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Multi-Modality Imaging in the Assessment of Diastolic Dysfunction

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Abstract:

Non-invasive evaluation of diastolic function continues to play a critical role in furthering understanding of diastole, improving the diagnosis of diastolic dysfunction, evaluating left ventricular filling pressures, and providing important prognostic information for patients with heart failure. Echocardiography, cardiovascular magnetic resonance, and nuclear cardiology each provide important tools for evaluating diastolic performance. This review will focus on the techniques from multiple cardiovascular imaging modalities which have been used for the clinical assessment of diastolic function.

Keywords: Multi-Modality Imaging, Diastolic Dysfunction, Echocardiography.

1. Introduction:

Key parameters assessing diastolic dysfunction and structural changes have been positively correlated with progression to clinical heart failure. Structural changes identified include larger end-systolic and end-diastolic dimension, greater left ventricular mass in the context of similar wall thickness and greater left atrial area. Several studies have assessed signs of pre-clinical diastolic dysfunction in patients with diabetes with consistent results. In the I-Preserve trial (Irbesartan in Heart Failure with Preserved Ejection Fraction) patients with diabetes were shown to have significant echocardiographic abnormalities associated with diastolic dysfunction comparing to non-diabetic counterparts (**1**).

This suggests that the pathogenesis of diabetic cardiomyopathy at the early stages includes higher left atrial pressures, increased left ventricular stiffness with reduced myocardial relaxation and impaired left ventricular filling. Interestingly, prior to the onset of overt cardiac disease the degree of diabetic control, microvascular complication or insulin requirement is not associated with indices of heart function or reflectivity in type 2 diabetic patients (**1**).

Noteworthy, the duration of diabetes has been associated with the progression to left ventricular diastolic dysfunction with early diastolic impairment noted in the first five years from diagnosis. Conversely, in type 1 diabetic patients, e' mean has been identified to correlate with HbA1c values and duration of DM1. Hence those echocardiographic features of diastolic dysfunction as well as left ventricular hypertrophy are often regarded as early signs that diabetes affected the myocardium(**2**).

Age, obesity, and hypertension can frequently affect those parameters of diastolic dysfunction. Obesity frequently coexists with type 2 diabetes and has an additive detrimental effect on diastolic function. Although diastolic dysfunction has been linked to such processes as myocardial fibrosis, myocardial triglyceride accumulation and insulin resistance, echocardiographic features of diastolic dysfunction have been also attributable to coronary microvascular dysfunction (**3**).

2. Pathophysiology of diastolic dysfunction

Diastole is conventionally described by four phases: isovolumic relaxation, rapid filling, diastasis, and atrial systole (late diastolic filling) as seen in **Figure** . LV relaxation is an active, energy-dependent process which lasts from the ejection phase of systole through the isovolumic relaxation phase and into the rapid filling phase. The pressure decay, untwisting and elastic recoil of the ventricle creates a suction effect which promotes LV filling by reducing the LV pressure below that of the left atrial (LA) pressure. During early diastole, rapid filling of the ventricles is driven by this LV-LA pressure gradient created by ventricular relaxation (**4**).

