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EACVI DOCUMENT

Multimodality imaging approach to left ventricular dysfunction in diabetes: an expert consensus document from the European Association of Cardiovascular Imaging

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Heart failure (HF) is among the most important and frequent complications of diabetes mellitus (DM). The detection of subclinical dysfunction is a marker of HF risk and presents a potential target for reducing incident HF in DM. Left ventricular (LV) dysfunction secondary to DM is heterogeneous, with phenotypes including predominantly systolic, predominantly diastolic, and mixed dysfunction. Indeed, the pathogenesis of HF in this setting is heterogeneous. Effective management of this problem will require detailed phenotyping of the contributions of fibrosis, microcirculatory disturbance, abnormal metabolism, and sympathetic innervation, among other mechanisms. For this reason, an imaging strategy for the detection of HF risk needs to not only detect subclinical LV dysfunction (LVD) but also characterize its pathogenesis. At present, it is possible to identify individuals with DM at increased risk HF, and there is evidence that cardioprotection may be of benefit. However, there is insufficient justification for HF screening, because we need stronger evidence of the links between

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the detection of LVD, treatment, and improved outcome. This review discusses the options for screening for LVD, the potential means of identifying the underlying mechanisms, and the pathways to treatment.

Keywords diabetes • diabetic cardiomyopathy • heart failure • mechanisms • screening

Key messages

- Heart failure (HF) is a frequent association of diabetes mellitus (DM), with a two-fold higher incidence in male, and five-fold higher incidence in female patients without DM. HF is now the most common initial cardiovascular presentation in DM.
- About 50% of patients with DM have diastolic dysfunction, and about 20% satisfy the diagnosis of diabetic cardiomyopathy [systolic dysfunction or at least moderate diastolic dysfunction, with or without left ventricular (LV) remodelling without a history of ischaemic heart disease, hypertension, significant valvular disease, or congenital heart disease].
- HF outcomes are particularly poor in patients with DM, with a frequent need for hospitalization, and a 5-year survival rate of <50%. Cardiac imaging may be useful in facilitating prevention by enabling early detection of myocardial disease and understanding the pathophysiological determinants of HF in patients with DM.
- The effects of DM on the heart are potentiated by obesity, hypertension, and coronary artery disease.
- The key diagnostic phenotypic findings of diabetic cardiomyopathy are LV mass, LV systolic function (LVEF and strain), and diastolic function (transmitral flow, annular tissue Doppler, right ventricular pressure, and left atrial volume and strain).
- The key pathophysiologic findings of diabetic cardiomyopathy are myocardial fibrosis [both scar and diffuse fibrosis, best identified with cardiac magnetic resonance (CMR)], diseases of the microcirculation [identifiable with a number of tools, especially positron emission tomography (PET)], metabolic disturbances (suitable for assessment by CMR and PET), and disorders of cardiac innervation (assessable mainly with PET).
- There is strong evidence of the ability of imaging to assess HF risk in DM, and there are now potent medical therapies to reduce HF risk. Additional imaging studies are needed to combine this information, and show that imaging screening for HF in DM alters risk. Similarly, given the heterogeneity of HF aetiology in DM, ongoing imaging studies are needed to subphenotype diabetic cardiomyopathy and discover targeted therapies.

Definition, epidemiology, and pathophysiology of diabetic heart disease

Myocardial involvement in diabetes mellitus (DM)—mainly type 2 DM (T2DM)—is a complex process that is incompletely understood. DM is a risk factor for heart failure (HF) with preserved ejection fraction (EF) (HFpEF), mildly reduced, and reduced EF (HFrEF), due to ischaemic heart disease (IHD) and non-ischaemic aetologies.[1] The age and gender of the investigated study population, DM duration, the prevalence of concomitant cardiovascular risk, hyperglycaemia, insulin resistance, and hyperinsulinaemia are all associations of left ventricular (LV) dysfunction in DM.[2]

The causes underlying HF in patients with DM are heterogeneous. The existence of a discrete diabetic cardiomyopathy is still controversial, and not applied in all studies.[3] Those that use this term generally include systolic dysfunction or at least moderate diastolic dysfunction, with or without LV remodelling in a person with DM but without a history of IHD, hypertension, significant valvular disease, or congenital heart disease. Whichever diagnostic label is used, common mechanisms include dysfunction of the renin–angiotensin–aldosterone system, oxidative stress, inflammatory processes, inappropriate immunity modulation, abnormalities of subcellular components, endothelial, and coronary microcirculation (*Figure 1*).[4,5] A contribution of pressure loading is important, because of the frequent co-existence of hypertension and valvular heart disease, especially aortic stenosis.[6] The prevalence of diabetic cardiomyopathy was addressed in a cross-sectional survey of Olmsted County, MN, USA.[7] Among patients with DM, aged 45 years or older, 17% met the criteria for diabetic cardiomyopathy, and 54% had diastolic dysfunction of all degrees of severity. Of those with diabetic cardiomyopathy, 31% died or developed HF at 9 years. Although the true prevalence remains difficult to establish, HF is a frequent association of DM—especially T2DM—with a two-fold higher incidence in male, and five-fold higher incidence in female patients without DM.[8]

HF outcomes continue to be poor in patients with DM, with a frequent need for hospitalization, and a 5-year survival rate of <50%—worse than most cancers. After peripheral vascular disease, HF has become the most common initial cardiovascular presentation in DM[9] (*Figure 2*). Indeed, the incidence of HF continues to increase in DM,[10] despite a substantial reduction in the incidence of myocardial infarction (MI) (by 25%) in patients with DM over the last 10 years. In addition, the increasing prevalence of T2DM in the community[11] is increasing the population-attributable risk of T2DM to HF. The goals of this consensus document are to review (i) the current use of cardiac imaging for early detection of subclinical cardiac damage and assistance with clinical decision-making regarding HF prevention in DM, and (ii) the potential of imaging modalities to understand the pathophysiological determinants of HF in a patient with DM.

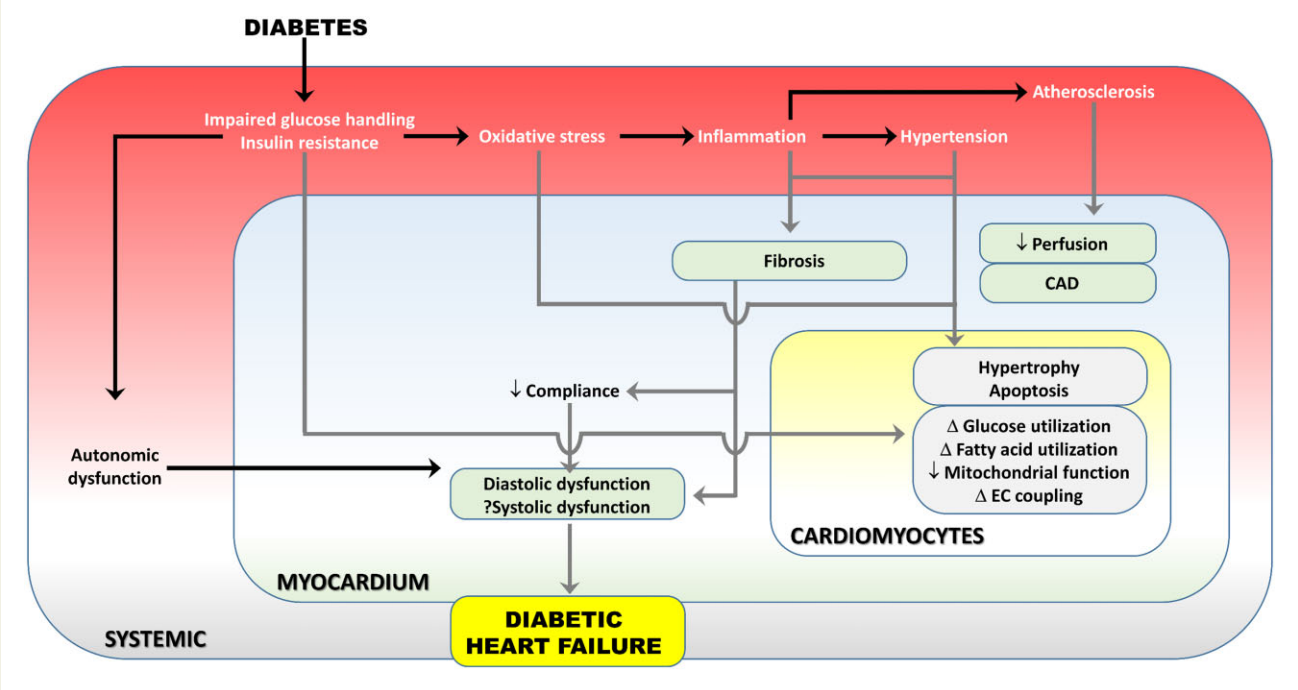

Figure 1 Systemic, myocardial, and cellular manifestations of diabetic heart failure. The glycaemic effects (glucose handling, insulin resistance) contribute to a variety of systemic effects (black arrows) and effects on the cardiomyocyte (grey arrows) including disturbances of glucose and fatty acid utilization, mitochondrial function, and excitation contraction (EC) coupling. Other systemic effects (autonomic dysfunction, oxidative stress, and its consequences) lead to coronary artery disease (CAD), and other myocardial and cardiomyocyte effects.[4]

Imaging of myocardial function

Although conventional indices (such as ejection fraction) are useful in some patients with DM and HF, the majority of presentations are of HFpEF, and there is often an interest in subclinical disease. In the subclinical stage, DM-induced remodelling including left ventricular (LV) concentric remodelling and hypertrophy (LVH) are observed in the presence of a normal EF (*Table* 1).[12–14] In addition to LV mass, imaging should address LV systolic function—including global longitudinal strain (GLS), and diastolic function—including left atrial (LA) strain.

Systolic function

EF is frequently normal in patients with diabetes and HF. Midwall fractional shortening is obtainable by a complex echo-derived formula. This takes into account the epicardial motion of the midwall during systole, based on a model assuming a spherical geometry.[15] This has been used to screen subtle decreases in LV systolic function in patients with DM and normal EF.[16]

At the stage of HF, an ancillary study of the RELAX trial evaluated the echocardiographic phenotype of patients with HFpEF (≥50%), with and without DM. Patients with DM had more severe LVH and a trend towards higher filling pressures as assessed by *E*/*e*′ ratio than those without.[17] Similar results were reported in the I-PRESERVE trial, where patients with DM had a greater LV diameter, LV thickness, and LV mass, features of increased filling pressures but similar systolic measurements including fractional shortening, EF, and mitral annular systolic velocity (*s*′) to those without DM.[18] While HFrEF in

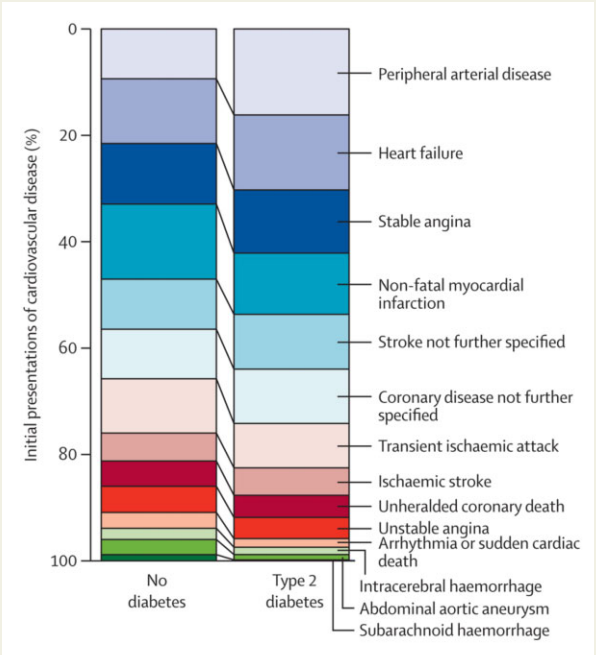

Figure 2 Initial presentations of cardiovascular diseases in participants with and without type 2 diabetes but no history of cardiovascular disease. Peripheral arterial disease and heart failure are more common initial presentations of cardiovascular disease than in those without diabetes.[9]

Table 1 Association of diabetes with LV hypertrophy[14]

Author	*n*	Study cohort	DM or IGT	Main findings
Galderisi, *AJC* 1991	4515	FHS	DM or IGT	Increase in LVM in women
Lee, *AHJ* 1997	5201	CV Health Study	DM or IGT	Increase in LVM in both sexes
Devereux, *Circulation* 2000	2754	Strong Heart Study	DM	Increase in LVM
Ilercil, 2001	1345	Strong Heart Study	IGT	Increase of LVM and RWT
Palmeri, *Circulation* 2001	1950	HyperGEN Study	DM + HTN	Increase in LVM and RWT
Bella, 2001	3155	Strong Heart Study	DM ± HTN	Progressive increase of LVM in both DM ± HTN
Rutter, 2003	2623	FHS	DM or IGT	Progressive increase in LVM, RWT, and LA

CV, cardiovascular; DM, diabetes mellitus; FHS, Framingham Heart Study; IGT, impaired glucose tolerance; HTN, hypertension; LA, left atrial; LVM, left ventricular mass; RWT, relative wall thickness.

