PATHOPHYSIOLOGY AND IMAGING TECHNIQUES OF DIABETIC HEART DISEASE

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ABSTRACT

Diabetic patients are at an increased risk of developing heart failure. The aetiology of diabetic heart disease is likely to be multifactorial, ranging from altered myocardial metabolism, increased interstitial fibrosis, endothelial dysfunction, microvascular disease, and coronary atherosclerosis. These factors act synergistically with resultant myocardial systolic and diastolic dysfunction. The aim of the present review is to illustrate the role of multimodality cardiac imaging such as echocardiography, nuclear imaging, computed tomography, and magnetic resonance imaging in providing insights into these pathological processes, and to quantify the extent of myocardial diastolic and systolic dysfunction.

Keywords: Diabetes mellitus, heart disease, echocardiography, magnetic resonance imaging, computed tomography.

INTRODUCTION

Diabetes mellitus is an increasingly common disease worldwide. Recent estimates suggest its incidence has more than doubled over the last three decades and that there are currently 347 million people living with the condition.[1] The risk of cardiovascular disease (CVD) has increased 2 to 3-fold in this population[2,3] and half of all diabetic patients will die from CVD.[4] In particular, heart failure is twice as common in diabetic men and 5-times in diabetic women as age-matched controls.[2] Even after correction for the presence of other risk factors including obesity, hyperlipidaemia, hypertension, and coronary artery disease (CAD), diabetic patients remain at an increased risk of developing heart failure.[2,5,6] Diabetic heart disease (DHD) is defined as myocardial dysfunction (MD) that occurs independently of CAD and hypertension. This dysfunction may be subclinical but patients are at high risk of developing clinical heart failure.[5] Furthermore, patients have a higher risk of developing heart failure secondary to traditional myocardial insults such as hypertension and CAD.[7] MD in diabetics is a consequence of multiple pathological processes, including altered metabolism, interstitial fibrosis, endothelial dysfunction (ED), autonomic dysfunction (AD), microvascular disease (MVD), and coronary atherosclerosis (AS). This review will outline how multimodality imaging can demonstrate each of these pathological processes, and their effects on myocardial diastolic and systolic function.

AETIOLOGY OF DHD

The metabolic disturbances that cause MD in DHD are not completely understood, but abnormal glucose supply, utilisation, and abnormalities of free fatty acid (FFA) metabolism contribute significantly.[8] Glucose metabolism is disrupted via multiple pathways in diabetes, resulting in reduced myocardial contractile function.[9] Hyperglycaemia and insulin resistance also increase myocardial oxidative stress.[10] Circulating FFA levels are elevated in diabetes and obesity, due to increased nutritional fatty acid intake and lipolysis.[11] This leads to increased uptake and β-oxidation in the heart.[11-13]

In a process called myocardial steatosis (MS), excess fatty acids are stored as triglycerides (TGs) within myocytes. However, toxic intermediates, generated when FFA uptake by the cardiomyocytes exceeds its oxidative capacity, disrupt normal cellular signalling, and alter myocyte structure and function.[11-14] The increased FFA oxidation also produces reactive oxygen species (ROS), impairing mitochondrial coupling and decreasing adenosine triphosphate (ATP) production. As such, diabetic patients develop impaired cardiac energetics, as reflected by reduced phosphocreatine/ATP ratio, independent of the duration of diabetes and coronary microvascular function.[15,16] This process, known as lipotoxicity, eventually leads to cellular apoptosis and replacement fibrosis.

Extracellular structural changes, such as interstitial fibrosis, also occur in the diabetic heart.[17,18] These fibrotic changes are due to increased deposition of collagen and advanced glycation end-products, as well as cell necrosis.[8,19,20] The increased interstitial fibrosis leads to extracellular matrix expansion and is associated with myocardial contractile and vasomotor dysfunctions, arrhythmias, and increased mortality.[21] Angiotensin has emerged as a likely driver of myocardial cellular necrosis.[22-24] Negative regulators of the renin-angiotensin system have been shown to reduce cardiac hypertrophy, lipotoxicity, and inflammation in rat models of DHD, resulting in the reversal of diastolic dysfunction (DD).[25] The metabolic abnormalities that characterise diabetes also lead to increased mitochondrial superoxide generation, reduced endothelial nitric oxide production, increased endothelin synthesis, and the production of prothrombotic factors.[26,27] This disruption of vascular homeostasis causes endothelial dysfunction and MVD Additionally, these processes are the precursor for coronary AS,[26] and together they impair myocardial function.

