2D repeatedly attest to a higher lifetime risk of HF and cardiac events in T2D, independent of incident MI, hypertension, obesity, or other traditional risk factors [64]. These observations have given rise to the hypothesis that diabetics experience unique changes in myocardial structure and function—termed "diabetic cardiomyopathy"—that finds its origins in myocardial tissue: expansion of the extracellular matrix, myocardial steatosis, and hypertrophy [4, 65–67].

Recently, LGE imaging techniques have been extended to look beyond macroscopic replacement fibrosis into the myocardial interstitium. Gadolinium distributes differentially, with higher gadolinium concentration in myocardial tissue with a greater degree of extracellular space (e.g., more fibrosis) versus space with pure cardiomyocytes (less gadolinium) (Fig. 5). This differential partitioning of gadolinium can be quantified using sequences sensitive to the T1 relaxation parameter of water. The "T1" time of a given myocardial segment therefore is an index of the gadolinium concentration within that segment, and by proxy the degree of extracellular matrix expansion in that segment. Ultimately, this approach can generate a "myocardial extracellular volume fraction" (ECV) that quantifies the amount of extracellular space not occupied by cardiomyocytes. Although different groups utilize different sequences to calculate T1 [68, 69], both ECV and T1 time have been validated against histologic collagen volume fraction in mice [70] and in patients with pressure

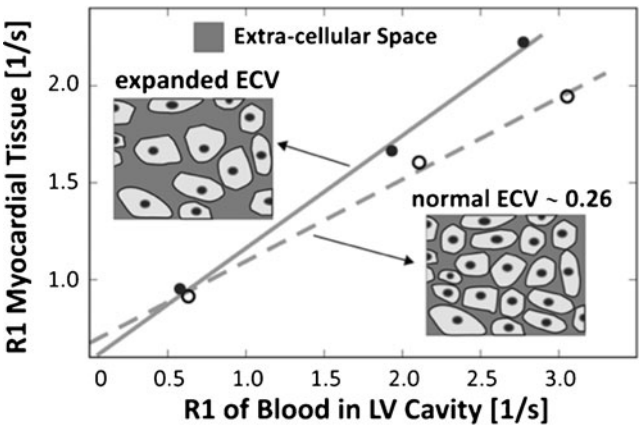


Fig. 5 Estimating diffuse fibrosis by T1 mapping. Gadolinium distributes differentially based on the amount of extracellular volume relative to the volume taken up by pure cardiomyocytes. By quantifying the relaxation times (R1=1/T1) of the myocardium versus the blood pool, the amount of extracellular volume can be estimated. (From: Ho CY, Abbasi SA, Neilan TG, et al.: T1 measurements identify extracellular volume expansion in hypertrophic cardiomyopathy sarcomere mutation carriers with and without left ventricular hypertrophy. Circ Cardiovasc Imaging 2013, 6:415-422) [76]

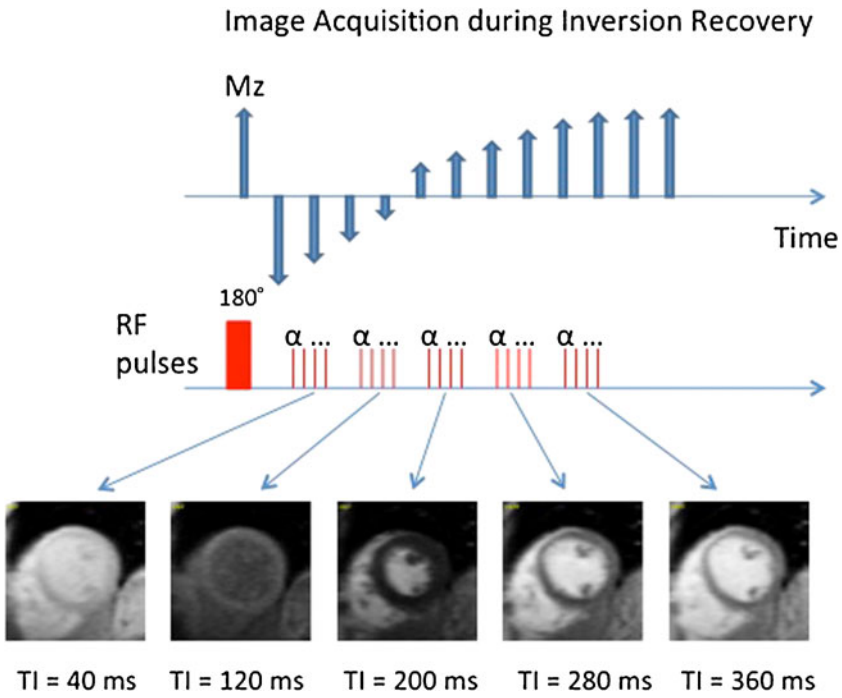


Fig. 6 T1 mapping using an inversion pulse and a look-locker sequence and a GRE readout. This is done once before and thrice after the administration of gadolinium, and ultimately results in a reproducible, histologically validated estimation of the extracellular volume (ECV) fraction

overload [71]. Recent reports confirm that ECV is associated with long-term prognosis in an overall referral population [72••]; reports of prognostic significance within a diabetic group are forthcoming.