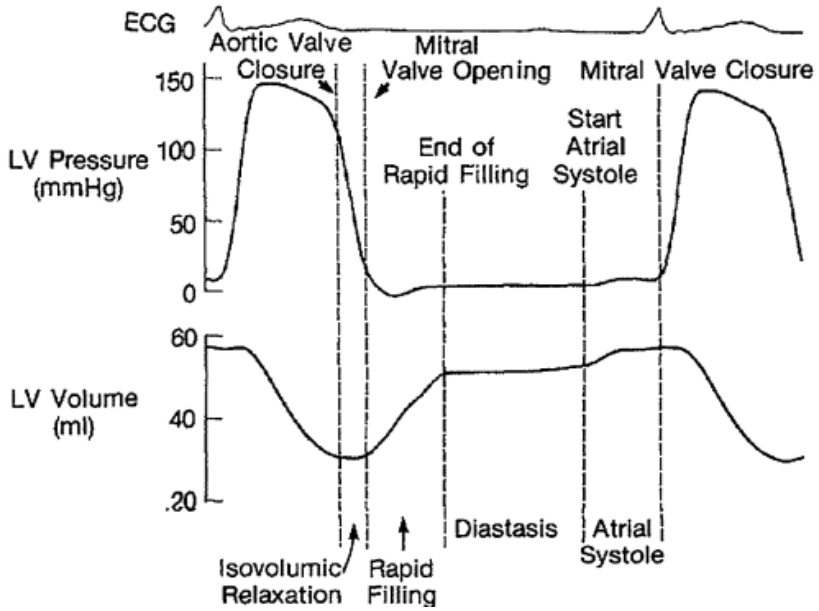

Figure 1: Relationships between LV pressure and volume during the four phases of diastole: isovolumic relaxation, rapid filling, diastasis, and atrial systole (5)

This relaxation process is enhanced during exercise by catecholamines which result in an increase in the LA-LV pressure gradient without increasing atrial pressures thus preventing pulmonary edema. In the normal ventricle, early diastole typically accounts for 60-80% of ventricular filling. Diastolic filling is dependent on properties of the left ventricle such as myocardial relaxation rate, untwisting, elastic recoil, diastolic stiffness, and contractile state. It is also dependent on the left atrial pressures, pericardial constraint, ventricular interaction, and properties of the pulmonary veins and mitral orifice (**6**).

In a normal ventricle, late diastolic filling occurs into a compliant ventricle as the myocardium is completely relaxed. Contraction of the atrium during late diastole creates a LA-LV pressure gradient driving further LV filling. Atrial systole generally contributes 25% of LV filling, Late diastolic filling is influenced by atrial inotropic state, preload, and afterload, as well as heart rate and PR interval (**7**).

The pathophysiology of diastolic dysfunction is largely related to impaired LV relaxation, and increased myocardial stiffness, but has also been shown to be related to increased vascular stiffness. Impaired LV relaxation is affected by alterations in calcium homeostasis and regulation by SERCA2a and phospholamban, alterations in myofilament sensitivity to calcium, as well as other changes in myocardial energetics as it is an ATP-dependent process. Increased myocardial stiffness is related to the changes in the extracellular matrix, the ratio of collagen I:III isoforms as well as collagen crosslinking (**8**).

It is affected by the change in the balance between metaloproteases and their inhibitors, and changes in isoforms of sarcomere proteins such as titin. These abnormalities result in an upward shift of the diastolic pressure-volume filling curve thus requiring the heart to work at higher filling pressures **Figure** . Both invasive and non-invasive techniques primarily assess alterations in LV relaxation, filling properties, or the passive

elastic stiffness properties of the ventricle. Imaging techniques also visualize the morphological changes in the atrium and ventricles which provide diagnostic clues to the presence of diastolic dysfunction (**9**).

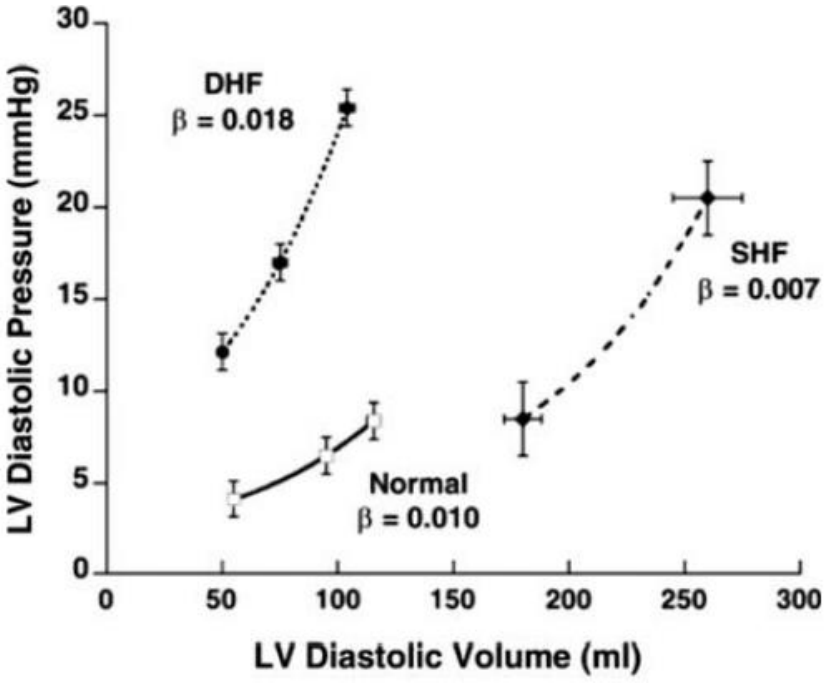

Figure 2: LV diastolic-pressure volume relationship enables calculation of the exponential stiffness constant b. In diastolic heart failure the curve is shifted up and leftward indicating an increase in passive stiffness of the ventricle (10).