Altered Metabolism

In a process synonymous with 'fatty liver disease', current evidence suggests altered FFA metabolism in the pathogenesis of DHD. It is generally accepted that intracellular TGs are probably inert but are reflective of increased intracellular concentrations of toxic fatty acid intermediates. Intramyocardial TGs can be quantified by hydrogen-1 magnetic resonance spectroscopy (^{1}H-MRS) (Figure 1).[28] A volume of interest triggered to both cardiac and respiratory motions is placed in the interventricular septum. A typical cardiac ^{1}H-MRS spectrum displays signals arising from water, creatine, choline, and TG. Using dedicated curve fitting software, signal amplitudes from intracellular TGs and water can be quantified and expressed as TG/water ratio.

Studies have correlated intramyocardial TG levels with left ventricular (LV) function.[28-33] van der Meer and co-workers[32] demonstrated that intramyocardial TG content increases with ageing and is inversely correlated with the age-related decline in myocardial function. Similarly, diabetic and obese patients have significantly higher intramyocardial TG levels when compared to controls, and this is associated with MD.[30,31,34] Animal models showing direct toxic effects of fatty acid intermediates on the myocardium provide further evidence for lipotoxicity.[35,36] Importantly, studies have demonstrated that weight loss is associated with a concomitant reduction in intramyocardial TG levels and improvement in LV function.[29,37] However, the effectiveness of pharmacological therapy for MS remains unclear, with studies showing conflicting results.[33,38] Diabetic patients can also develop impaired cardiac energetics due to increased ROS production from increased FFA production.[15,16] This results in reduced phosphocreatine/ATP ratio compared to normal controls as quantified by phosphorus-31 MRS (^{31}P-MRS).[16] Similar to ^{1}H-MRS, pharmacological intervention studies to date failed to demonstrate changes in cardiac energetics by ^{31}P -MRS despite improvements in cardiac function.[33]

Interstitial Fibrosis

Histological studies of diabetic hearts without significant CAD demonstrated increased collagen deposition in the perivascular and interstitial regions.[18,39,40] These structural changes lead to increased LV stiffness, impaired systolic and diastolic functions, and the development of clinical heart failure. Currently, both echocardiography and magnetic resonance imaging (MRI) can non-invasively quantify the burden of interstitial fibrosis. Echocardiographic integrated backscatter analysis was the first imaging modality to non-invasively quantify the burden of myocardial fibrosis (Figure 2, left panel). From the parasternal long-axis view, volumes of interest are placed in the anteroseptal and inferolateral walls at end-diastole, and the value of myocardial integrated backscatter is corrected for the pericardial integrated backscatter, thereby providing a calibrated backscatter value. Picano and co-workers[41] demonstrated that there was

a linear correlation between calibrated integrated backscatter and the burden of fibrosis on histology. Other studies have demonstrated increased calibrated integrated backscatter in diabetic patients compared to controls.[42,43]

MRI can quantify the burden of interstitial fibrosis using T1 mapping sequences and gadolinium-based contrast agents. Normally, gadolinium-based contrasts accumulate within myocardial fibrous tissues due to the absence of viable myocytes.[44] Iles and co-workers[45] histologically validated and demonstrated an inverse linear relationship between global contrast-enhanced myocardial T1 time and the burden of interstitial fibrosis (Figure 2, right panel). Ng and co-workers[46] were first to

demonstrate that diabetic patients had significantly shorter global contrast-enhanced myocardial T1 time compared to normal controls ($p < 0.001$), suggesting an increased burden of interstitial fibrosis. Furthermore, there was an independent correlation between global contrast-enhanced myocardial T1 time and myocardial function.[46]