The use of CMR "T1 mapping" techniques is especially attractive in T2D, not only to reaffirm the existence of the earliest changes within the diabetic heart, but also to provide another mechanism for characteristic subclinical changes of diabetic cardiomyopathy. In a study of 50 diabetic patients with normal LV function undergoing CMR (without evidence of LGE), Ng and colleagues demonstrated that despite no differences in LV volumes or ejection fraction relative to healthy volunteers, patients with T2D had a significantly shorter myocardial T1 time, indicating more gadolinium distribution and more extracellular matrix expansion [19••]. In turn, the T1 time was highly associated with global longitudinal strain by echocardiography ($r=-0.73$, $p<0.001$), and remained the strongest predictor of strain and tissue Doppler e' velocity on multivariable analysis. In a similar study, Jellis and colleagues reported on 67 patients with T2D without

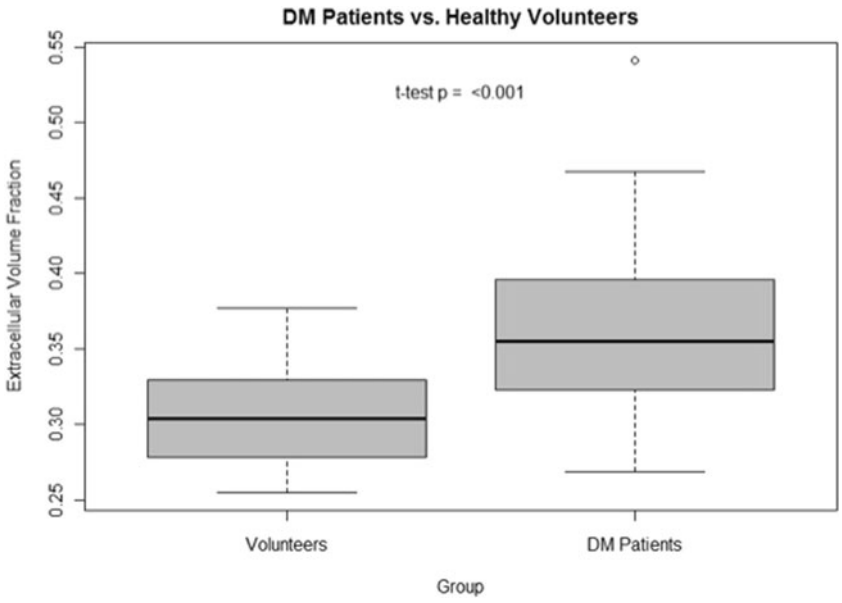


Fig. 7 T1 mapping demonstrates a significant difference in extracellular volume (ECV) fraction between patients with type 2 diabetes (right) and normal controls (left), despite the lack of any evidence of coronary artery disease, diastolic dysfunction, or ventricular hypertrophy. (Reprinted with permission from: Rao AD, Shah RV, Garg R, et al.: Aldosterone and myocardial extracellular matrix expansion in type 2 diabetes mellitus. Am J Cardiol 2013, 112(1):73-8) [75]

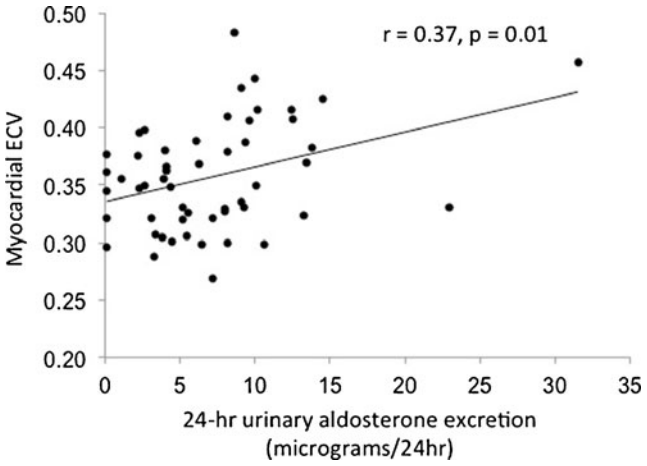


Fig. 8 Correlation of endogenous aldosterone production and extracellular volume (ECV) fraction by T1-mapping in 21 patients with type-2 diabetes. (Reprinted with permission from: Rao AD, Shah RV, Garg R, et al.: Aldosterone and myocardial extracellular matrix expansion in type 2 diabetes mellitus. Am J Cardiol 2013, 112(1):73-8) [75]