3. Assessment of diastolic dysfunction

Diastolic function is most commonly assessed by echocardiography which has revolutionized both our understanding and the clinical assessment of diastolic dysfunction. Nuclear imaging techniques such as RNA and SPECT can also provide information about diastolic function. Cardiac magnetic resonance (CMR) with its high spatial resolution, inherent 3D capabilities, and multitude of contrast mechanisms has the potential to provide unique information about diastolic performance (**11**).

3.1. Echocardiography

Echocardiography can provide a morphologic assessment of both the atrium and ventricles which can provide insight into the chronicity of diastolic dysfunction. In patients with chronic diastolic dysfunction, there is remodeling of the left atrium which results in left atrial enlargement. Atrial enlargement can be assessed by measuring the linear dimension of the LA, the 2D area in a 4-chamber view, or by measuring left atrial volume (**12**).

Echocardiography can assess ventricular chamber size and ventricular wall thickness which are altered in LV hypertrophy (LVH) and may be a clue to HF-PEF. The rate of ventricular relaxation during the isovolumic relaxation phase can be assessed by measuring the isovolumic relaxation time (IVRT) which is the time between aortic valve closure and mitral valve opening (Normally the IVRT is approximately 70-90 ms, however, as LV relaxation is impaired the IVRT increases (**13**).

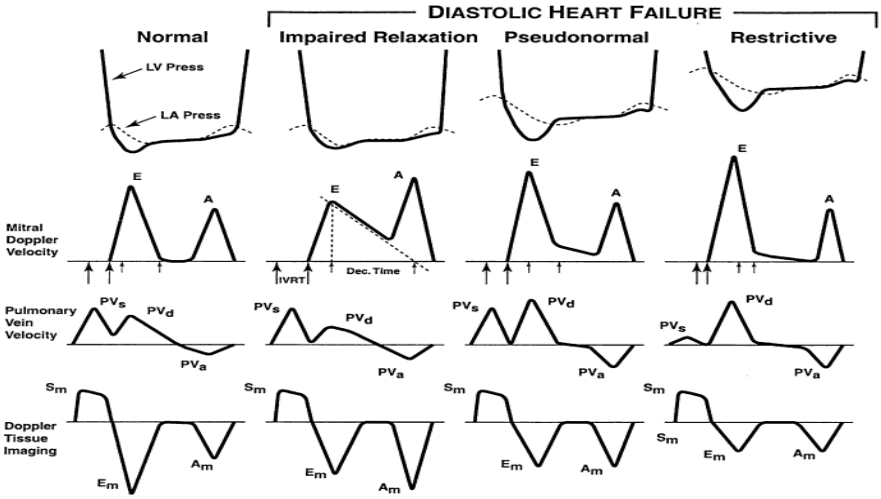

Figure 3: Progression of diastolic dysfunction as depicted by LV and LA pressures, and Doppler measurements of mitral inflow velocity, pulmonary vein velocity, and mitral annular tissue velocity (13).

As left ventricular compliance decreases, the IVRT begins to decrease, and with restrictive filling the IVRT is less than 70 ms. Direct assessment of IVRT has limitations as it is dependent on preload of the ventricle. The IVRT can be normalized by the time between the onset of the mitral inflow E wave and tissue Doppler e′ waves (TE-e′) to provide an estimate of the LA pressures and an IVRT/TE-e′ \2 has been used to predict increased LA pressures (**14**).