CARDIAC AD

Diabetic AD is a well-known complication of diabetes. Its pathophysiology is likely to be multifactorial, involving metabolic alterations, neurohormonal growth factor deficiency, microvascular dysfunction, and autoimmune nerve damage.[47]
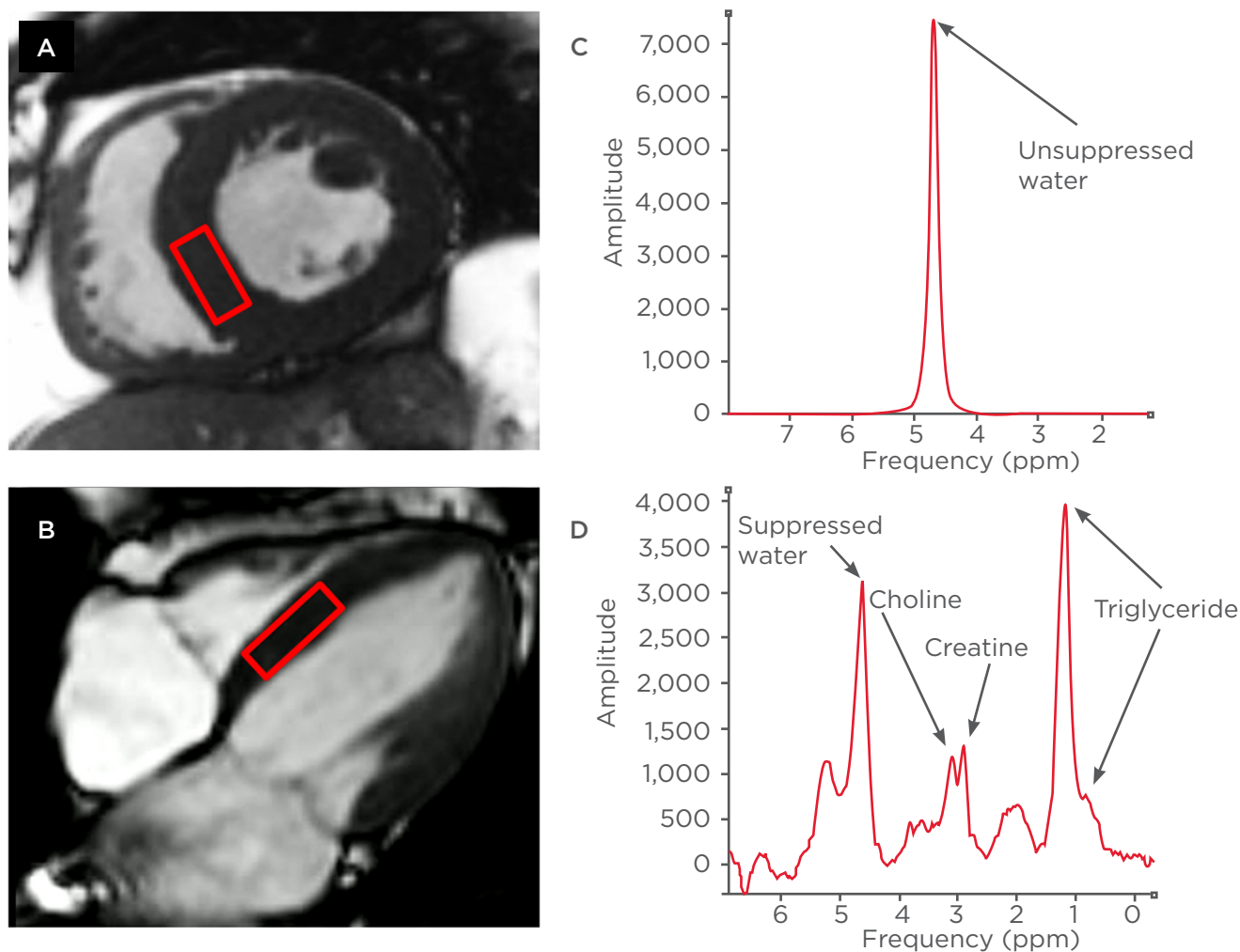

