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Diagnostic approaches for diabetic cardiomyopathy and myocardial fibrosis

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Abstract

In diabetes mellitus, alterations in cardiac structure/function in the absence of ischemic heart disease, hypertension or other cardiac pathologies is termed diabetic cardiomyopathy. In the United States, the prevalence of diabetes mellitus continues to rise and the disease currently affects about 8% of the general population. Hence, it is imperative the use of appropriate diagnostic strategies for diabetic cardiomyopathy, which may help correctly identify the disease at early stages and implement suitable corrective therapies. Currently, there is no single diagnostic method for the identification of diabetic cardiomyopathy. Diabetic cardiomyopathy is known to induce changes in cardiac structure such as, myocardial hypertrophy, fibrosis and fat droplet deposition. Early changes in cardiac function are typically manifested as abnormal diastolic function that with time leads to loss of contractile function. Echocardiography based methods currently stands as the preferred diagnostic approach for diabetic cardiomyopathy, due to its wide availability and economical use. In addition to conventional techniques, magnetic resonance imaging and spectroscopy along with contrast agents are now leading new approaches in the diagnosis of myocardial fibrosis, and cardiac and hepatic metabolic changes. These strategies can be complemented with serum biomarkers so they can offer a clear picture as to diabetes-induced changes in cardiac structure/function even at very early stages of the disease. This review article intends to provide a summary of experimental and routine tools currently available to diagnose diabetic cardiomyopathy induced changes in cardiac structure/function. These tools can be reliably used in either experimental models of diabetes or for clinical applications.

1. Introduction

It has been more than thirty years since diabetic cardiomyopathy (DCM) was first reported by Rubler et al [1]. DCM is defined as the changes induced by diabetes mellitus (DM) in cardiac structure/function in the absence of ischemic heart disease, hypertension or other cardiac pathologies. The prevalence of DM continues to rise and the disease now constitutes the fastest growing pathology in the USA currently affecting about 8% of the general population. The rise in the incidence of DM in particular type 2, parallels that seen in obesity. As the prevalence of obesity/DM impacts younger individuals the possibility of increased incidence of DCM becomes apparent. Thus, the urgency of adopting diagnostic strategies for DCM that may help correctly identify the disease at early stages and implement appropriate corrective therapies.

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Currently, there is no single diagnostic method for the identification of DCM. Most of the technology that is currently used to diagnose DCM has evolved from its experimental use by scientists. DCM is known to induce changes in cardiac structure that include the development of myocardial hypertrophy, fibrosis and fat droplet deposition. Early changes in cardiac function are typically manifested as abnormal diastolic function that with time leads to loss of contractile (systolic) function [2–4]. Changes in cardiac structure/function can be identified using various imaging modalities. These diagnostic tools can be complemented with the assessment of circulating biomarkers resulting from alterations in biochemical tissue composition or turnover. The best strategy that can be adopted is to utilize diagnostic tools that may be able to identify these changes and collectively as a group provide a probable diagnosis of DCM. This review article intends to provide a summary of experimental and routine tools currently available to diagnose DCM induced changes in cardiac structure/function. These tools can be reliably used in either experimental models of DM or for clinical applications.

2. Echocardiography

Echocardiography is an inexpensive tool that allows clinicians to evaluate changes in heart structure/function that are echogenic. As echocardiography has evolved the technology has improved substantially and there are multiple practical and research specific derivations of its use that are described below.

2.a. Doppler – blood flow velocities

Mitral valve blood inflow measured by pulsed wave Doppler, also known as transmitral Doppler (TD), is a commonly used technique used to assess diastolic function in the heart [5]. There are numerous factors involved in altering normal left ventricular (LV) diastole, including myocardial fibrosis, hypertrophy, contractile asynchrony, cellular disarray, changes in calcium cycling and pericardial abnormalities amongst others [6]. The presence of any of these factors can lead to alterations in blood flow velocities observed by Doppler [5]. However, many of these changes are not particular to DM as they can be observed in a variety of cardiac pathologies [7,8].