The rate and extent of LV filling can be assessed by evaluating the mitral inflow patterns with pulsed-wave Doppler. The mitral inflow pattern has an ‘‘E’’ wave resulting from early ventricular filling and an ‘‘A’’ wave resulting from atrial contraction. In the normal ventricle, the E-wave is typically larger than the A-wave with deceleration time (DT) greater than 140 ms, with a typical E:A ratio of 0.8-1.5. With impaired LV relaxation there is prolongation of the E-wave DT, a decrease in the E-wave velocity and increase in the A-wave velocity resulting in an E:A ratio less than 0.8 (**15**).

As LV compliance decreases and LA pressure increases, there is a large LA-LV pressure gradient which decreases quickly as blood enters the stiff ventricle. This results in an increase in E-wave amplitude, and a decrease in both the E-wave DT and a reduction of the atrial wave amplitude resulting in an E:A ratio <2.10 Multiple investigations have demonstrated that alterations in the mitral inflow pattern, particularly in patients with reduced EF are correlated with LV filling pressures. In patients with normal systolic function, this relationship is considerably weaker (**16**).

Furthermore, many of these parameters are not load independent. Pulse-wave tissue Doppler mitral annular motion provides a more load independent assessment of diastolic function **Figure .** During early diastole the mitral valve moves away from the apex resulting in an e′ wave, and in late diastole there is an a' wave resulting from ventricular filling due to atrial contraction. Normally the ratio of the E/e′ velocities is <10, however, when relaxation is impaired the e′ velocity decreases, and as the ventricle becomes stiffer, the e′ velocity continues to decrease resulting in an increase in the E/e′ ratio (**16**).

A ratio of E/e′ <15 is considered to be one of the more reliable indicators of increased filling pressures, even in patients with normal systolic function. An E/e′ ratio less than 8 is consistent with normal filling pressures, where as other Doppler parameters are necessary in determining LV filling pressures in patients with an E/e′ ratio between 8 and 15. The flow in the pulmonary veins also changes as a function of worsening diastolic dysfunction (**17**)**Figure** .

Normally there is pulmonary vein flow during systole when the atrium acts as a reservoir and during diastole when it acts as a conduit. During atrial contraction there is a reversal of flow in the pulmonary veins

(Ar). When there is impairment of LV relaxation, there is a decrease in diastolic pulmonary vein flow with a predominance of systolic flow. As the LV becomes stiffer and LA pressures are increased, the flow during systole is decreased since the atrium is noncompliant and diastolic flow predominates (**18**).

The difference between the duration of the pulmonary vein atrial reversal (Ar) and mitral inflow A waves (Ar-A) is increased when LV pressures are increased. All of the above hemodynamic parameters for diastolic properties change during the aging process, and standardized reference ranges for these parameters have been published. For proper assessment of diastolic function, age related changes need to be considered. For example, a majority of patients older than age 60 have DTs <200 ms and E/A ratios <1 which, in the absence of other cardiovascular disease would be considered normal (**19**).

Changes in the rate of ventricular filling can also be assessed by the propagation velocity of the wavefront of ventricular filling (Vp) using color m-mode. This is done by lowering the Nyquist limit and measuring the slope of the first aliasing velocity during ventricular filling. Normally this propagation velocity is greater than 50 cm s -1. The assessment of Vp is a more reliable marker of impaired relaxation in patients with depressed EF, as some patients with normal LV volume and EF may have normal Vp despite abnormalities in their filling pressures (**20**).

Two-dimensional speckle tracking imaging is a clinically useful technique for evaluating LV diastolic function. The variables of the technique are moderately associated with sPAP and can be used to predict PAH in CTD patients, but the SR parameters may not superior to the common E/E'_{sep} ratio (**21**).

3.2. Nuclear cardiology

Both Multi-Gated-Radionuclide Angiography (MUGA) and Gated SPECT have been used to assess diastolic function. By creating count-time curves, the time to peak filling rate (TPFR), peak filling rate (PFR), and E/A ratio can be determined. Normal values have been established for the measurement of these parameters by RNA. Time-volume curves can be determined from gated SPECT imaging and similar parameters can be derived. Typical values for these parameters are in the range of: TPFR<180 ms; PFR <2 end diastolic volume (EDV)/s; E:A ratio >40 (**22**).