Figure 1: Example of hydrogen-1 magnetic resonance spectroscopy acquisition from a patient.
Panel A and B: short axis and 4-chamber view with the volume of interest placed in the interventricular septum; Panel C: unsuppressed spectrum showing the water peak; Panel D: water-suppressed spectrum showing peaks from choline, creatine, and triglyceride. Intramyocardial triglyceride (IMT) is quantified by summing the amplitudes of lipid resonances at 0.9 and 1.3 ppm, whilst water peaks at 4.7 ppm. IMT content relative to water is then calculated and expressed as a percentage based on: (signal amplitude of triglyceride)/(signal amplitude of water) x100.
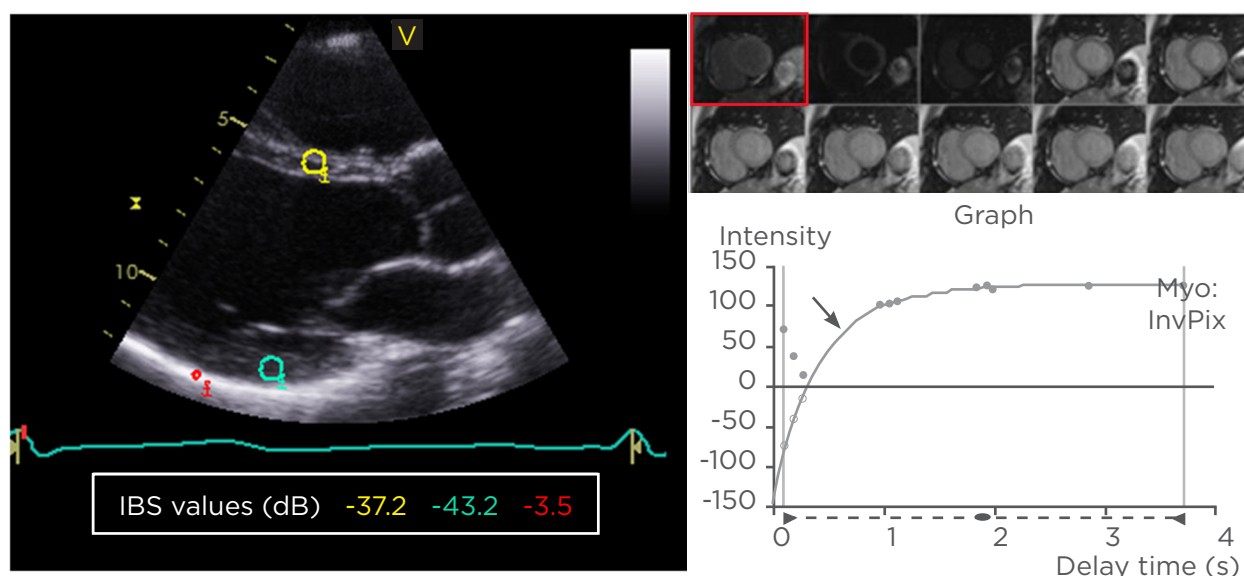
Figure 2: Echocardiographic quantification of myocardial fibrosis.
Left panel: using calibrated integrated backscatter (IBS). From the parasternal long-axis view, the IBS of the myocardium is measured at the anteroseptal and inferolateral walls and corrected for the pericardial IBS value. Therefore, calibrated IBS is calculated as the average IBS of the anteroseptal and inferolateral myocardium minus the pericardium. A less negative value calibrated IBS value indicates more interstitial fibrosis. Right panel: magnetic resonance imaging example of myocardial fibrosis quantification by T1 mapping. Left ventricular endocardial and epicardial borders were outlined for all images (top right panel). The myocardial signal intensities (y-axis) were plotted against the inversion time (x-axis) (bottom right panel). Finally, the global contrast-enhanced myocardial T1 time is calculated by the software which performed curve-fitting of the data points to an exponential recovery curve (arrow) representing the recovery of myocardial longitudinal magnetisation. Therefore, a short global contrast-enhanced myocardial T1 time indicates a higher burden of interstitial fibrosis due to a greater concentration of gadolinium within the fibrous tissues, and vice versa.

Cardiac autonomic neuropathy (CAN) is associated with increased risk of silent myocardial infarction (MI) and sudden cardiac death.[48] Clinical manifestations of CAN include resting tachycardia, postural hypotension without an appropriate reflex increase in heart rate, and exercise intolerance due to blunting of cardiac output in response to exercise.[49,50] Single photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging are available for the assessment of cardiac sympathetic adrenergic innervation and activation.[51-53]

Currently, sympathetic innervation is most commonly assessed using 123-iodine metaiodobenzylguanidine (^{123}I-MIBG), a norepinephrine analogue which is taken up and accumulated in the presynaptic nerve terminals.[54-56] Planar and SPECT images are acquired 10-20 minutes (early) or 3-4 hours (late) after ^{123}I-MIBG administration. From the planar images, semi-quantitative measurements such as heart-to-mediastinum (H/M) ratio and cardiac washout rate are used to evaluate global sympathetic innervation. SPECT images are used to assess regional abnormalities in sympathetic innervation. Previous studies demonstrated reduced ^{123}I-MIBG uptake in diabetic patients,[57] and the presence of CAN and reduced H/M ratio on delayed ^{123}I-MIBG imaging were independently associated with increased all-cause mortality.[58] Unlike SPECT, PET allows absolute quantification of the myocardial sympathetic innervation. Previous study demonstrated that carbon-11 meta-hydroxyephedrine PET imaging can detect regional differences in sympathetic innervations in diabetic patients compared to healthy controls.[52] In addition, patients with more severe autonomic neuropathy had significantly more extensive regional sympathetic denervation.[52] Importantly, defects in sympathetic innervation can regress or progress in diabetic subjects with good and poor glycaemic control respectively.[59]