Table 2 Association of diabetes with abnormal global longitudinal strain (GLS)[14]

Author	Findings
Fang, *JACC* 2003	Both DM only and DM + HTN showed significant decreases in peak strain and peak strain rate c/w controls
Fonseca, *AJC* 2004	MRI tagging strain: peak systolic strains and diastolic relaxation lower in patients with T2DM and normal LVEF
Chung, *JACC* 2006	MRI tagging strain: paradoxical increase in myocardial torsion in DM
Moir, *Heart* 2006	Impaired strain and SR in T2DM not a/w abnormal transmural flow
Ng, *AJC* 2009	LV longitudinal systolic and diastolic function were impaired, but radial and circumferential functions preserved in uncomplicated T2DM
Yang, *Open Heart* 2016	Pts with DM had impaired GLS and diastolic function
Leung, *Circ CV Img* 2016	Reversibility in diabetic cardiomyopathy with intensive treatment including optimization of treatment for blood glucose, BP and lipids

DM, diabetes mellitus; HTN, hypertension; MRI, magnetic resonance imaging; SR, strain rate; T2DM, type 2 diabetes mellitus.

DM is usually associated with regional wall motion abnormalities (as the main cause is IHD[19]) diabetic cardiomyopathy can also lead to dilated cardiomyopathy in the absence of coronary artery disease (CAD).[3]

Strain imaging, including tissue Doppler imaging (TDI) and speckle tracking, provide more reliable methods than EF to assess minor decreases in LV systolic function. In asymptomatic patients with DM and a normal EF, alterations of systolic strain are frequent and are considered as part of a preclinical form of diabetic cardiomyopathy (*Table 2*).[14] Similar echocardiographic phenotypes to DM have been reported in pre-diabetic states, obesity and hypertension. Using TDI, alterations of longitudinal LV systolic function were thought to be compensated by an increased radial function,[20] although changes of both radial and longitudinal function have been described using speckle tracking.[16] However, radial function is not reliably measured with this technique. A significant decrease of GLS (≥18%), has been described in about one-quarter of the patients, but may not necessarily coincide with the presence of diastolic dysfunction or LV remodelling (*Figure 3*). Different phenotypes have different prognostic implications (*Figure 4*).[21,22]

Echocardiography is the most widely available technique that will provide information on myocardial function in patients with DM (*Figure 5*).[23] Although this can certainly also be provided by cardiac magnetic resonance (CMR), echocardiography is better for assessing diastolic function and CMR is the reference standard for assessment of volumes, EF, and mass. CMR can be used for the assessment of myocardial strain.[24] Nuclear imaging techniques are well-validated for the assessment of LV systolic function.[25] Functional analysis has improved the accuracy of myocardial perfusion scintigraphy (MPS) for the detection of CAD and provides important prognostic information in people with and without DM.[26–28] In addition, electrocardiogram (ECG) gating permits evaluation of global and regional LV function and is now a routine part of myocardial perfusion imaging protocols.[29] ECG-gated single-photon emission computed tomography (SPECT) provides measurements of LV volumes and EF which are highly reproducible, have a good agreement with other imaging techniques[25] and allow the analysis of LV dyssynchrony through phase evaluation.[25] Nonetheless, the radiation exposure of nuclear imaging and lack of evaluation for valvular heart disease and other potential confounders mean that this modality is suboptimal for the assessment of subclinical LV dysfunction (LVD) in T2DM.

Diastolic function

The features of LV diastolic dysfunction (LVDD), including abnormal transmitral flow (*E* velocity), annular tissue Doppler (e′), and their ration (*E*/e′) are commonly present in diabetic cardiomyopathy (*Table 3*).[14] In addition, total and positive LA strain (corresponding to reservoir and conduit function respectively), are reduced in T2DM and independently related with functional capacity.[30]

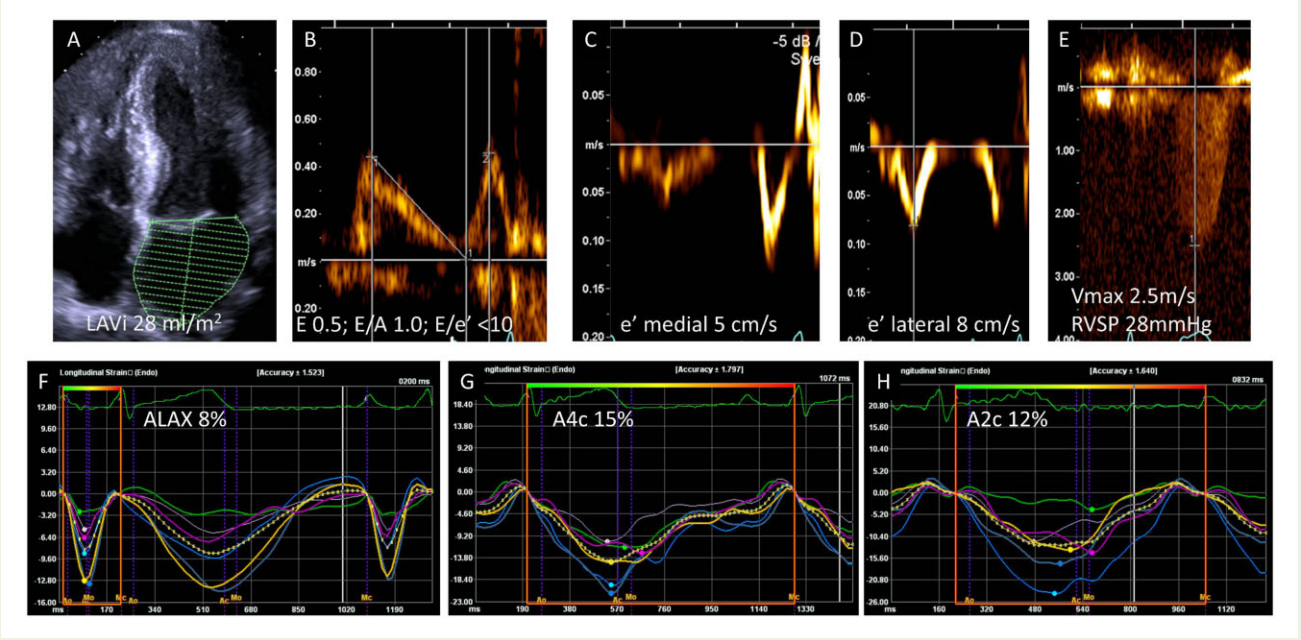

Figure 3 Predominant systolic dysfunction. This asymptomatic patient with normal EF has reduced regional longitudinal strain (*F–H*) (GLS <12%), despite minimal diastolic dysfunction—normal left atrial volume (*A*), equal passive and active components of transmitral flow (*B*), mildly reduced tissue velocity (*C* and *D*), and no pulmonary hypertension (*E*). This type of presentation seems more frequent when the dominant problem is diabetes mellitus.[4]

Whilst LVDD often precedes both the onset of systolic dysfunction and the development of symptoms,[2,31,32] systolic dysfunction may also occur without diastolic dysfunction (*Figure 6*), so these processes are not necessarily related. In a group of 114 asymptomatic patients with T2DM but without heart disease, Ernande *et al.*[22] showed that the prevalence of subclinical diastolic dysfunction (present in 47%) was influenced by age, hypertension, and haemodynamics, whereas abnormal LV-GLS (present in 32%) was associated with DM and gender. Importantly, there was a 28% prevalence of abnormal LV-GLS in patients with normal diastolic function.

LVDD is often attributed to myocardial fibrosis and apoptosis, but diastole is also energetically intense, and abnormalities may be attributable to coronary microvascular dysfunction[33] and metabolic abnormalities, i.e. uncontrolled glycaemia and insulin resistance.[34] These themes are well-exemplified in a classic study of LV endomyocardial biopsies in 28 patients with normal LVEF (16 with DM) and 36 with reduced LVEF (10 with DM), all without IHD (*Figure 7*).[35] The authors showed that HF patients with DM had higher diastolic LV stiffness irrespective of LVEF, but that DM increased the myocardial collagen volume fraction (from 14.6 ± 1.0% to 22.4 ± 2.2%, $P < 0.001$) only in patients with reduced LVEF. Conversely, DM increased cardiomyocyte resting tension only in patients with normal LVEF (from 5.1 ± 0.7 to 8.5 ± 0.9 kN/m^2, $P = 0.006$). Thus, mechanisms responsible for the increased diastolic stiffness of diabetic cardiomyopathy differ in HFrEF and HFpEF: fibrosis and advanced glycation products are more important when LVEF is reduced, whereas cardiomyocyte resting tension is more important when LVEF is normal.

Microalbuminuria is strongly related to LVDD, whereas systolic dysfunction is associated with macroalbuminuria.[36] Age, retinopathy, and hypertension are predictive of an increased risk of LVDD[37] in T2DM patients.[38] Patients with T2DM have more reduced average mitral annular e′ velocity than non-diabetic subjects,[32] e′ is particularly impaired in poorly controlled, older patients with micro-albuminuria.[36] The combination of pulsed tissue Doppler with transmitral inflow (*E*/*e*′) and LA volume index may be extremely useful for characterizing LVDD and LV filling pressure (LVFP),[39,40] particularly in symptomatic stages.

Obesity is often a confounding factor and T2DM patients have similar average mitral annular e′ velocities as overweight patients without DM.[21,38] In a study of 653 patients with and without DM, both DM and category of body mass index had an additive detrimental effect on LV systolic and diastolic function, but the impact of obesity on LVD seemed greater than that of DM.[32] Another study used early diastolic GLS rate (SR) to assess the detrimental LV myocardial functional changes secondary to T2DM. Patients with both obesity and DM have the most impaired early diastolic global longitudinal SR, although overweight patients with DM have similar early diastolic SR to obese non-diabetic patients, just as lean diabetic patients have similar early diastolic SR to overweight non-diabetic subjects.[32] Finally, surgical intervention for obesity in the recent prospective FatWest Study showed an improvement of GLS, which remained significant after[41] adjustment for diabetes.

Other common non-invasive tests can provide some insight into diastolic dysfunction, although probably not with the versatility and accessibility of echocardiography. Multidetector computed tomography (CT)-derived measurements of LV filling correlate with the findings of TDI echocardiography in asymptomatic DM,[42] but the value of this modality for assessment of LVDD is limited by radiation

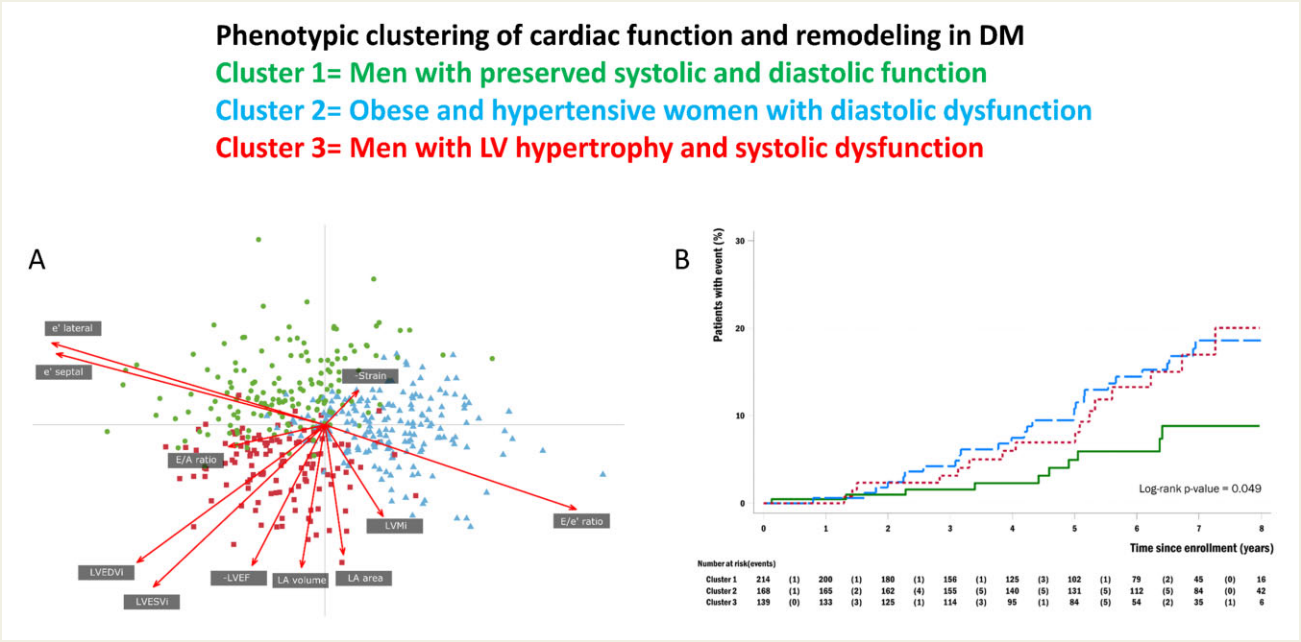

Figure 4 Myocardial phenotypes in asymptomatic subjects with diabetes mellitus. Cluster analysis (*A*) shows three groups; Cluster 1—preserved systolic and diastolic function, mainly male; Cluster 2—diastolic dysfunction with obesity and hypertension, mainly women; Cluster 3—LV hypertrophy and systolic dysfunction, mainly men. Follow-up (*B*) shows that cluster 1 follow a benign course, relative to Clusters 2 and 3.[21]