TD uses the blood flow characteristics of high frequency and low amplitude, to generate several indices for analysis of diastolic function [9,10]. The variables measured are; the early ventricular filling wave (E-wave) and the late ventricular filling wave (A-wave), which can be reported as the E/A ratio, the isovolumic relaxation time (IVRT), E-wave peak velocity (E), E-wave deceleration time (EDT) and A-wave duration (A-dur). Based on these primary measurements and their results, diastolic function can be categorized as (1) normal pattern, (2) impaired relaxation or grade I, (3) pseudonormal pattern or grade II and (4) restrictive pattern or grade III [11]. In the normal pattern the E/A ratio is greater than 1 as a result of the rapid LV relaxation generating a large E velocity. The IVRT and the EDT are high as well. Although these set of diastolic values (E/A >1) are grouped under the “normal pattern”, they may also be observed at early stages of ischemia, hypertrophy or cardiomyopathies [11]. The impaired relaxation or grade I pattern shows E/A<1, which results from a decreased early and increased late diastolic flows [12]. There is typically also an increase in the IVRT and EDT [13]. Grade I diastolic dysfunction is more prevalent in geriatric patients and can also be seen in those with ischemia [10]. In the pseudonormal pattern or grade II the E/A >1 resulting from an increase in left atrial pressure [11] in the presence of defective relaxation. The impaired LV relaxation leads to an increase in filling pressures in order to maintain normal cardiac output [12,14]. The pseudonormal pattern can be observed with ischemia, hypertension or LV overload, making its distinction from normal diastolic function difficult [11,14]. In the setting of a pseudonormal pattern of diastolic function the use of a Valsalva maneuver can potentially discriminate it from a true “normal” pattern. The rationale behind the Valsalva maneuver is to transiently revert left atrial pressure, causing a decrease in the LV preload. This potentially unmasks the

pseudonormal pattern, resulting in an E/A ratio < 1 [15]. In the restrictive pattern or grade III diastolic dysfunction, the deteriorated LV compliance and the rapid blood flow to it, cause an increase in filling pressure, leading to an increase in the E-wave, resulting in a E/A ratio > 2. IVRT and EDT are reduced. This pattern is seen in advanced stages of heart failure [11].

Pulmonary venous (PV) flow is assessed similarly as TD. In PV blood-flow velocities are acquired from the apical four-chamber view by placing a 2 to 4 mm pulsed waved Doppler sample volume in the right upper pulmonary vein [5,16]. The indices derived from PV flow velocities are: systolic peak, diastolic peak, (including their ratio), the flow peak of reverse atrial velocity and its duration, which is assessed in late diastole with atrial contraction [11, 17]. Although, the assessment of PV flow provides additional information to values obtained by TD, PV flow is also affected by loading conditions. Moreover, PV flow is difficult to measure using conventional transthoraccic echocardiography with a range of success between 37–86% [5,16].

Color M-mode Doppler echocardiography allows the measurement of blood flow propagation velocity from the mitral valve to the apex by placing the M-mode cursor in the direction of the mitral inflow jet and thus, can be used to evaluate LV relaxation. It specifically yields information about the spatiotemporal distribution of these velocities across a vertical scanline [18]. Thus, the information displayed on a color M-mode recording is similar to that of multiple simultaneous pulse Doppler tracings at different levels from the mitral orifice to the apex. There is information suggesting that Color M-mode Doppler echocardiography is preload independent [19]. However, measurements may be difficult in patients with fast heart rates, with dilated LV and with first degree atrioventricular blocks [16,18].

2.b. Limitations of Doppler flow measurements

As noted above, blood flow at the LV can be affected by several factors, such as the patient's age, heart rate, venous return, hypertension, loading conditions and location of the Doppler sample volume [11,16,20]. These factors can compromise results derived from blood flow velocities obtained by Doppler [5]. There are in fact several studies in which previously undiagnosed DM patients with LV diastolic dysfunction (as based on Doppler flow measurements) turned out to suffer from impaired relaxation when assessed using alternative diagnostic tools [15,21,22].

2.c. Doppler – myocardial tissue velocities

Tissue Doppler imaging (TDI) is a diagnostic tool that can be used in tandem with Doppler flow measurements. TDI as it name implies, measures myocardial tissue velocities during the cardiac cycle and appears to be relatively load-independent [9,23,24]. TDI assesses quantitatively global and regional systolic and diastolic functions of the myocardium, by employing low frequency and high amplitude ultrasound signals reflected from the tissue [25,26]. The myocardial velocities assessed by TDI, are a result of the long-axis motion of the ventricle. Once the myocardial velocity is acquired, systolic and diastolic indices can derive. Systolic indices usually include, (a) the systolic wave (Sm or S'); (b) myocardial peak velocity of Sm (m/s); (c) myocardial pre-ejection time (Q-Sm) obtained from the onset of the ECG QRS complex to the beginning of the S wave; (d) ejection time (ETm) obtained from the beginning to the end of the S wave [27]. Diastolic indices include the early (Em or E') and atrial (Am or A') wave, their peak velocities both in m/s; the Em/Am ratio and the regional relaxation time (RTm) obtained from the time interval between the end of Sm and the onset of Em [28].