MVD AND ED

ED and MVD can be evaluated directly using various imaging techniques including flow-mediated dilatation (FMD), myocardial contrast echocardiography, nuclear SPECT perfusion imaging, PET imaging, and MRI perfusion imaging. Endothelial function can be assessed non-invasively by FMD of the brachial artery (Figure 3, top panel). The brachial artery diameter is measured with ultrasound at baseline and at maximal vasodilation achieved during reactive hyperaemia. A blood pressure cuff is used to occlude the distal brachial artery and, when it is deflated, the increased flow causes endothelium-dependent dilatation. FMD is expressed as the percentage change relative to the baseline diameter. The related technique of low-flow-mediated constriction can be used to assess vascular tone at rest.[60] Impaired FMD in the brachial artery has been shown to correlate with coronary artery ED[61] but clinical applications for FMD testing are still emerging.[60,62] The technique has been used to demonstrate ED in patients at risk of AS before there is anatomical evidence of plaque formation.[63] In diabetic patients without obstructive CAD, Djaberi and co-workers[64] demonstrated that impaired FMD is associated with abnormal myocardial perfusion (MP).

Myocardial contrast echocardiography can be used to detect microangiopathy by evaluating MP and blood flow.[65,66] Microbubble contrast agents have similar rheology to red blood cells, so they stay within the intravascular compartment. These microbubbles resonate and appear bright on echocardiography when imaged using a low mechanical index, but are destroyed if a high mechanical index ultrasound pulse is transmitted. After a high mechanical index pulse is used to destroy microbubbles within the myocardium, the rate of replenishment is dependent upon the presence of intact microvasculature and myocardial blood flow rate. The intensity at which the contrast effects plateaus is dependent on myocardial blood volume. Therefore, areas with impaired perfusion appear dark and patchy. Moir and colleagues[67] used stress myocardial contrast echocardiography to demonstrate reduced myocardial blood flow reserve in diabetic patients in the absence of obstructive CAD.

MP imaging by thallium-201 or technetium-99m sestamibi SPECT is a widely used and well validated tool for evaluating cardiac function and MP (Figure 3, bottom panel). MP defects with stress may be caused by obstructive epicardial CAD or ED of the coronary vasculature, leading to an insufficient vasomotor response and relative hypoperfusion.[64,68] MP defects can be identified in 20-40% of asymptomatic diabetic patients.[69,70] Although prognostic for future cardiac events,[70-72] it may be reversible. The Detection of Ischemia in Asymptomatic Diabetics study[69] demonstrated that inducible myocardial ischaemia in asymptomatic diabetic patients resolved with 3 years of medical treatment (including aspirin, statins, and angiotensin converting enzyme inhibitors) in almost 80% of patients. This is likely due to both improvements in ED and stabilisation of atherosclerotic plaques.

PET has superior sensitivity and specificity compared to SPECT for the assessment of MP to detect underlying CAD.[73,74] It can also provide quantitative measures of myocardial blood flow and coronary flow reserve.[75,76] PET has been used to demonstrate ED in diabetic patients without epicardial CAD.[77-79] Despite these benefits, cardiac PET is still not widely used in clinical practice. MRI MP imaging employs a gadolinium-based contrast agent that can be detected on T1-weighted images as it travels through the cardiovascular (CV) system and into the myocardium. This allows quantification of MP at rest and during maximal hyperaemia induced by a pharmacological stressor. There is limited data on the use of MRI and MP imaging in diabetic patients. A small study found Type 1 diabetic patients with autonomic neuropathy had a significantly lower MP index than diabetic patients without autonomic neuropathy and controls.[80]