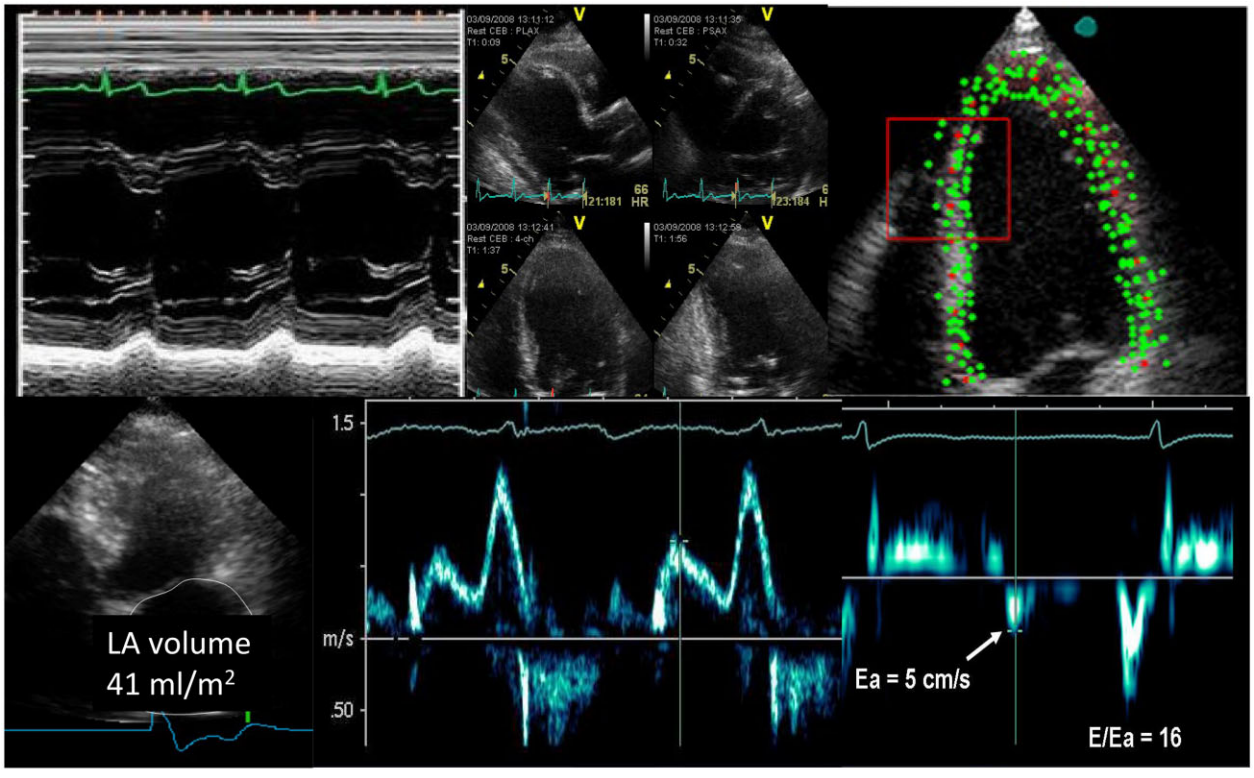

Figure 5 Echocardiographic assessment of LV dysfunction. Essential components include LV mass, EF, strain, LA volume and function, transmitral flow, and annular tissue Doppler.[23]

Table 3 Association of diastolic dysfunction with diabetes[14]

Author	Findings
Zarich, *JACC* 1988	Lower *E/A* ratio and higher A in T1DM vs. controls
Celentano, *AJC* 1995	Lower *E/A* ratios in patients with T2DM or IGT than in normoglycaemic subjects
Hansen, *Diabetes* 2002	Lower e′ in T1DM than in normal controls
Fang, *Diabetologia* 2005	Subclinical DD a/w poor DM control, age, HTN; ACEi, and insulin protective
Liu, *JACC* 2001	Progressive reduction of *E/A* ratio and prolonged DT in DM ± HTN
Bajraktari, *IJC* 2006	Insulin resistance is associated with diastolic dysfunction
Moir, *Heart* 2006	Higher *E*/e′ in T2DM than in controls
From, *AJC* 2009	>4 years DM a/w DD. DD a/w all-cause mortality independent of HTN, CAD
From, *JACC* 2010	E/e'_{sept} >15 a/w subsequent HF and mortality independent of HTN, CAD, or other echo parameters
Sacre, *JACCi* 2010	DD a/w cardiac autonomic neuropathy (MIBG)
Falcão-Pires, *Circulation* 2011	DM further worsens diastolic function in severe AS, via greater fibrosis, AGE accumulation, and stiffened myocytes
Poulsen, *JACC* 2013	Increased LAVi an independent/incremental predictor of CV morbidity/death

AGE, advanced glycation products; AS, aortic stenosis; CAD, coronary artery disease; CV, cardiovascular; DD, diastolic dysfunction; DM, diabetes mellitus; DT, deceleration time; HTN, hypertension; IGT, impaired glucose tolerance; MIBG, meta-iodo-benzylguanidine; MRI, magnetic resonance imaging; SR, strain rate; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

exposure. In addition to perfusion data, ECG-gated cardiac SPECT offers the chance to obtain LV filling parameters—specifically peak filling rate (PFR) and time to PFR (TPFR),[43,44] although in general, nuclear techniques lack the temporal resolution for the detailed assessment of diastolic function. Nonetheless, PFR is lower in patients with DM than in controls and is a possible marker of LVDD in T2DM.[45] A composite index of reduced PFR and increased TPFR can identify patients with increased LVFP, who are at risk of cardiac adverse events.[43] Post-stress PFR, a marker of stress-induced LVDD (potentially a measure of ischaemia-derived diastolic stunning), may provide an early sign of non-obstructive coronary atherosclerosis in diabetic patients.[43] Finally, CMR provides information about diastolic function both indirectly (LV mass, LA volume, and identification of scar) and directly by assessment of mitral inflow and flow propagation.[46]

Imaging of myocardial fibrosis

In addition to providing functional information discussed in the preceding sections, the main incremental information from CMR pertains to myocardial tissue characterization. The most widely studied CMR technique for tissue characterization is that of late gadolinium enhancement (LGE), which is mainly used to identify focal areas of replacement fibrosis due to expansion of the interstitial space. An observational study of patients with DM showed that MI on LGE, 'silent' on the basis of absent history, medical record or Q-wave evidence, was present in 28% of patients, and was associated with worse cardiovascular outcome.[47] In fact, the event-free survival of these patients with MI on LGE was similar to patients with clinically apparent MI. These findings were confirmed in the community-based ICELAND-MI study,[48] which showed that LGE diagnosis of unrecognized MI was associated a 45% increment of mortality, independent of age, sex and DM. However, not all LGE lesions are ischaemic; Bojer *et al.*[49] reported LGE in >20% of patients with DM, including 9.5% who had only non-ischaemic LGE lesions. These were typically mid-myocardial in the basal lateral or inferolateral LV. Compared to patients without LGE, those with non-ischaemic lesions had microvascular disease, increased myocardial mass, diastolic dysfunction, and elevated biomarkers (N-terminal pro B-type natriuretic peptide and high-sensitivity troponin).

While LGE detects focal fibrosis or scar, diffuse myocardial fibrosis can be detected using T1 mapping (*Figure 8*) including in patients with DM.[50] T1 mapping provides a quantitative measure of the myocardial T1 relaxation time and can be performed without contrast (native) or post-gadolinium contrast [allowing calculation of the myocardial extracellular volume fraction (ECV%), ECV, and the myocardial cell volume]. CMR-derived ECV reflects the presence and extent of myocardial fibrosis and correlates well with collagen-proportionate area on histology samples.[51] T1 can be used to detect focal or diffuse disease (*Figure 9*), as well as for detection of asymptomatic tissue remodelling, which cannot be identified with other non-invasive imaging techniques. T1 mapping techniques can differentiate between groups of patients with cardiomyopathy and healthy controls independent of LVEF and are also related to exercise capacity, subclinical LVD and prognosis.[52,53] The reported association of fibrosis on CMR with LVD is variable, with a large study demonstrating no significant increase in ECV and native T1 mapping in patients with well-controlled T2D, suggesting the absence of significant extracellular matrix expansion, even in the presence of LV concentric remodelling and diastolic dysfunction.[54] In other studies, asymptomatic T2DM patients with microalbuminuria had higher ECV% and high-sensitivity troponin as well as diastolic dysfunction[55] and patients with prediabetes and DM showed increased myocardial cell volume without extracellular matrix expansion.[50] It should be acknowledged that there is significant overlap between T1 mapping and ECV in DM and non-DM groups, implying that the tests are useful in population studies but probably less useful in assessing the individual patient.

Depending on the pathophysiological processes and the predominance of metabolic disturbance or pro-fibrotic processes, tissue characteristics by CMR may vary. Thus, where these sophisticated tests may be of value is in understanding the phenotypes of LVD in DM. In some instances, subclinical abnormalities of LV strain and

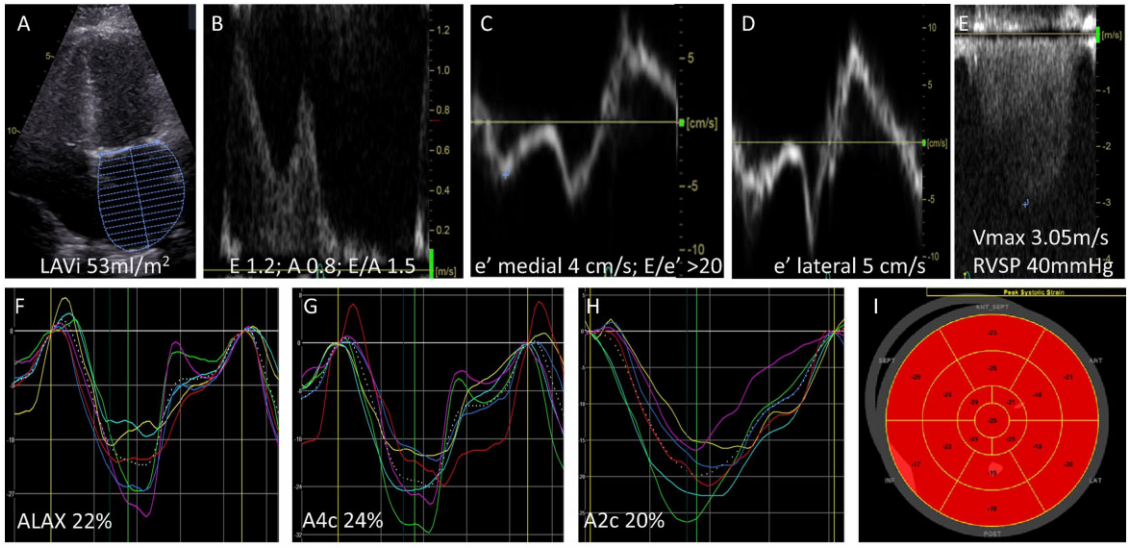

Figure 6 Predominant diastolic dysfunction. This asymptomatic patient with normal EF and GLS has diastolic dysfunction—increased left atrial volume (*A*), predominant passive transmitral flow (*E* velocity, *B*) in the setting of reduced tissue velocity (*e'* velocity, *C* and *D*), with pulmonary hypertension (*E*), with normal regional (*F–H*) and average GLS (22%, *I*). This pattern seems to be more frequent when the dominant problem is hypertensive heart disease.[4]

LVDD may be the first recognizable stages of diabetic cardiomyopathy. In other situations, the underlying mechanism of myocardial dysfunction is interstitial fibrosis, and the unique tissue characterization properties of CMR may be the key to timely diagnosis and sufficiently early treatment to lead to disease reversal. Although there is no specific prognostic data for T1 mapping or ECV in patients with T2DM, given that these patients have higher ECV than controls it is likely that a similar prognostic association would be seen as in the general population.

CMR in patients with DM can also allow investigation of stress responses. In particular, in the absence of arterial hypertension and significant CAD, patients with DM show a reduction of perfusion, oxygenation (using change of blood-oxygen level-dependent signal intensity) and energetics (exercise phosphocreatine to ATP ratio using phosphorus-MR spectroscopy) at rest and during leg exercise.[56]

Imaging of coronary microcirculation and endothelial function

The role of coronary imaging has not been formalized when diabetic cardiomyopathy is identified. Our approach is to consider this on the basis of the presentation—concern about silent ischaemia when patients present with exertional dyspnoea often leads to evaluation of the coronary arteries.