As stated above, pseudonormal LV diastolic dysfunction often appears as normal in TD flow measurements. TDI has been shown to detect pseudonormal patterns in patients who present a normal E/A ratio. TDI has proven to be specially a good tool in patients suffering from

myocardial infarction, heart failure, hypertension, and dyssynchrony [25,26]. TDI is also a valuable tool in diagnosing abnormal regional changes in the myocardium. In a systematic study by Boyer et al, type 2 DM patients without symptoms of coronary artery disease, hypertension, valvular heart disease or congestive heart failure, underwent diastolic assessment by TD, Valsalva maneuver and TDI. Results showed that from the initial sample of 57 patients 26 (46%) had LV diastolic dysfunction when diagnosed by TD alone. The percentage increased to 63% when Valsalva maneuver was used; finally TDI raised the number of diagnosed cases to 42 patients (74%). A 28% increase from the initial diagnosed pool [15]. The use of TDI in and of itself can diagnose more cases than TD with the Valsalva maneuver. Nevertheless, it is suggested to use TD in conjunction with TDI. The Valsalva maneuver is not highly endorsed due diverse issues associated with this technique, such as difficulties with obese patients, or patients with obstructive airway disease [15]. In a second study done by Di Bonito et al, LV diastolic dysfunction was assessed in type 2 DM patients and non-diabetic controls. LV diastolic dysfunction was measured with both, standard pulsed-wave TD and TDI. Rigorous inclusion criteria was used for DM subjects; the duration of diabetes needed to be of 4 years or less, patients needed to be normotensive, non-obese and have no co-morbidity associated with diabetes. The non-diabetic control group was similar in age to the experimental group. Results from standard pulsed-wave Doppler echocardiography did not show any significant LV diastolic dysfunction difference between diabetics and controls. In contrast, when diastolic function was assessed by means of TDI, 50% of DM patients who had normal diastolic function with standard Doppler imaging had indeed a lower Ea/Aa, characteristic of early LV diastolic dysfunction. The strict parameters used in this study strengthen the validity of their results. The absence of confounder variables that might have altered LV diastolic dysfunction, suggest that TDI is a more sensitive technique than standard TD. Most importantly TDI also makes possible the detection of LV diastolic dysfunction even at early stages of DM [9].

2.d. Limitations of Doppler – myocardial tissue velocities

Neighboring myocardial segments influence regional tissue velocities determined by TDI. Moreover the so-called tethering between myocardial regional segments, in conjunction with translational and rotational motion, prevents TDI from properly differentiating active contracting muscle vs. passive [29–31]. Lastly the signal-to-noise ratio decreases as heart velocities decrease toward the apex, making TDI less appropriate to measure apical velocities [30].

With respect to regional tissue velocity, strain and strain-rate (SR) imaging have been shown to yield regional myocardial velocities more independent of tethering effects than TDI [32, 33]. The technical term for myocardial strain is deformation of tissue as a function of force over area (stress). This theoretical definition is overly simplified in biological tissues, since they hardly follow a linear relationship. The velocity at which myocardial tissue contracts or relaxes can be obtained by computing the temporal derivative of strain this is called SR. In both strain and SR a positive value represent elongation or thickening, while a negative value reflects shortening or thinning of the tissue [30]. Strain and SR can be obtained in one, two and three dimensions [34,35]. The inherent problems associated with a one-dimension approach involve errors due to torsional motion, myocardial wringing, which will result in inadequate strain measurements. This in turn, can affect the proper assessment of diastolic phase [34]. Strain and SR can also be acquired by speckle tracking techniques [34]. Speckle tracking by means of acoustic signals can characterize regional myocardial tissue in two dimensions (2-D) [29]. Despite the fact that echocardiography derived SR and strain measurements are done in 2-D, the simplification from three dimensions 3-D may eliminate valuable speckle information from view by through-plane motion. Nonetheless, speckle strain and SR have been validated with magnetic resonance imaging (MRI) tissue tagging. In specific, myocardial torsional deformation may be successfully assessed by 2-D speckle techniques and

still produce similar results to those of MRI tissue tagging [36]. Newer 3-D echocardiographic applications to speckle tracking may mostly do away with these limitations.