CAD, finding that a shorter myocardial T1 time was associated with poorer diastolic function, more impaired exercise capacity and more insulin resistance [73••]. Interestingly, they did not find association between T1 time and collagen turnover peptides (e.g., N-terminal propeptide of procollagens type III), consistent either with the insensitivity of these peptides or their ability to reflect turnover (and not overall deposition). Interestingly also reported in this study, interventions that limit myocardial fibrosis in animal models (e.g., phosphodiesterase-5 inhibition) appear to favorably alter torsion by CMR tagging in patients with T2D [74]. Our group favors the use of sequential T1 mapping (one before and three after contrast injection) in quantifying myocardial partition coefficient that is used to estimate ECV (Fig. 6). This approach captures the exchange of gadolinium between extracellular compartment and the blood pool over a 15-20 minute after contrast injection and is potentially more robust than T1 time in estimation of ECV, reducing the variability in

Table 2 Representative studies using CMR techniques in the assessment of patients with diabetes

MRI technique	Author	Year	Patient population	Significance/Findings	Reference
Late gadolinium enhancement	Kwong	2008	Diabetics without evidence of infarction by history or resting ECG	In diabetic patients without prior clinical myocardial infarction, the presence of "silent" unrecognized LGE is a potent risk marker for future mortality and cardiovascular events	[28]
Late gadolinium enhancement	Schelbert	2012	Older (>67 years) community-based cohort (including 266 diabetics)	CMR detected unrecognized myocardial infarctions, and this finding was associated with a higher mortality risk compared to individuals with recognized myocardial infarction. This was particularly true in diabetics	[29••]
Steady-state free precession (SSFP)	Velagaleti	2010	1,603 patients in the Framingham cohort	Demonstrates relationship between insulin resistance and myocardial structure in a community-based population	[51]
Steady-state free precession (SSFP)	Turkbey	2011	Type-1 diabetics	Demonstrates a relationship between glycemic control and aberrant LV structure and function in patients with Type 1 diabetes	[30•]
Steady-state free precession (SSFP)	Bertoni	2006	4,991 patients with diabetes in the MESA cohort	Aberrancies in LV mass, LV volume, and LVEDV was observed in ethnic subgroups with diabetes	[49]
T1 mapping	Ng	2012	50 diabetics patients with normal LV function and no history of CAD	Diffuse myocardial fibrosis as assessed by T1 mapping CMR techniques is associated with diastolic dysfunction and strain in diabetes	[19••]
T1 mapping	Jellis	2011	67 patients with Type-2 diabetes	Demonstrated the relationship between myocardial fibrosis by T1 mapping, metabolism (i.e., insulin resistance), and cardiac function in diabetes	[74]
T1 mapping	Wong	2012	793 adults (including 151 diabetics)	Demonstrated the value of T1 mapping to forecast mortality in an adult population	[19••]
^{1}H-spectroscopy	Rijzewijk	2008	Type 2 diabetics	Demonstrates the relationship between myocardial triglyceride content (as determined by CMR spectroscopic techniques) and diastolic dysfunction in diabetics	[21]
^{31}P-spectroscopy	Rijzewijk	2009	Type 2 diabetics	^{31}P-spectroscopic CMR techniques in conjunction with positron emission tomography in diabetics, demonstrating that decreased diastolic function and altered myocardial substrate utilization are present early in diabetes	[20]
^{1}H-spectroscopy and ^{31}P-spectroscopy	van der Meer	2010	72 type 2 diabetic men randomized to pioglitazone or metformin and placebo	Demonstrates the use of CMR in tracking therapeutic responses in patients with diabetes	[57•]

measurement introduced by time after injection, contrast dosage, and baseline T1 value. In one study, we found that ECV was substantially elevated among T2D patients despite the lack of any evidence of CAD, clinical diastolic dysfunction, or ventricular hypertrophy (Fig. 7). In addition, we found that endogenous aldosterone production was implicated as a strong potential pro-fibrotic factor in this early diabetic cardiac remodeling (Rao AJC 2013) (Fig. 8). Although the clinical application of T1 mapping techniques to diabetic heart disease still requires consensus on methods of acquisition, it reflects the unique ability of CMR to synthesize whole organ physiology with cellular phenotypes, and is a very exciting area of research relevant to diabetic cardiovascular remodeling.

A summary of the major findings of studies that employed CMR in studying patients with diabetes is shown in Table 2.

Conclusion

The spectrum of phenotypes within diabetic cardiovascular disease spans myocardial scar, ischemia, and non-ischemic remodeling. With a unique array of sequences dedicated to myocardial function, structure, perfusion, energetics, lipid metabolism, and diffuse extracellular matrix expansion, cardiac magnetic resonance imaging offers a comprehensive, quantitative, reproducible alternative to interrogate the diabetic heart. With increasing speed of acquisition, less reliance on breath-holding, and less technical demands on execution, CMR is rapidly becoming more accessible to clinical populations and for important research questions on subclinical disease.

Compliance with Ethics Guidelines

Conflict of Interest Ravi V. Shah has been a consultant for Novartis and Ventripoint.

Siddique A. Abbasi declares that he has no conflict of interest.

Raymond Y. Kwong declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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