Coronary Doppler flow velocity reserve

The standard dipyridamole (Dip) stress echocardiogram requires the presence of ischaemia to cause wall motion abnormalities. In contrast, the echo-Doppler derived coronary flow velocity reserve (CFVR) to adenosine or Dip is a feasible and accurate tool to detect abnormal perfusion reserve—which is more frequently detected than wall motion evidence of myocardial ischaemia.[57] A reduced Dip-CFVR (<2) is indicative of impaired coronary microcirculation. Dip-CFVR has demonstrated an independent prognostic power in diabetic patients with negative stress Dip stress-echo by wall motion criteria,[58] and the combination of reduced Dip-CFVR (<2) and LV contractile reserve (<1.1) has shown a nine-fold increase of cardiovascular risk in patients with DM and non-ischaemic Dip stress.[59] In patients with DM but without significant CAD, the magnitude of Dip-induced CFVR has been found to be independently associated with the extent of LV mass and both the diabetic and the hypertensive status.[60] The same measurement in response to the cold pressor test (CPT) is an expression of vascular endothelial function (*Figure 10*), which is particularly abnormal in DM. The reduction of CPT-CFVR appears to be associated with fasting glycaemia but not with glycated haemoglobin in patients with DM but without obstructive CAD.[61]

Myocardial perfusion scintigraphy

Stress MPS is an accurate tool to detect obstructive CAD, with similar sensitivities and specificities in patients with and without DM.[62] The amount of inducible myocardial ischaemia exceeds what is expected from the extent of coronary involvement,[63] emphasizing the role of plaque burden and diffuse involvement of both coronary structure and function disease and the presence of silent myocardial ischaemia are common in T2DM, the latter being detectable by MPS in 20–25% of asymptomatic patients with T2DM.[64–66] Sometimes, although angina is absent, dyspnoea is an angina-equivalent in these patients (*Figure 11*). For any degree of myocardial ischaemia, the risk of cardiac events is higher with than without DM.[67] Silent ischaemia

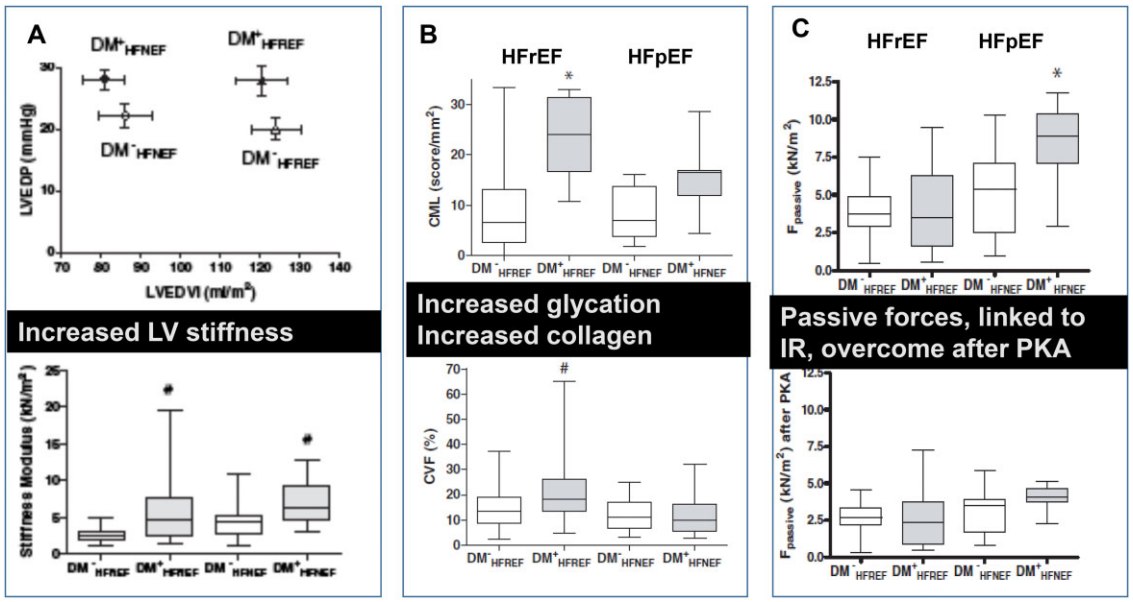

Figure 7 Contribution of fibrosis and muscle tension to LV stiffness in DM. (*A*) Invasive haemodynamics show that LV filling pressure in DM exceeds those without DM irrespective of LV volume, confirmed by *in vitro* measurement of LV stiffness. (*B*) Fibrosis, evidenced by histological extent of carboxymethyl lysine (CML) and collagen volume fraction (CVF) is increased in DM, but most markedly so in HFrEF. (*C*) Passive forces are most increased in patients with HFpEF and DM. Their association with insulin resistance is shown by resolution after administration of protein kinase A (PKA), which overcomes the phosphorylation deficit linked to insulin resistance.

in DM is also associated with events,[68] although given the results of the COURAGE and ISCHEMIA trial this association does not seem to be influenced by revascularization.[69,70]

Coronary vasodilator dysfunction is common in T2DM, even without evidence of obstructive CAD, probably related to diffuse non-obstructive coronary atherosclerosis or coronary endothelial/microvascular dysfunction.[71–73] Positron emission tomography (PET) is a validated tool to measure coronary vasodilator function based on quantified myocardial blood flow (MBF, mL/min/g of myocardium). Measurements obtained with a blood flow radiotracer (^{82}Rubidium, ^{13}N-ammonia or ^{15}O-water) at rest and after vasodilator-stress allow for calculation of coronary flow reserve, an integrated measure of blood flow responses in the epicardial coronary arteries and the microcirculation.[74] Microvascular/endothelial dysfunction assessed by quantitative PET is an independent predictor of adverse outcomes[75] and cardiovascular mortality[73] in DM. Coronary vasodilator dysfunction is common in HF, but its role in diabetic cardiomyopathy is unclear—some findings show no meaningful cross-sectional association with myocardial function,[33] but others show microvascular dysfunction to be associated with the subsequent development of HF.[76]

Myocardial perfusion CMR

Akin to PET, first pass dynamic contrast-enhanced myocardial perfusion CMR can be used to derive quantitative estimates of hyperaemic and resting MBF for a combined assessment of both epicardial coronary disease and myocardial microvascular function.[77] MBF reserve by CMR is reduced in DM[78] and impaired global stress MBF and MBF reserve by CMR is associated with adverse clinical outcome including in patients with DM.[79] Automated methods for MBF estimation from routine clinical CMR investigations are becoming available and may soon provide new opportunities for screening of microvascular disease in DM in routine clinical care.[79]

Cardiac CT

The strength of cardiac CT lies in its ability to non-invasively depict the coronary artery wall (plaque) and lumen. Several coronary CT angiography (CCTA) studies have shown a higher prevalence of obstructive and non-obstructive CAD and fewer normal coronary arteries in patients with T2DM, compared with patients without DM.[80,81] The latest advances in CT technology have allowed coverage of the entire heart with a half gantry rotation, providing a combination of coronary anatomy and quantification of MBF at a single test.[82] Even in the absence of overt ischaemia, DM is associated with lower perfusion parameters than in patients without DM.[83] Cardiac CT is therefore a well-suited imaging modality with a future potential to identify patients with non-obstructive coronary arteries and reduced MBF, which might be a useful tool to diagnose coronary microvascular dysfunction.[84]

In conclusion, abnormalities of coronary microcirculation and endothelial function are important and under-diagnosed in patients with DM. The extent to which they influence the processes underlying diabetic cardiomyopathy is not well defined, but limited data do not show a strong association. For example, although coronary flow reserve is often compromised, it is not associated with abnormal GLS, and the association with e′ is modest ($r = -0.49$, $P = 0.004$).[33] There does not seem to be justification to exclude patients with

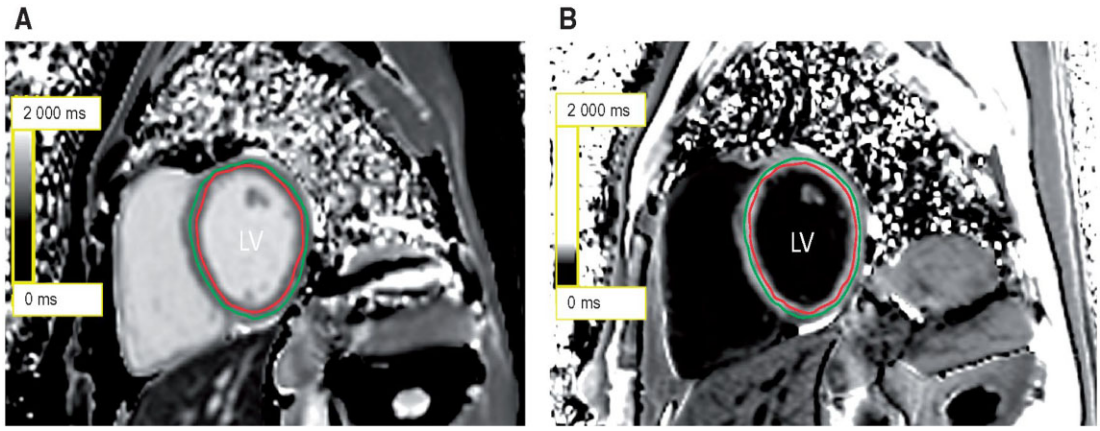

Figure 8 Pre- and post-contrast myocardial T1 mapping on mid-ventricular short-axis images in an asymptomatic patient. These T1 maps are acquired using a modified Look-Locker inversion recovery sequence (MOLLI) before (*A*) and after (*B*) administration of gadolinium.[50]

abnormal coronary function from the diagnosis of diabetic cardiomyopathy.

Molecular mechanisms and the role of metabolic imaging in diabetic heart disease

Due to constantly varying cardiac workload, efficient matching of energy supply to demand is essential for maintaining normal LV function.[85] Altered myocardial substrate metabolism is potentially an important driver of cardiac remodelling in T2DM.[85] Different substrates have different metabolic efficiencies, both in terms of energy (ATP) yield and oxygen requirement, and the available substrate may therefore have an impact on its resulting performance.[86] Altered cardiac metabolism may contribute to the development of LVD by affecting myocardial oxygen demand and impairing metabolic flexibility. As a result, cardiac metabolism and altered substrate utilization are attractive targets for novel treatments to prevent, or even reverse HF in DM. The most useful modalities for these studies are PET and magnetic resonance spectroscopy (MRS).

Positron emission tomography

This technique permits assessment of both myocardial perfusion (using rubidium, ammonia, or water) as well as a number of metabolic markers (including glucose and fatty acids). For example, a classic paper using PET documented insulin resistance as a cornerstone of metabolic heart disease.[87] In this study of fatty acid uptake, utilization and oxidation with PET in 31 young women (19 of whom were obese), showed that insulin resistance correlated with uptake ($r = 0.55$, $P < 0.005$), utilization ($r = 0.62$, $P < 0.001$), and oxidation of fatty acids ($r = 0.58$, $P < 0.005$). The problem is that the cost and availability of PET make it a tool that is able to shed light on mechanisms, but less able to guide the management of individual patients.

Phosphorus magnetic resonance spectroscopy

MRS is a good tool for the non-invasive study of metabolism, due to the extensive range of compounds it can detect, using carbon (13C) and phosphorus (^{31}P-MRS). The observations regarding the use of PET for assessment of metabolism apply equally to spectroscopy. Although this is unsuitable for clinical decision-making, it also provides a means of elucidating mechanisms of diabetic cardiomyopathy.

Spectroscopy is used to interrogate cardiac energy metabolism in preclinical and clinical studies. The relative concentration of phosphocreatine to ATP (PCr/ATP) is a marker of the myocardium's ability to convert substrate into ATP for active processes, and a sensitive index of the energetic state of the myocardium. ^{31}P-MRS allows non-invasive assessment of the myocardial PCr/ATP ratio.[88] Advanced techniques can also quantify absolute concentrations of these metabolites, but this has not yet been done in the diabetic heart. Using ^{31}P-MRS, multiple studies have shown compromised myocardial energetics to be an important feature of the metabolic phenotype of diabetic heart.[56,89,90] Decreased PCr/ATP ratio was detected even in asymptomatic individuals with T2DM, who were free of known DM complications and other common comorbidities such as obstructive CAD and arterial hypertension.[89,90] In an exercise study, changes were not limited to the myocardium, as PCr loss and pH decrease in skeletal muscle occurred faster during exercise in DM and PCr recovery was slower in DM. Moreover, reoxygenation times correlated with glycaemic control.[89]

Myocardial metabolism is profoundly affected by changes in cardiac workload. The onset of exercise triggers a rapid increase in demand for substrate, and oxygen.[91] Metabolic reserve affects the heart's capacity to respond to increases in workload.[92] The healthy myocardium has rapid response mechanisms to deal with acute changes in energy demand,[93] including increased rates of phosphotransferase reactions.[94,95] The use of 31P-MRS to assess the cardiac energetic response to exercise has shown exacerbation of the pre-existing energetic deficit during increased workload in patients with T2DM.[92] Furthermore, despite having no obstructive CAD, mean