The use of TDI-derived SR and strain has provided useful information for the diagnosis of DCM. Strain and SR can be used to detect subtle changes in regional systolic function and LV contractility respectively, in type 2 DM patients before overt symptoms of myocardial dysfunction are observed [37]. A study [38] of type 2 DM patients, free of coronary artery disease, found that 27% of the total experimental group (n=120) exhibited subclinical LV dysfunction as detected by TDI. TDI-derived SR demonstrated that longitudinal contraction is decreased in type 2 DM patients [39]. Strain and SR have also uncovered evidence of cardiac dysfunction in DM patients under dobutamine stress [40].

Currently, it is recommended that standard echocardiographic evaluation in DM patients include TD and TDI. In the future as more research validates 2-D/3-D strain and SR, these should be included in routine analysis.

3. Magnetic resonance imaging (MRI)

3.a Principles of Magnetic Resonance imaging

Magnetic resonance (MR) is a relative new diagnostic tool that allows the accurate determination of cardiac structure/function. [41]. Hydrogen atoms attached to water molecules represent the main signal for proton nuclear MR. The magnetic field created by MR makes water protons rotate, which in turn generate a magnetic field that will align with the conducting magnet. Alternatively, a radiofrequency pulse is used to excite protons rotating at the same frequency and when this radiofrequency pulse is stopped, the protons relax emitting energy. This energy is the key component for the MR image formation [42].

Cardiac magnetic resonance (CMR) affords safe myocardial measurements; moreover, due to its high contrast and spatial resolution, low noise, and multimodal capability it has allowed for the accurate measurement of chamber size, ejection fraction and myocardial mass [43]. CMR is usually sort into black-blood imaging also known as dark-blood imaging and bright-blood imaging. In the case of black-blood imaging, the production of a good cardiac image is its main attribute. Basically, it is performed with a T1 weighted spin echo sequence. Fine quality images of the cardiac chambers, tumors, and vessels can be achieved by double inversion recovery spin echo [42,44]. Bright-blood imaging uses steady state free precession to acquire myocardial function information. Usually functional information, like ejection fraction, is obtained when the bright –blood images are assessed with a cine-loop format. This is due to the rapid speed of acquisition of the CRM sequence [42,45]. In addition to the aforementioned CMR characteristics, the use of contrast-enhanced agents have allowed the assessment of myocardial damage, scar tissue, fibrosis and inflammation [46].

3.b. Late gadolinium enhancement in myocardial fibrosis

Gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) is the most used clinical contrast agent. Gd-DTPA is well suited for CMR because Gd has an odd number of electrons that make it an effective paramagnetic element. Gd needs to be bonded to a ligand; due to the toxicity that it poses when exists by itself. Gd-DTPA successfully decreases the spin-spin time and spin-lattice time without emitting a signal; in addition, it intensifies the relaxation rate of hydrogen atoms in water molecules [47,48]. These characteristics make Gd-DTPA an appropriate contrast agent for the identification of structural cardiac pathologies. There are basically two processes by which Gd-DTPA has been suggested to work, volume distribution and rate of incorporation/elimination by the cell, also known as wash-in and washout kinetics. A mechanism is given more weight depending on the sort of myocardial damage. However,

volume distribution and rate of incorporation/elimination often play a similar role in contrast-enhanced CMR.

In myocardial infarction, Kim et al [49], demonstrated that the rate of Gd-DTPA incorporation/elimination by damaged cells plays a primary role in late contrast enhancement observed by CMR. The infarcted area, has both a slow wash-in and washout time. At the beginning of Gd-DTPA infusion, damage tissue takes longer than normal myocardium to incorporate the agent; and after a few minutes, when normal tissue has cleared Gd-DTPA, damage tissue has still a great concentration of the contrast agent. This results in a late enhancement effect characteristic of infarcted myocardium. In addition to the wash-in/washout kinetics, it was observed that a low functional capillary density increases the wash-in and washout times.