CORONARY AS

Some authors consider the diagnosis of diabetes equivalent to pre-existing CAD in terms of predicting future CV events and prognosis.[81,82] Although the effects of CAD on myocardial function do not generally fall within the definition of DHD, they complicate its assessment. Diabetic patients have high rates of silent MI and asymptomatic myocardial ischaemia. Silent MI in diabetic patients was recognised >40 years ago in the Framingham Heart Study.[83] More recently, evaluation of the UK Prospective Diabetes Study showed 326 of 1,967 patients (16.6%) had electrocardiographic evidence of silent MI at baseline.[58] Silent MI in diabetic patients is independently associated with an increased all-cause mortality. In an observational study of 1,899 asymptomatic diabetic patients

without prior CAD or MI, 60% had abnormal stress myocardial contrast echocardiography, and of these, 65% had CAD confirmed on angiography.[84] In that study, the presence of two or more other CV risk factors did not result in more abnormal tests or a higher percentage of confirmed CAD; however, CAD was more diffuse and severe in patients with additional risk factors.
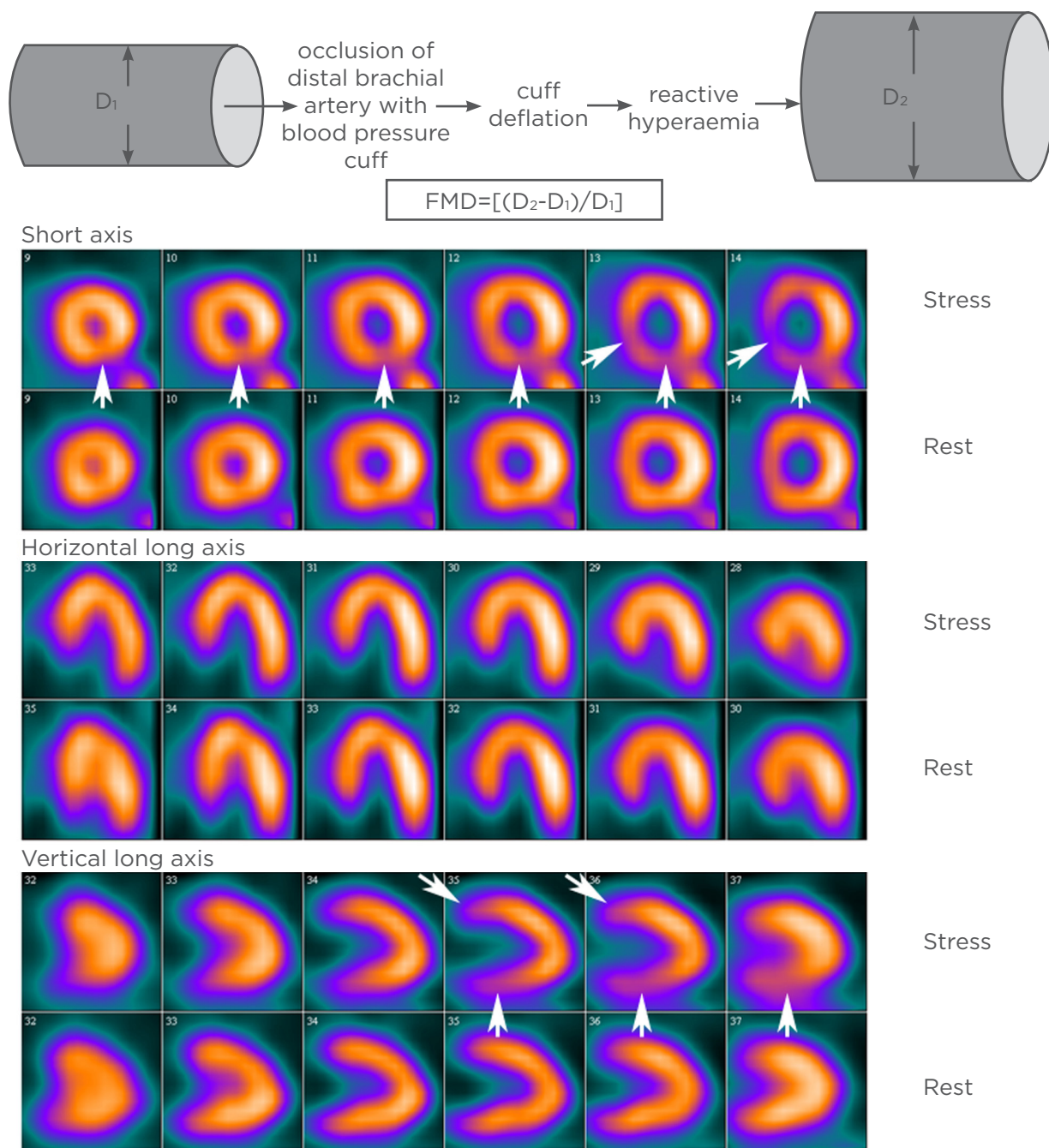