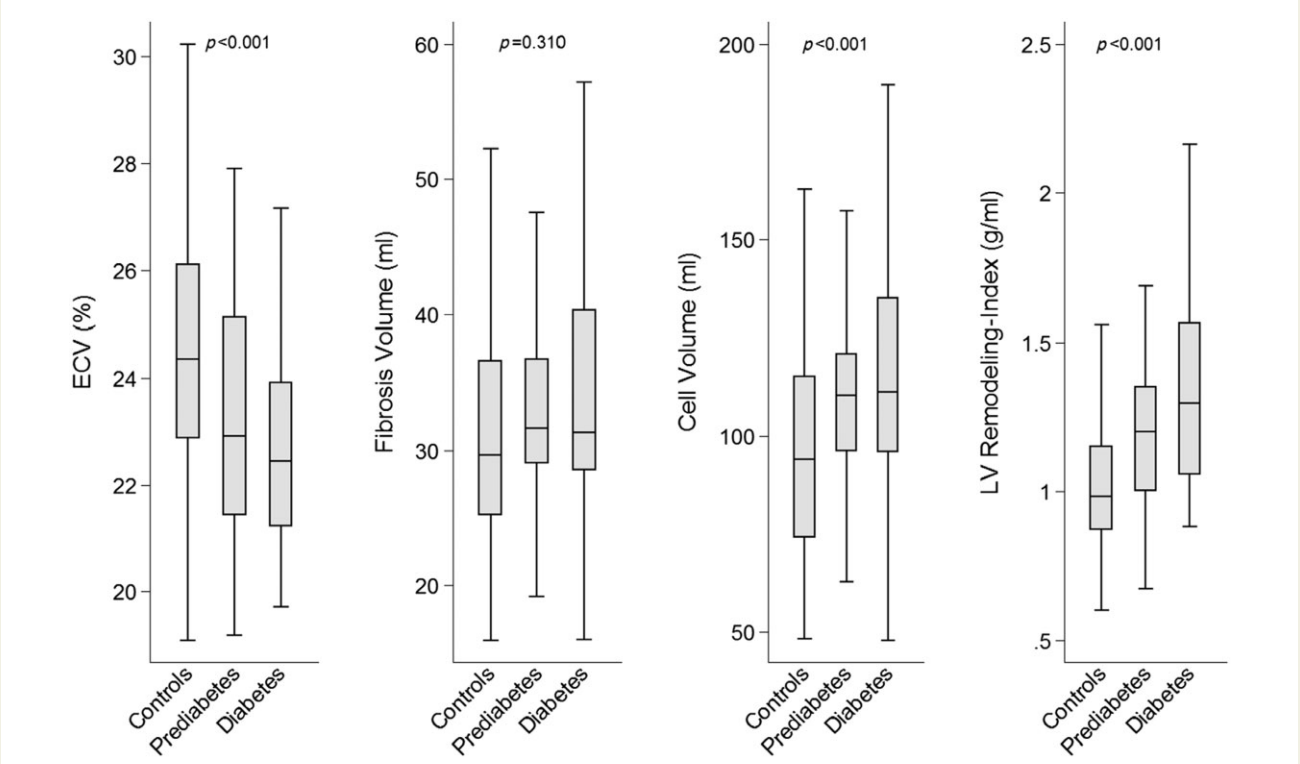

Figure 9 Tissue characterization markers in the diabetic heart. In this study, although average extracellular volume (ECV), cell volume, and left ventricular remodelling index (but not fibrosis volume) were different in subjects with diabetes, prediabetes, and controls, there was substantial overlap.[50] This emphasizes the role of these parameters in population studies rather than for individual decision-making.

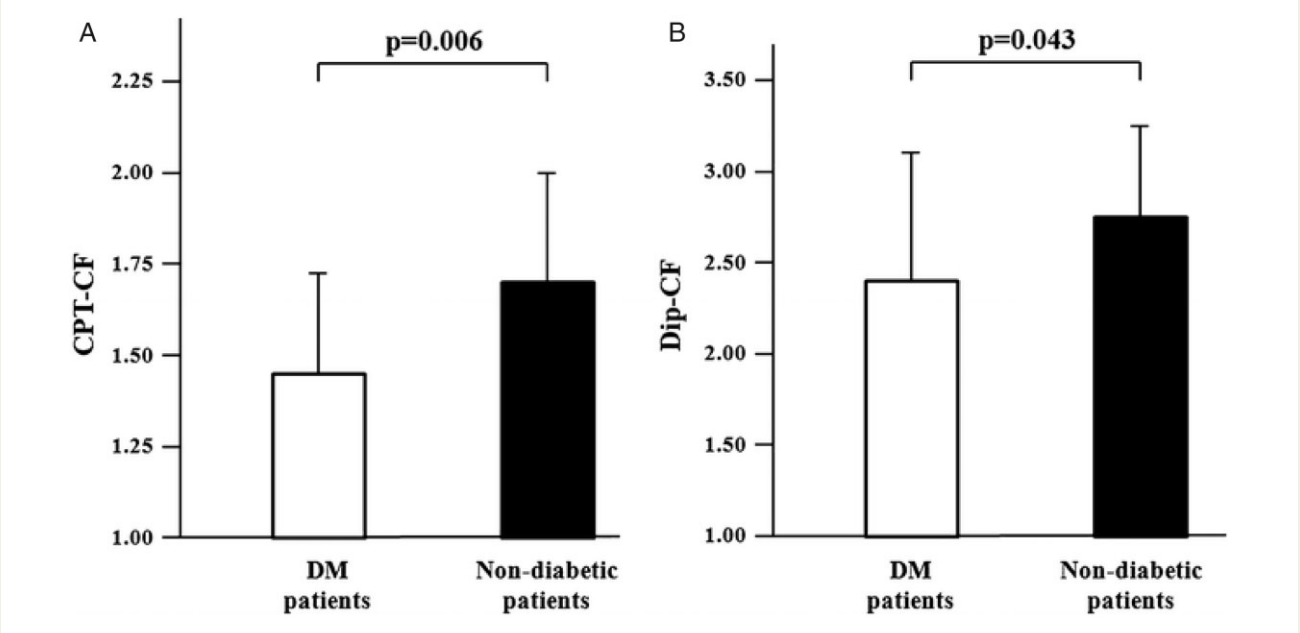

Figure 10 Hyperaemic responses to the cold pressor test (CPT-CF ratio, *A*) and dipyridamole-CF ratio (*B*) in patients with type 2 diabetes mellitus (DM) and nondiabetic patients, reflecting the importance of endothelial dysfunction.[61]

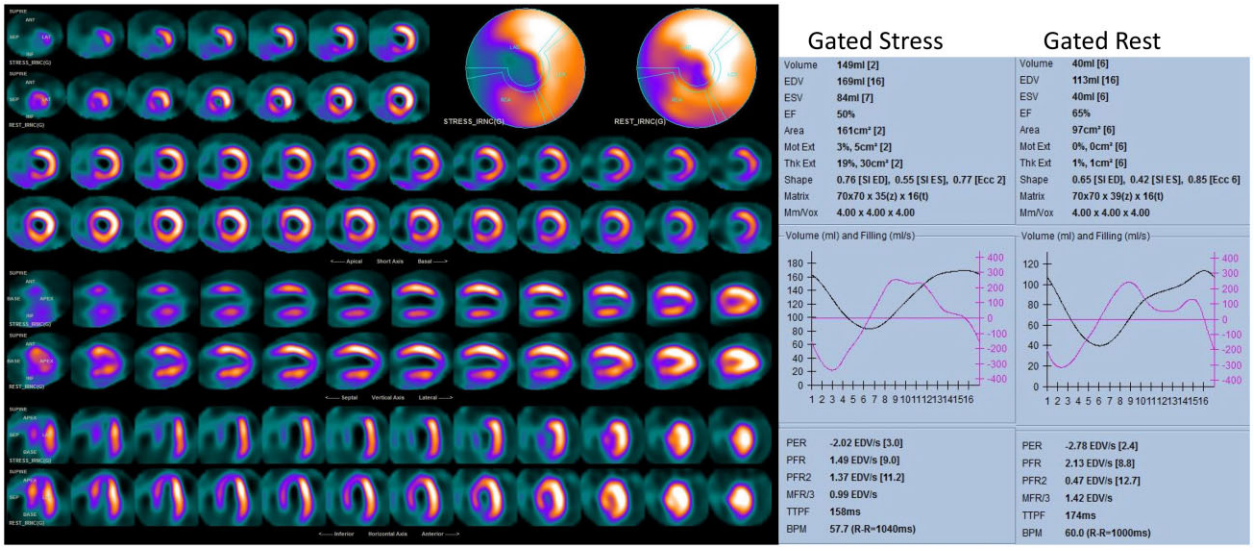

Figure 11 Exertional dyspnoea as an angina-equivalent in T2DM. This 57-year-old man with type 2 diabetes, on oral anti-diabetic therapy had a normal ECG, normal right and left ventricular function and volumes by echocardiography, despite dyspnoea on effort. An exercise stress/rest ^{99m}Tc tetrofosmin SPECT showed a large area of ischaemia in the LAD territory, as confirmed by semiquantitative analysis (summed stress score: 19, summed rest score 3, summed defect score 15, extension of risk area >10%). The gated images showed the presence of a reduced post-stress LVEF (50%) and diastolic dysfunction (PFR 1.49 EDV/s). In the presence of normal resting systolic LV function (EF 65%), this indicates the presence of stunning post-stress, associated with the large area of ischaemia in the LAD territory.

myocardial perfusion reserve index (MPRI) was significantly reduced in these patients.[84,89] The presence of significant correlations between MPRI with exercise energetics and absolute reduction in PCr/ATP during exercise, confirms the importance of appropriate hyperaemic response during exercise activity to maintain cellular energy metabolism.[92]

Finally, the recent development of hyperpolarized 13C MRS has made it possible to measure cellular metabolism *in vivo*, in real time. Hyperpolarized [1-13C]pyruvate MRS was successfully utilized to assess downstream metabolism of [1-13C]pyruvate via pyruvate dehydrogenase (PDH) in patients with T2DM. Significant reductions in cardiac metabolic flux through PDH were demonstrated in patients with T2D compared to controls. Moreover, these measurements were repeated 45 min after a 75 g oral glucose challenge showing significant increase in metabolic flux through PDH both in controls and in patients with T2DM.[96]

Proton magnetic resonance spectroscopy and myocardial steatosis

Proton (1H)-MRS allows for the non-invasive measurement of myocardial triglyceride content. Using this non-invasive technique, myocardial triglyceride content has been shown to be increased 1.5- to 2.3-fold in patients with T2DM.[95,97] Myocardial triglyceride levels were recently shown to be independently associated with concentric LV remodelling and subclinical contractile dysfunction in T2DM (*Figure 12*).[95]

In DM, insulin fails to suppress hormone sensitive lipase secretion in adipose tissue and very low-density lipoprotein secretion in the liver, leading to high circulating FA.[98] Elevated circulating levels of FA in combination with increased capacity for myocardial FA uptake appear to cause cardiac steatosis in patients with T2D. When the FA availability and/or uptake exceed FA oxidation capacity,[98] intracellular long chain fatty acyl-CoA concentrations increase.[95] The intracellular lipid pool is labile and has a dynamic relationship with FA destined for β-oxidation.[99] Since cardiomyocytes are not specialized to store lipid, cellular lipid overloading underlies the concept of 'lipotoxicity' as a potential mechanism for impaired cardiac function.[100,101] It is unlikely that long chain fatty acyl-CoA itself is cytotoxic, but the excess long chain fatty acyl-CoA can be diverted towards non-oxidative processes with the production of lipotoxic intermediates such as ceramide and diacyl-glycerol.[99] These lipotoxic intermediates have been shown to play a role in cardiac remodelling by activating distinct signalling pathways affecting ATP production, myo-cellular contractility, and apoptosis.[102,103] Cardiac steatosis may be documented by CMR and correlates with functional alterations. In addition, it has been demonstrated that cardiac steatosis potentiates the effects of angiotensin 2 on the myocardium[103] and successful reduction of cardiac steatosis with the glucagon-like peptide-1 receptor agonist exendin-4,[104] has been shown to reverse concentric LV remodelling. Taken together, these studies suggest a mechanistic link between cardiac steatosis, lipotoxicity, and concentric LV remodelling in diseases of up-regulated FA metabolism such as T2DM.