Similarly to acute myocardial infarction, regional myocardial fibrosis yields an accumulation of Gd-DTPA. The mechanics behind the increase in Gd-DTPA leading to late gadolinium enhancement have been explained as a decrease in capillary density, which potentiates the wash-in washout kinetics' effects. In addition, the tissue blood partition coefficient, λ, a parameter used to determine the equilibrium distribution of a contrast agent, has been shown to be elevated in chronic infarctions [50]. These results suggest that a delayed accumulation of Gd-DTPA in fibrous tissues is responsible for the late effect seen by CMR. The clinical use of Gd-DTPA has been coupled with the inversion time (TI) sequence. Simonetti et al. designed TI for its use in T1-weighted magnetic resonance. Once Gd-DTPA is infused, TI basically nulls the signal coming from normal myocardium. With the advent of TI, the difference between normal and damage myocardium produced by Gd-DTPA is further increased [51]. Late gadolinium enhancement has been used to detect regional myocardial fibrosis in patients with Anderson-Fabry disease [52,53] hyperthophic cardiomyopathy [54] and patients with heart failure [55]. Late gadolinium enhancement-CMR results have been correlated as predictors of major adverse cardiac events, such as acute myocardial infarction, development of heart failure, ventricular arrhythmias and others, in DM patients without clinical evidence of MI [43]. There are other promising technologies in particular, positron emission tomography (PET) that can measure myocardial metabolism using various tracers which in combination with classical computer tomography makes them powerful in their ability to asses DM induced changes in cardiac structure/function.

3.c. Metabolic MRI

In DM, the use of energy substrates is altered. These metabolic changes often appear in the asymptomatic stage of diabetes. Recently, ^{1}H magnetic resonance spectroscopy (^{1}H-MRS) and phosphorus-31-nuclear MR spectroscopy (^{31}P-MRS) have been shown to be good diagnostic tools in recognizing subtle changes in myocardial metabolism. Increased lipid supply to cardiac myocytes is seen in DM. With the use of proton magnetic resonance spectroscopy and MRI Rijzewijk et al. demonstrated that myocardial triglyceride content is related to alterations in cardiac function in type 2 DM patients. Myocardial triglyceride content was found to be elevated in DM patients and was associated with impaired LV diastolic function (as assessed by standard MRI) and increased hepatic triglyceride content [56]. The observation that elevations in hepatic triglyceride content correlated with those seen in the heart raises the interesting possibility that liver MRI scans (which are easier and less costlier to do) may provide a "window" to similar changes in the myocardium. In addition to triglyceride changes detected by ^{1}H-MRS, there may be alterations in high-energy phosphate (HEP) metabolism. Myocardial HEP metabolic changes are assessed via ^{31}P-MRS, by measuring the phosphocreatine to ATP (PCr/ATP) ratio. Two studies done separately on type 2 DM patients, independently demonstrated that the PCr/ATP ratio is decreased. In one study, the reduced ratio was associated with LV diastolic dysfunction [57]. Whereas the second study found a PCr/ATP ratio 35% lower in DM patients than in controls, in the absence of cardiac dysfunction [58]. The exact

molecular mechanisms leading to decreased PCr/ATP ratio are still unclear, nevertheless, alternative modalities of MR spectroscopy provide a new route to assess and diagnose DM patients on the basis of myocardial metabolic changes.

4. Plasma markers involved in cardiac remodeling

The classical indicators of the status of a diabetic patient are blood glucose levels and HbA1c. However, these indicators do not relate information pertaining to DM induced changes in cardiac biochemical composition or function. Currently, there is no specific indicator for such purposes. However, there is a strong correlation between changes in serum levels of biomarkers for the turnover of extracellular matrix (ECM) proteins and ongoing cardiac remodeling. One class of biomarkers is comprised by those that relate information pertaining to the synthesis and/or degradation of types I and III fibrillar collagens, which are the most abundant collagens in the myocardium as well as many other tissues. Indicators of type I and III collagen synthesis are serum aminoterminal propeptide of type I (PINP) and type III (PIIINP) respectively [59]. Quilliot et al., demonstrated increases in PIIINP in obese subjects with insulin resistance and suggested that this biomarker may represent an early indicator of LV dysfunction [60]. An indicator of type I collagen degradation is carboxyterminal telopeptide of type I collagen (ICTP). Increases in ICTP biomarkers have been correlated with remodeling of the cardiac ECM as seen in patients with hypertension or heart failure [61–62]. A recent study published by Ihm et al. correlated increases in ICTP and echocardiographic evidence of altered LV diastolic function. These results support the concept that the combined used of ECM biomarker assays and imaging techniques may provide valuable information as to DM induced changes in cardiac structure/function [63]. There are other biomarker assays available to detect ongoing ECM remodeling which are more indirect in nature. These bioassays are those that measure matrix metalloproteinase activities or their inhibitors (tissue inhibitors of matrix metalloproteinases) [59]. The use of these assays is still experimental and need to be further validated in large trials.