$$FMD=[(D_2-D_1)/D_1]$$

Figure 3: Assessment of flow mediated dilatation (top panel) and myocardial perfusion using gated single photon emission computed tomography at rest and after adenosine stress (bottom panel).
Top: the brachial artery diameter distal to the elbow is measured using ultrasonography (D1). Ischaemia is induced by inflating a distal blood pressure cuff to at least 200 mmHg for 5 minutes. After cuff deflation, the brachial artery diameter is measured every 30 seconds for 5 minutes and the widest diameter recorded is considered the maximal vasodilation achieved during reactive hyperaemia (D2). Bottom: resting images and stress images in the short axis, horizontal, and vertical long axes are depicted. In the current example, no persistent perfusion defects were observed. Reversible perfusion defects were observed in the inferior, inferoseptal, anterior, and anteroseptal regions (arrows).
Permission obtained from Ng et al.[108]

Traditionally, invasive coronary angiography (and its complementary imaging techniques, including intravascular ultrasound, virtual histology intravascular ultrasound, and optical coherence tomography) allowed direct visualisation of coronary AS. However, increasing availability and improved quality of cardiac computed tomography (CT) has led to widespread adoption of this technique to evaluate coronary AS. Coronary artery calcium (CAC) scoring detects calcium present within atherosclerotic plaques. As a marker of AS, CAC scores predict cardiac event risks in both diabetic and non-diabetic patients.[85] Anand and co-workers[86] have demonstrated that in diabetic patients, CAC scores of <10 were associated with very low clinical cardiac event rates and no perfusion abnormalities on MP imaging. CAC score is superior to established CV risk factor models for predicting silent myocardial ischaemia and short-term outcomes.

Cardiac CT angiography (CCTA) can provide detailed information on coronary artery anatomy, and assess both coronary artery atheroma and luminal stenosis (Figure 4). Advances in cardiac CT scanners have led to significant improvements in the accuracy of CCTA for the detection of coronary artery stenosis. The technique is now highly sensitive in detecting AS and has a negative predictive value that approaches 100%. Furthermore, CCTA allows detection of early non-obstructive atherosclerotic plaques without calcium. Compared to non-diabetic patients, CCTA has shown that diabetic patients have higher coronary artery atheroma burden and more extensive coronary artery stenoses.[87,88] All types of plaques (soft, calcified, and mixed) were more common in diabetic patients independent of other CV risk factors.

MD, DD, AND SD

Whether DHD is clinically evident or not, reliable and consistent methods of demonstrating LV DD and systolic dysfunction (SD) are needed to diagnose and assess progression of the disease. Echocardiographic techniques, including tissue Doppler imaging (TDI) and speckle tracking strain/strain rate, remain most useful for this purpose. Similarly, MRI tagging also permits quantification of myocardial strain/strain rate. However, due to the need for complicated image post-processing compared to the ease of echocardiographic speckle tracking strain/strain rate, it has failed to gain significant traction clinically and in research.
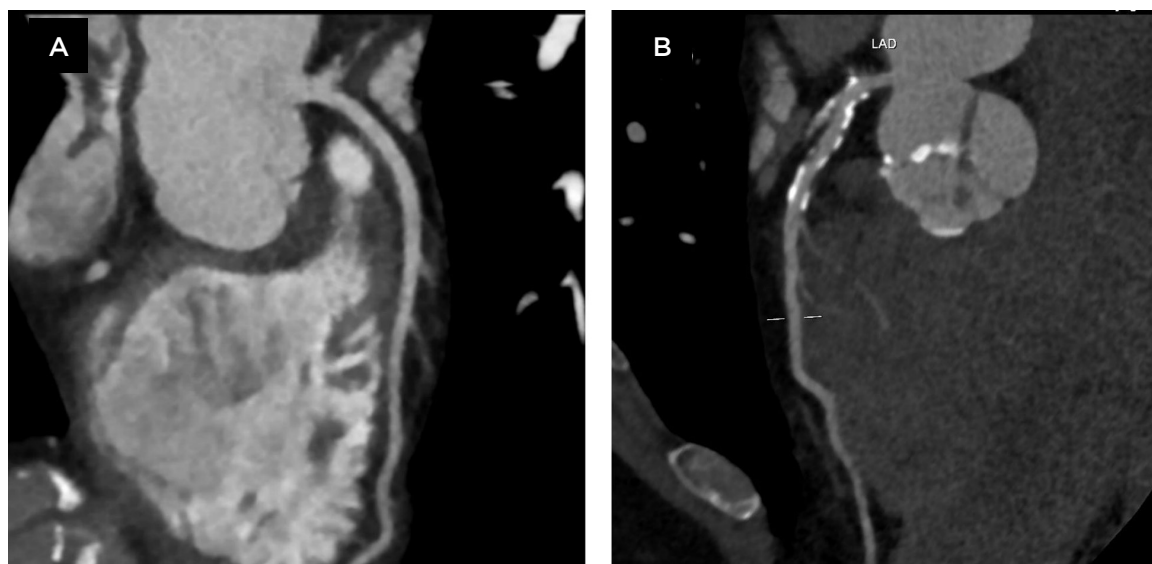