Ectopic adiposity and diabetic heart disease

Accumulating evidence suggests that the distribution of excess fat is an important determinant of cardiovascular risk, and ectopic and visceral adiposity confer a higher risk than subcutaneous adiposity.[105,106]

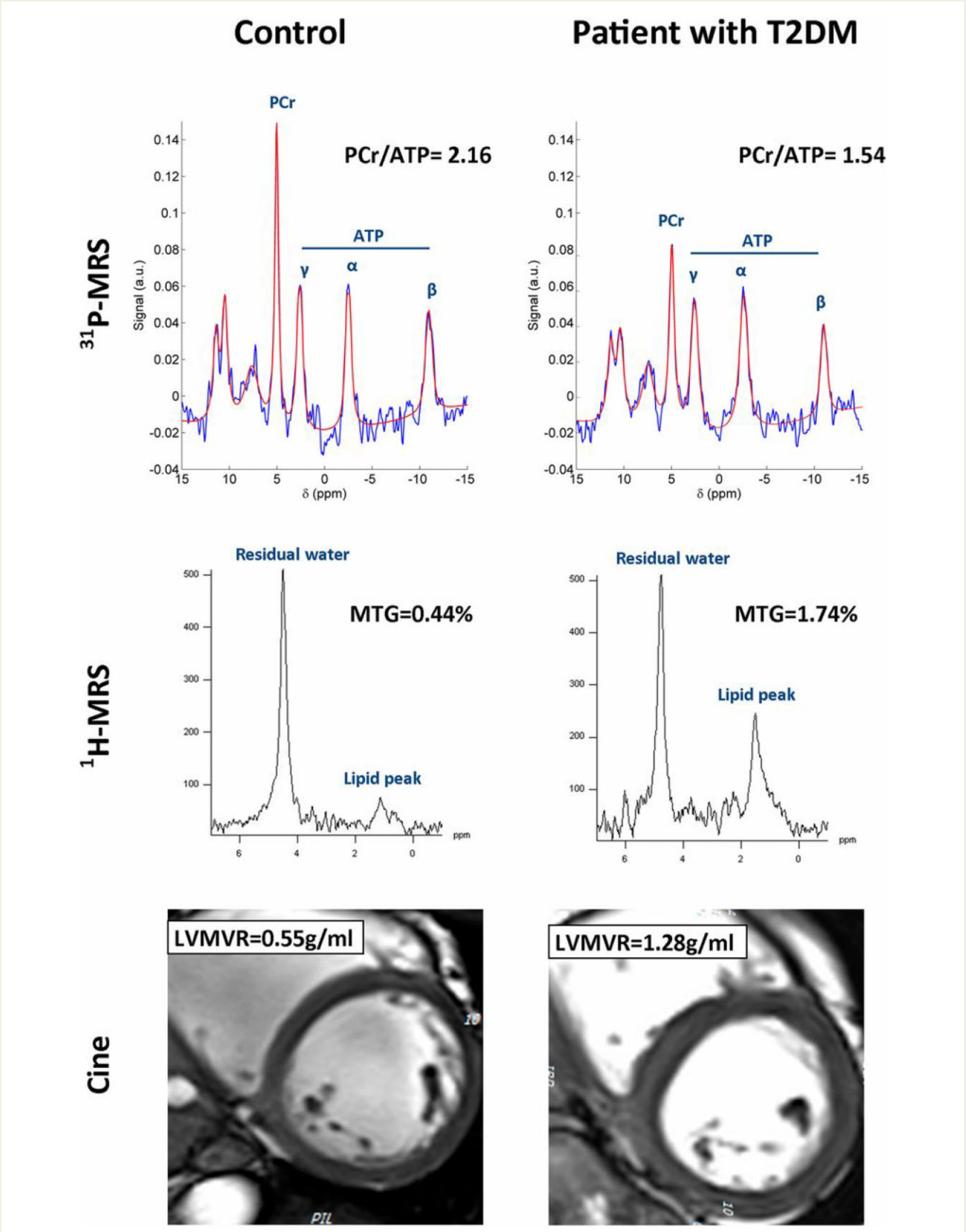

Figure 12 Examples of cardiac ^{31}P-MRS, ^{1}H-MRS, and LV mass/volume ratio (LVMVR) in a control subject and a patient with T2DM. *Top panels*: normal control ^{31}P-MRS [PCr-to-ATP ratio (Pcr/ATP) = 2.16] vs. a patient with T2DM (PCr/ATP = 1.54). *Middle panels*: normal control ^{1}H-MRS (myocardial lipid-to-water ratio = 0.44%) vs. a patient with T2DM (myocardial lipid-to-water ratio = 1.74%). MTG, myocardial triglyceride content. *Bottom panels*: normal control cine image (LVMVR = 0.55 g/mL) vs. a patient with T2DM (LVMVR = 1.28 g/mL).[95]

CT, magnetic resonance imaging, ultrasonography, and 1H-MRS have all been used to quantify adipose tissue amount or lipid content within an organ, and to examine the association of various fat depots with both systemic and local manifestations of disease.[107–109] Recently, using these techniques, it was demonstrated that, irrespective of body mass index, DM is associated with hepatic and cardiac steatosis. Intriguingly, cardiac triglyceride levels were not associated with hepatic or epicardial fat deposition and while obese patients with T2DM showed a greater propensity for epicardial and hepatic fat deposition, cardiac triglyceride levels were similarly elevated in lean and overweight patients with T2DM.[97] This dissociation of cardiac steatosis from epicardial and hepatic fat suggests that cardiac triglyceride accumulation represents a separate entity that is influenced by factors beyond visceral adiposity.

Epicardial adipose tissue (EAT) has no anatomical barriers with the myocardium, and, by secreting proinflammatory adipokines and cytokines through paracrine/autocrine signalling pathways, EAT may play a significant role in diabetic heart disease. Supporting this theory, an inverse correlation was demonstrated between EAT volumes with cardiac systolic strain.[110]

Sympathetic innervation

Cardiac autonomic neuropathy (CAN) due to structural and functional changes has been described in many disease states, such as HF, T2DM, chronic kidney disease, myocardial ischaemia and infarction, and hibernating myocardium.[111,112] Unfortunately, while CAN is associated with higher resting heart rate, systolic and mean blood pressures, aortic stiffness, HbA1c, and urine albumin/creatinine ratio, in addition to lower peak heart rate, chronotropic index, and exercise capacity,[113] none of these are specific. The imaging of cardiac sympathetic innervation depends on radiolabelling neurotransmitter analogues; the one used with SPECT is the norepinephrine analogue meta-iodobenzylguanidine, which is labelled with 123-iodine (^{123}I-mIBG) (*Figure 13*). The uptake and transport kinetics of ^{123}I-mIBG are very similar to norepinephrine and, due to its characteristics, may be viewed as an adrenergic presynaptic analogue. Neurocardiac imaging with PET, using 11C-epinephrine, 11C-hydroxyephedrine or other tracers, allows for adrenergic pre- and postsynaptic and parasympathetic imaging.

The importance of innervation in patients with DM was initially evidenced by reduced myocardial ^{123}I mIBG activity in diabetic patients without evidence of underlying heart disease.[114] These findings could reflect either cardiac autonomic dysfunction or down-regulation of the norepinephrine uptake-1 transporter and depletion of presynaptic sympathetic nerve vesicles as a result of progressive HF.[114] These ^{123}I-mIBG SPECT defects are seen in 80% of patients with T2DM, and imaging evidence of CAN has been associated with a worse clinical status.[115] Sympathetic nerve dysfunction in DM is associated with reduced MBF response to cold pressor stimulation and to adenosine administration, indicating that diabetic autonomic neuropathy is associated with an impaired vasodilator response of coronary resistance vessels to increased sympathetic stimulation. Diastolic function shows a modest association with heart/mediastinum ratio ($r = 0.41$, $P = 0.017$),[113] but regional tracer deficits indicative of local denervation are not necessarily matched by regional changes in function. Nonetheless, ^{123}I-mIBG shows prognostic value for detecting the clinically relevant endpoint of HF progression; the wash out kinetics of the heart/mediastinum ratio complements data derived from LVEF, B-type natriuretic peptide, and DM status for the prediction of HF progression.[116] These findings showed a low rate of progression of HF in subjects with a normal H/M ratio, irrespective of DM status.

Impact of comorbidities on imaging of diabetic heart disease

Risk factors

Arterial hypertension, obesity, and dyslipidaemia are risk factors for LVD and HF, and the co-existence of these risk factors with T2DM make it difficult to isolate the contribution of DM to cardiac pathology. Thus, the existence of a distinct diabetic cardiomyopathy has been questioned for a long time.[117,118] There have been efforts to dissociate these entities—for example, Fang *et al.*[119] reported on the impact of LVH and hypertension in 93 patients with and 93 without DM. The resulting four groups (*Figure 14*) showed peak strain and strain rate to be impaired to a similar degree with 'pure' LVH or DM, compared with controls, but the effects of hypertension and DM appeared to be additive. Calibrated integrated backscatter (a surrogate of fibrosis) was abnormal in all three, perhaps a little less in patients with 'pure' DM. The degree to which patients display different phenotypes of diabetic heart disease may relate to the contributions (and responses to) hypertension and other confounders—for example, the 'diastolic phenotype' is particularly associated with obesity and hypertension, especially in women. A better understanding of these processes will help to better define optimal treatments according to phenotype.

Coronary artery disease

Reduction of coronary flow in patients with DM may involve atherosclerosis or apparently normal coronary arteries with abnormal coronary vasodilator reserve. The contribution of the former may be relatively easy to recognize based on the presence of wall motion abnormalities and/or wall thinning. The co-existence of coronary disease with LVD carries a particularly adverse prognosis (*Figure 15*).[7]

Abnormalities of coronary function are more difficult to study, but seem to be common. Using PET to assess myocardial blood-flow (*Figure 16*),[120] endothelium-dependent coronary vasomotion was significantly diminished in insulin resistance (-56%), impaired glucose tolerance (-85%), normotensive (-91%), and hypertensive DM (-120%). In contrast, vasodilator capacity measured in response to vasodilators was similar in normoglycaemic individuals (impaired glucose tolerance, insulin resistance), but reduced in normotensive (-17%) and hypertensive (-34%) DM.

However, at issue is not merely the presence of reduced coronary flow, but the association of reduced coronary flow or flow reserve to impaired function—presumably mediated by impaired substrate supply. One way this has been studied is by assessing the impact of DM on contractile reserve during dobutamine infusion or exercise.[119,121,122] However, the results have been inconsistent—Galderisi *et al.*[121] demonstrated an impaired inotropic response as assessed by myocardial strain variation during dobutamine infusion in

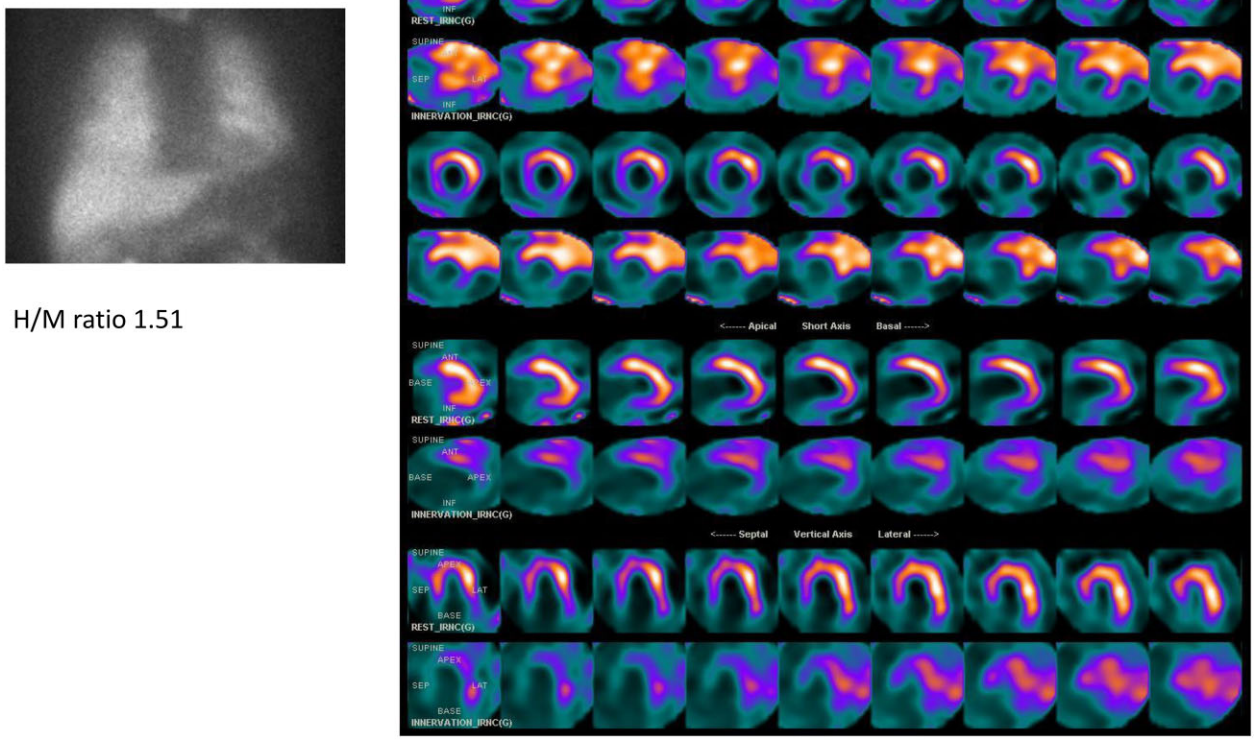

Figure 13 Cardiac autonomic neuropathy. This 62-year-old man with insulin-requiring type 2 diabetes was referred because of palpitations, in the context of a previous inferior MI (inferior akinesia with LVEF 48%), due to chronic occlusion of the RCA. The Holter ECG showed ventricular arrhythmias and the patient underwent evaluation of cardiac innervation and perfusion. The rest perfusion images with ^{99m}Tc Tetrofosmine (upper row, indicated as Rest) showed the RCA territory scar, and the MIBG images (lower row, indicated as innerv) showed a larger area of denervation, that included the infero-lateral wall, the inferior part of the septum and the apex, with a reduced MIBG uptake in the anterior wall, as well. These findings are typical in T2DM, where denervation may reflect CAD and microcirculatory abnormalities.

diabetic patients compared with controls, whereas Fang *et al.*[119] reported a normal response to dobutamine. Ha *et al.*[122] showed impairment of longitudinal function reserve (as assessed by TDI-derived systolic velocity at the mitral annulus) during exercise. This variability may be attributable to differences in progression and underlying pathophysiology of LVD in DM.