B-natriuretic peptide (BNP) is a cardiac neurohormone predominantly released from ventricular myocardium in response to LV volume expansion and pressure overload. BNP levels are elevated in patients with LV dysfunction and correlate to New York Heart Association class and prognosis [64]. In previous studies, in which BNP was examined in relation to echocardiography, it was clear that patients with DM often had high BNP levels and LV dysfunction [64]. Epshteyn et al. [65] measured BNP levels and compare them to echocardiographic findings in DM patients. Results indicate that in DM patients, BNP levels showed a high positive predictive value for the detection of LV dysfunction (96% with BNP levels > 90 pg/ml). Thus, this serum bioassay also offers a powerful screen for DCM in patients with diabetes.

There are a range of other emerging experimental biomarkers that may provide good correlation between serum indicators of DM status and potential changes in cardiac structure/function. One such group of candidate assays are those that measure levels of enzymatic beta O-linkages of GlcNAc (O-GlcNAc) to proteins [66]. The enzymatic modification of proteins by a glucose dependent event is distinct from the non-enzymatic modification by glucose of HbA1c. The practical use of these markers awaits further research.

5. Concluding remarks

DM is the fastest growing disease in the USA. The criteria to define pre-diabetes and DM is becoming narrower due to the recognition of the impact that the early stages of the disease have on patient's wellbeing. These are compelling reasons to perform extensive clinical studies to evaluate the development of DCM and fibrosis in patients in early stages of the disease which are currently non-existent. These studies should eventually include the use of therapies directed

towards controlling the severity DM and/or the development of DCM. It will be interesting to determine the effects that agents such as rosiglitazone and losartan (which have reported anti-fibrotic effects) have on the evolution of DCM. Ultimately, clinical study outcomes may help successfully implement preventive and/or treatment strategies which may limit the development of DCM. Table 1 summarizes the diagnostic tools and findings that can complement each other to provide a DCM diagnosis. Echocardiography based methods such as TDI currently stands as the preferred diagnostic approach. With the advent of late gadolinium enhancement-CMR, myocardial fibrosis has been easier to detect. Novel MR techniques have studied metabolic changes in the diabetic myocardium; opening state of the art approaches for DCM diagnosis. These techniques if complemented with serum biomarkers may truly offer a clear picture as to DM-induced changes in cardiac structure/function even at early stages of the disease. It should be noted that many of these diagnostic tools may also help in assessing changes in cardiac structure/function in DM patients following a myocardial infarction as their progression is often worse and is also marked by an accelerated development of myocardial fibrosis.

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Table 1

Diagnostic tools and typical findings observed in diabetic cardiomyopathy

Diagnostic tool	Modality	Results
Echocardiography	Transmitral Doppler	Increased left ventricular mass and diameter
	Pulmonary venous blood-flow	Diastolic dysfunction by flows
	Color M-Mode	Systolic dysfunction
	Tissue Doppler imaging	Decreased tissue velocities
	Tissue Doppler imaging-strain	
	Tissue Doppler imaging-strain-rate	
Magnetic Resonance Imaging	Magnetic resonance imaging (MRI)	Increased left ventricular mass and diameter.
	Late gadolinium enhancement – MRI	Diastolic and systolic dysfunction Myocardial fibrosis
	^{1}H-Magnetic resonance spectroscopy	Triglyceride content
	^{31}P-Magnetic resonance spectroscopy	Myocardial phosphocreatine to ATP ratio
Serum biomarkers	Serum aminoterminal propeptide of type I and type III, carboxyterminal telopeptide of type I collagen.	Extracellular matrix turnover BNP left ventricular synthesis
	Matrix metalloproteinases, tissue inhibitor metalloproteinases	
	B-natriuretic peptide (BNP)	