Figure 4: Evaluation of coronary artery disease with cardiac computed tomography angiography in diabetic patients.
A) Curved multiplanar reformation (cMPR) of a left anterior descending artery with no evidence of atherosclerosis. B) cMPR of the left anterior descending artery in a diabetic patient with both calcified and soft plaque in the proximal portion of the vessel.
LAD: left anterior descending artery.

On echocardiography, transmitral inflow patterns and TDI of the peak early diastolic early velocities are used to categorise diastolic function.[89] Interpretation of the transmitral inflow pattern in isolation is limited by its load and age dependency and may be impossible in cases of mitral valve disease. TDI myocardial velocities may be influenced by passive translational motion and tethering effects from surrounding myocardial tissue. Myocardial strain and strain rate imaging (obtained using TDI or speckle tracking) overcome these limitations by providing site-specific quantification of active myocardial deformation.[90-92] Speckle tracking strain is also angle independent. Wang and colleagues[93] have demonstrated in animal models that global strain rate during the isovolumic relaxation time strongly correlates with LV relaxation. The prevalence of DD amongst diabetic patients depends not only on the population studied, but also the sensitivity of the imaging modality employed. Amongst 86 young normotensive diabetics with adequate blood glucose control and no clinically detectable ischaemic heart disease, the prevalence of DD was 47% based on transmitral filling pattern alone[94] but rose to 75% when TDI was also employed.[95] Other groups have reported lower incidence, even when using all available echo parameters.[96,97] The incremental value of using strain and strain rate imaging in the assessment of DD remains unclear.[90]

DHD also affects systolic function. This is particularly evident when sensitive markers of systolic function are used for assessment. Left ventricular ejection fraction (LVEF) has traditionally been the clinical standard of assessing global LV systolic function. However, tissue velocity, strain, and strain rate imaging may be used as more sensitive methods of detecting LV SD. Tissue velocity measurements have been shown to correlate with radionuclide ventriculography in the assessment of global LV function.[98] Strain and strain rate have also been shown to correlate with LVEF by 2D echocardiogram[99] and invasive measures of LV contractility.[100] The sensitivity of tissue velocity, strain, and strain rate imaging makes them useful tools in the assessment of subclinical MD[90-92] and they have been used extensively for this purpose in DHD.[43,101-103] It has been demonstrated that strain and strain rate are significantly reduced in diabetic patients with normal LVEF who have no LV hypertrophy or CAD.[43] Strain and strain rate imaging are also particularly useful to compare within the same individual when assessing response to treatment.[104,105] The site specificity of strain imaging has also allowed regional differences in diabetic MD to be demonstrated, with longitudinal function being impaired early in DHD whilst there is relative preservation of radial function.[101-103,106] These regional variations may account for the initial preservation of LVEF in DHD. Structure and function of the right ventricle may also be affected by DHD. In diabetic patients with satisfactory blood glucose control and without ischaemic heart disease, cardiac MRI has demonstrated right ventricular remodelling and significant impairment of diastolic and systolic function compared to controls.[107]

CONCLUSION

DHD is a significant cause of increased morbidity and mortality. Our understanding of the underlying pathological processes is steadily growing, particularly through the use of multimodality imaging. Multimodality imaging can be used to define and assess both DD and SD in DHD.

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