Prognostic value of cardiac imaging in the diabetic heart

Imaging of the diabetic heart may involve assessment for LVD or CAD, and although the outlook of both is worsened by DM, the implications are different.

LV dysfunction and HF

The combination of HF and DM is prognostically adverse, and particularly so in the setting of CAD. In 1246 patients with LVD undergoing cardiopulmonary exercise testing, cardiac catheterization and echocardiography, the effect of DM on cardiac survival differed according to HF aetiology. DM was independently associated with cardiovascular mortality in ischaemic patients [hazard ratio (HR) = 1.54 (1.13–2.09), $P = 0.006$] but the same magnitude was not seen in non-ischaemic patients [HR = 0.65 (0.39–1.07), $P = 0.09$] (*Figure 17*).[123] However, in 1760 asymptomatic patients with DM, the 411 (23%) patients with diastolic dysfunction (E/e' ratio >15) had twice the risk of developing HF (37% vs. 17%) at 5 years of follow-up. Each 1 unit increase in E/e' was associated with a 3% increment of HF risk, and this association was independent of hypertension, CAD, and other echocardiographic parameters (*Figure 18*).[124] Using a broader definition of stage B HF (E'/e'>13; LA enlargement >34 mL/m^2; LV mass >115 g/m^2 for men, >95 g/m^2 for women; GLS < 16%), Wang reported a worse outcome with increasing numbers of echocardiographic abnormalities, especially LVH and abnormal GLS (*Figure 19*).[125]

Coronary artery disease

Compared to patients without DM, those with DM tend to have more rapidly progressive CAD and worse outcomes. The impact of DM on the major adverse cardiovascular event risk varies according to patient characteristics, such as age, sex, or the presence or extent of cardiovascular disease.[126,127] The annual event rate increases with

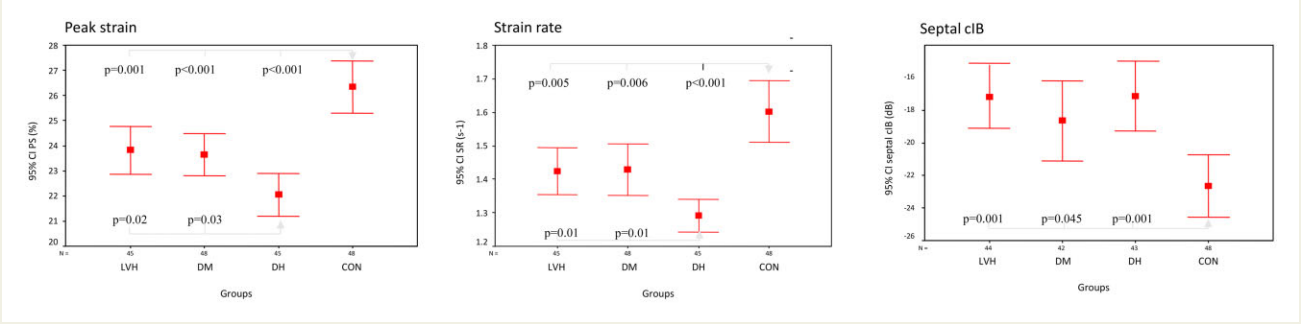

Figure 14 Roles of hypertension and LVH in LV function abnormalities in diabetic heart disease. Peak strain and strain rate are impaired to a similar degree with 'pure' LVH or DM, compared with controls, but the effects of hypertension and diabetes appear to be additive. Calibrated integrated backscatter (a surrogate of fibrosis) is abnormal in all three.

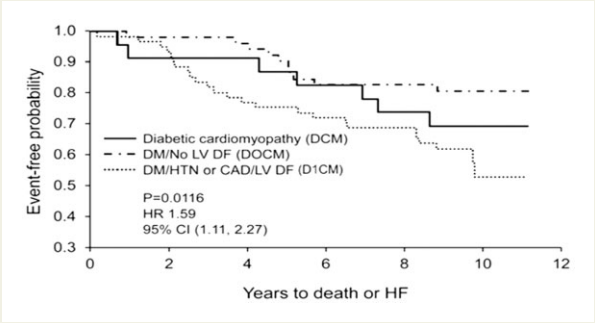

Figure 15 Survival and incident HF in a population-based study of DM. Events during follow-up are most common in subjects with LV dysfunction in the presence of CAD, diabetes, or hypertension, followed by subjects with diabetic cardiomyopathy (diabetes and any systolic or at least moderate diastolic dysfunction without a history of coronary disease, hypertension, significant valvular disease, or congenital heart disease) and DM without LV dysfunction.

higher ischaemic burden,[128] so SPECT myocardial perfusion imaging improves cardiovascular risk assessment and can be used to guide treatment strategy in patients with DM.[129,130] In a recent study, the differences in major adverse cardiac event (MACE) risk between patients with and without DM increased with greater stress perfusion abnormalities ($P < 0.001$ for interaction).[131] Conversely, the smallest difference in the annualized MACE rate between patients with and without DM was in patients with normal perfusion scan. This suggests that patients with DM are more vulnerable to a greater myocardial ischaemic burden, even if they have similar risk factors to patients without DM. Finally, the incorporation of myocardial flow reserve into PET assessment allows identification of the 40% of diabetic patients who were at high risk compared with the remainder, who experienced event rates comparable to individuals without DM.[73]

These findings have been confirmed by CMR; the presence of inducible ischaemia by stress perfusion CMR was associated with an almost five-fold increased likelihood of cardiac death and nonfatal MI in DM, while the annual rate of cardiac death and nonfatal MI was only 0.5%/year in the absence of inducible ischaemia or LGE.[132]

These outcomes are similar to those published regarding anatomical testing in diabetic patients presenting with stable chest pain. The PROMISE trial demonstrated that a CCTA-based strategy of evaluating symptoms suggestive of CAD resulted in fewer adverse cardiovascular outcomes than a functional testing strategy.[133] CCTA has the benefit of strong negative predictive value,[134] making it considered by some as the initial diagnostic strategy in symptomatic patients with diabetes and suspected CAD.[133]

Screening in diabetic heart disease

Should we screen for cardiovascular disease in DM?

The process of screening involves a number of considerations about both the clinical setting and the nature of the proposed investigation (*Table 4*). Although both LVD and CAD have prognostic significance in DM, appropriate therapeutic responses impact on the feasibility of changing outcome after screening. Although we have accurate non-invasive tests for both LVD and CAD, testing groups with a low prevalence will carry a heavy burden of 'false positive' scans. Therefore, if screening for LVD is considered for patients with DM, some preliminary selection based upon clinical risk assessment tools,[135] testing for reduced functional capacity,[136] or natriuretic peptides,[137] is warranted.

Screening for CAD

The results of functional testing for CAD are influenced not only by coronary stenoses but also by distal vessel involvement, diastolic dysfunction, and other causes of reduced functional capacity. The balance of these abnormalities impacts on appropriate management decisions pertaining coronary angiography and revascularization. In the Detection of Ischemia in Asymptomatic Diabetics (DIAD) trial, SPECT-MPI identified risk as expected, but screening showed no benefit because of failure to intervene on this risk.[138]

CT has also been used for screening. In the FACTOR-64 trial, 900 patients with type 1 or type 2 diabetes of at least 3–5 years' duration and without symptoms of CAD were randomly assigned to CAD

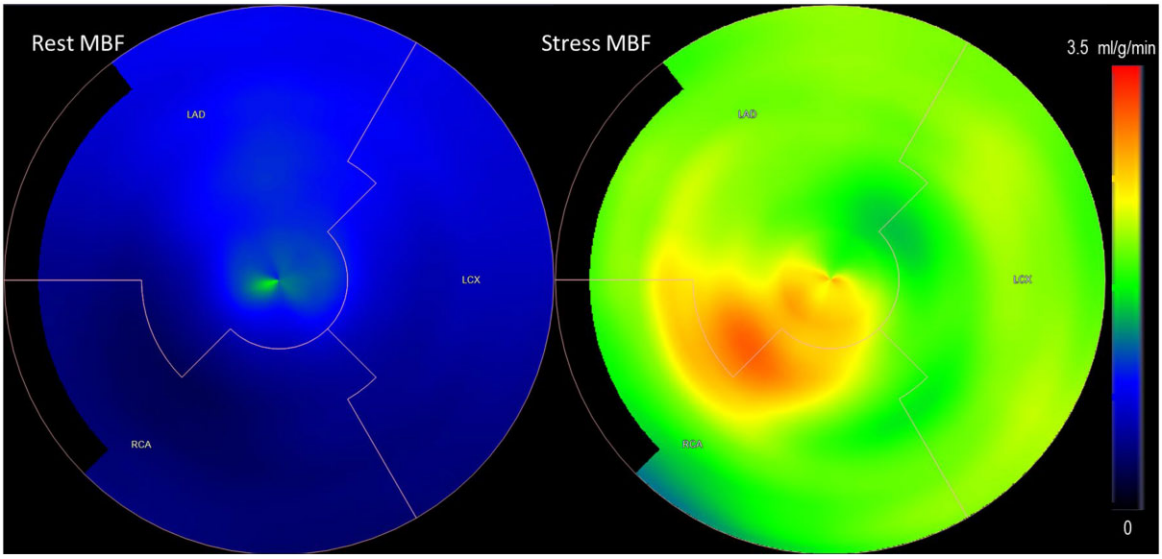

Figure 16 Assessment of coronary vasodilator dysfunction by ^{15}O-water PET. Polar maps show mild, diffuse reduction in myocardial blood flow (MBF) during adenosine stress in a patient with type 2 diabetes and non-obstructive coronary atherosclerosis (coronary calcium score 751, no obstructive lesions on invasive coronary angiography). Global stress MBF and myocardial flow reserve were 2.0 mL/g/min and 2.3, respectively.

screening with CCTA ($n = 452$) or to standard national guidelines-based optimal diabetes care ($n = 448$). With respect to the primary outcome (all-cause mortality, non-fatal MI, or unstable angina requiring hospitalization), this trial showed no significant difference between the CCTA (28 events, 6.2%) and the control groups [34, 7.6%; HR 0.80 (95% confidence interval, CI, 0.49–1.32), $P = 0.38$] after a mean follow-up of 4 years.[139] The incidence of the secondary outcome (a composite CAD death, non-fatal MI, or unstable angina) was also no different [4.4% (20 events) vs. 3.8% (17 events); HR 1.15 (95% CI, 0.60–2.19), $P = 0.68$]. Although lipid results were more favourable after a year in the CT-guided group (a benefit of detection of non-significant stenoses using CT), most of the at-risk patients were probably already on statin therapy, as evidenced by low LDL (<90 mg/dL) in both groups.

In fact, irrespective of imaging technique, four of five randomized controlled trials on the topic of CAD screening of asymptomatic patients with DM have shown no significant reduction of cardiac events.[140] As newer modalities are added, additional signals may be captured than influence risk assessment. For example, using CMR, silent MI would be discovered in a large proportion of patients, triggering intensified secondary prevention and potential further investigation. The point remains however that showing risk does not necessarily equate to being able to provide benefit—some risk is untreatable, and not all treatments can (or should) be provided to all patients, and not all treatments change outcome. An additional challenge for CAD screening relates to patient implications, which have led the process to have more 'cons' than 'pros'.[141] The 2019 European Society of Cardiology Guidelines on diabetes, prediabetes, and cardiovascular disease concluded that in asymptomatic patients with diabetes, routine screening for CAD is controversial and still under debate.[142]

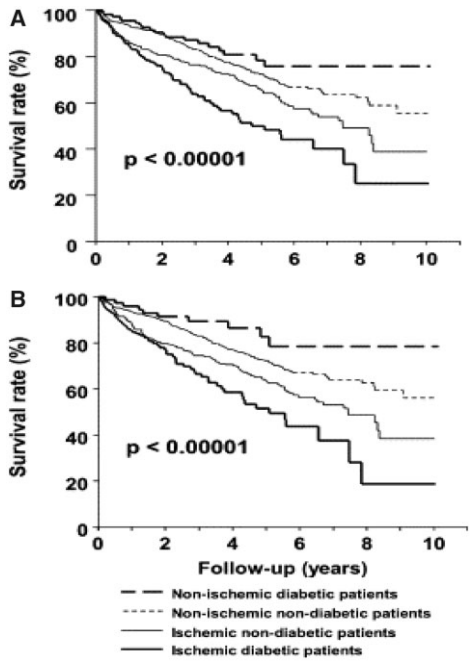

Figure 17 Relationship of cardiovascular mortality to diabetic status and aetiology of LV dysfunction. Irrespective of the definition of DM as including hypoglycaemic drugs or fasting blood glucose, or hypoglycaemic drugs alone, patients with ischaemia had the worst outcome.

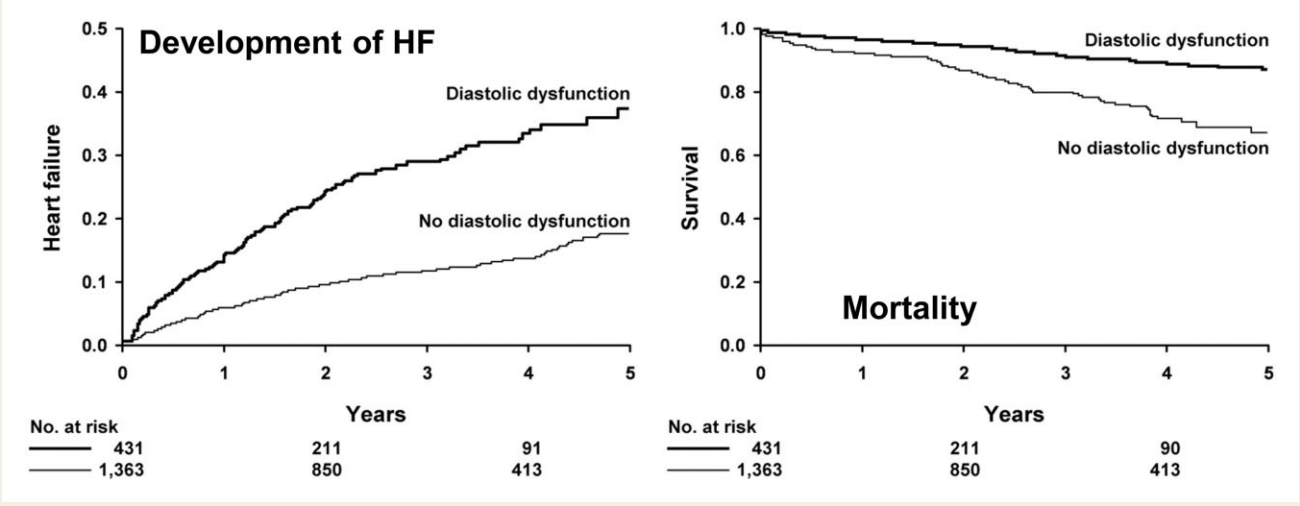

Figure 18 Association of diastolic dysfunction (*E*/*e*′ ratio >15) with outcome in DM. In patients with DD, HF occurred in 13% at 1 year and 37% at 5 years compared with 5% at 1 year and 17% at 5 years without diastolic dysfunction ($P < 0.001$). Likewise, mortality in patients with DD was 7% at 1 year and 31% at 5 years compared with 3% at 1 year and 12% at 5 years without diastolic dysfunction ($P < 0.001$).[124]

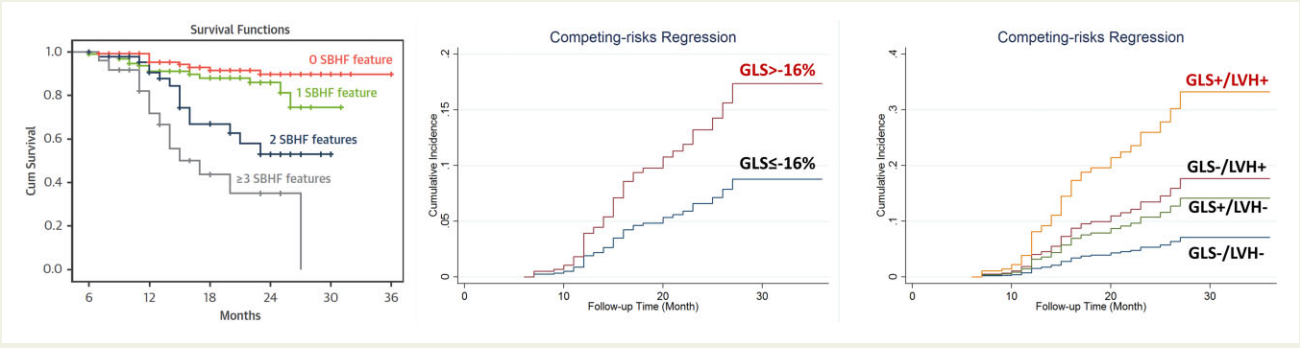

Figure 19 Events (heart failure and death) in non-ischaemic LV dysfunction. Patients with features of Stage B HF (SBHF) have a worse outcome than those with a normal echocardiogram (*A*), and outcomes worsened with without SBHF features, and (*B*) increasing numbers of SBHF echocardiographic features.[125]

Screening for LVD

The situation with LVD and the prevention of HF is perhaps more attractive. LVD is highly prevalent in DM, with abnormalities from 20% to 50%, so this is less of a concern than for CAD. Two studies have suggested that screening with natriuretic peptides can guide therapy to reduce HF risk.[143,144] If screening were to be undertaken, echocardiography with strain imaging is the most feasible tool for screening large numbers of patients at relatively low cost. Testing patients of middle age or older would be a good starting point as HF is generally a disease of the elderly. In addition, the 'at risk' group may be enriched by consideration of factors associated with HF (*Table 5*),[135] including evidence of microvascular disease. This is most feasible if these variables are incorporated in a clinical HF risk score such as the ARIC score or WATCH-DM.[145] After imaging has been performed, the spectrum of risk can be further quantified by combining findings.

Table 4 Considerations pertinent to screening for CVD in DM

Requirements	Considerations
Prevalence of the underlying disease	Is prevalence high enough? Selection required?
Accuracy of tests	Sensitivity and specificity Differentiation of low and high risk
Does identification of pathology alter outcome?	Aggressive Rx of risk factors Impact of specific interventions
Need for repetition	Warranty of a negative test
Cost-effectiveness	Potential numbers

Table 5 Risk factors for incident heart failure[135]

Clinical risks	Comorbid diseases	Other markers
Age	Diabetes	Fast glucose
Gender (male)	Chronic obstructive pulmonary disease	C-reactive protein
Race (black)	Coronary artery disease	Creatinine
Family history	Hypertension	Albumin
Obesity	Valvular heart disease	Dyslipidaemia
Education	Abnormal electrocardiogram	BNP
Low physical activity	Resting heart rate	NT-proBNP
Smoking	Atrial fibrillation	Troponin
Alcohol	Renal dysfunction	LVEF (echo, MRI)
	Sleep disorder	BP medication
	CVA or TIA	Other medication

BNP, brain natriuretic peptide; CVA, cerebrovascular accident; TIA, transient ischaemic attack.

Table 6 HF prevention strategies in DM

Management strategy	Comment
Treatment of standard risk factors	Ineffective
Cardioprotective therapies	
• ACEi, beta-blockers	Extrapolated from other stage B HF, but pertains to HFrEF[1]
• Aldosterone receptor blockers	Effective in improving LV function markers
Metabolic intervention	
• Better glycaemic control	Better glycaemic control linked to lower HF risk[148]
• Metformin	Meta-analysis shows metformin-treated T2DM patients do not increase *E*/*e*′ or *e*′[149]
• SGLT2 inhibitors	Reduction of HF risk in DM[146]
Antifibrotic therapies	Experimental

ACEi, ACE inhibitors; DM, diabetes mellitus; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; T2DM, type 2 diabetes mellitus.

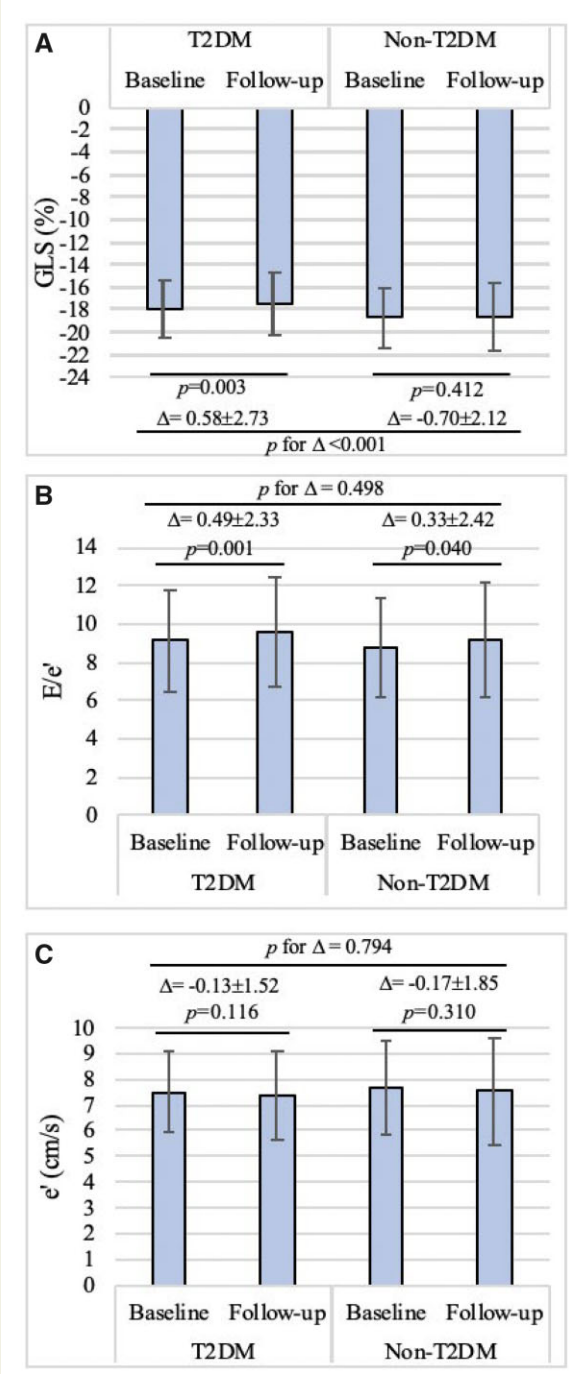

Figure 20 Evolution of LV dysfunction (A. GLS, B. E/e', C. e') in patients >65 years, with HF risk factors, with and without DM. Diastolic dysfunction worsens over time in both groups, with worsening GLS in DM only.[151]

While not yet resolved, it seems likely that the identification of subclinical LVD will lead to management changes that will alter outcome. The cardioprotective effect of sodium-glucose cotransporter 2 inhibitors (SGLT2i) has been reported in patients over a spectrum of risk,[146] with the most recent evidence (the EMPEROR-Preserved study)[147] pertaining to patients with HFpEF. Other preventive strategies for HF in patients with DM may also be useful[148,149] (*Table 6*). Glycaemic control continues to be considered important,[150] with every 1% increment in HbA1c associated with 3.0 g higher LV mass, 0.5 unit higher *E*/*e*′ and 0.3% worse GLS. The use of these agents in most jurisdictions pertains to DM with established cardiovascular disease, and the central (and unanswered) question pertains to whether these should be given to all patients—keeping in mind that HF risk is hugely variable, including in DM—or focused on patients at risk. This question will be answered by studies about efficacy (not just of the agent but also regarding program delivery), the benefits (if any) of phenotype-specific therapy, and health economics.

Table 7 Use of multimodality imaging to understand the underlying mechanisms/phenotypes of diabetic cardiomyopathy

Process	Aetiology	Investigation
Fibrosis	Focal (scar from CAD)	CMR—late gadolinium enhancement
	Diffuse	CMR—ECV and T1 mapping
Abnormal coronary structure or function	Flow reserve (relative)	Doppler flow reserve
		Single-photon emission computed tomography perfusion imaging
		CT perfusion
	Relative and absolute flow (microcirculatory disease)	Positron emission tomography
		Perfusion CMR
Metabolic imaging		Positron emission tomography
		CMR spectroscopy
Sympathetic innervation		Single-photon emission computed tomography, positron emission tomography

CMR, cardiac magnetic resonance; CT, computed tomography; ECV, extracellular volume.

If a screening strategy is selected and considered cost-effective, the need for repetition will be an important consideration regarding cost-effectiveness. While LVD is progressive, many HF cases identified within a year of screening are probably previously unrecognized. In a study of 982 community-based patients (71 ± 5 years) with at least one HF risk factor, 431 with T2DM, E/e' increased in both T2DM group ($P = 0.001$) and non-T2DM ($P = 0.04$) but there was a reduction in GLS ($P = 0.003$) only in DM over a median follow-up of 19 months (*Figure 20*).[151]

Conclusions

Asymptomatic impairment of functional capacity is common in T2DM and correlates with the degree of LVD. However, although asymptomatic LVD is associated with adverse outcomes in DM, the role of actively screening for LVD remains unproven because of the lack of proof of impact of downstream therapy. This situation is analogous to CAD screening, which also identifies risk but is unjustified because of the absence of evidence that this risk can be curtailed. There are multiple mechanisms underlying LVD, with primary roles for both myocardial dysfunction (relaxation) and fibrosis. LVH, systolic, and diastolic dysfunction represent different phenotypes with different outcomes (and maybe therapies). Potentially, the role of multimodality imaging, possibly in combination with biomarkers, will be to define the underlying phenotypes (*Table 7*) and elucidate the most effective approaches to providing targeted treatment and prevention. Much of the evidence about HF risk is derived from population studies, and the provision of better phenotyping will enable this evidence to be better personalized.

Conflict of interest: none declared.

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