The PFR has been shown to vary with age, end-diastolic and systolic volumes, heart rate (HR), and EF which must be taken into consideration when comparing these parameters across patients. The PFR has been normalized to the peak ejection rate to create a HR-independent assessment of diastolic filling. In the patient with diastolic dysfunction there is a decrease in peak filling rate, a prolongation of time to peak filling, and a reduction in the E/A ratio. **Figure** shows count-time curves for a patient who underwent anthrocycline therapy (**23**).

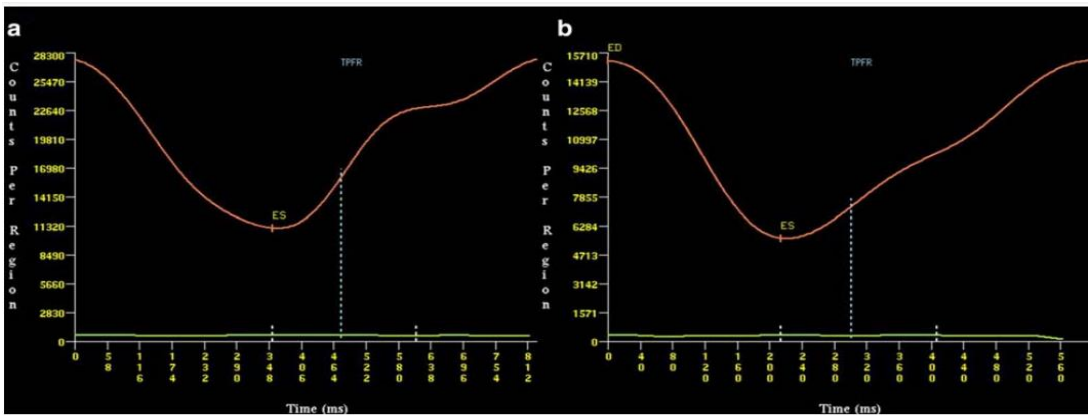

Figure 4: Count-time curves from (A) a patient before and (B) after anthrocycline therapy; there is a marked reduction in the slope of the count-time curve after anthrocycline therapy consistent with abnormal diastolic filling

There is a marked reduction in the slope of the count-time curve after anthrocycline therapy consistent with abnormal diastolic filling. This alteration in diastolic filling has been demonstrated in clinical studies. Alterations in diastolic function have also been evaluated using SPECT in patients with hypertensive heart disease hypertrophic cardiomyopathy (HCM), and coronary artery disease. Accurate assessment of diastolic function requires adequate temporal sampling with a suggested rate of 16-frames per cardiac cycle (**24**).

Using modern SPECT gated acquisitions volumetric diastolic function parameters can routinely be used for evaluation of diastolic function as an adjunct to rest-stress protocols. However, gated-SPECT acquisitions only allow for assessment of volumetric parameters, and thus provide far less information than that available from echocardiography or CMR fononinvasive assessment of diastolic function (**25**).

Emerging nuclear techniques, such as 99mTc Annexin 5 and mIBG imaging, are gaining attention for assessing myocyte apoptosis and sympathetic activity, which are associated with HFpEF **(26).**

3.3. Cardiac magnetic resonance imaging

Left ventricular (LV) diastolic dysfunction and diastolic heart failure (DHF) account for approximately 40–50% of all patients with congestive heart failure (CHF). Diastolic dysfunction can be evaluated directly by invasive cardiac catheterisation techniques or non-invasively by transthoracic echocardiography (TTE) or cardiac magnetic resonance (CMR) imaging. Due to its high spatial and temporal resolution, CMR is the accepted gold standard for evaluating ventricular systolic function. Using the cine-phase contrast technique, CMR can interrogate inflow through the mitral valve and pulmonary veins towards evaluation of diastolic dysfunction and has shown good correlation with TTE. Additionally, CMR can evaluate direct myocardial diastolic parameters that have no echo correlate, such as diastolic torsion rate. As CMR has the ability to characterise a range of diastolic impairments, it will likely become an important diagnostic test in the future, capable of comprehensive LV function evaluation. In this article, we focus on LV diastology, and review CMR methodology and parameters for the diagnosis of diastolic dysfunction (**27**).

Cardiac magnetic resonance can provide a variety of information which can be used to assess diastolic function. CMR can provide a morphological assessment of the atrial and ventricular chamber volumes, as well as myocardial wall thickness and myocardial mass. Conditions such as HCM including apical variants and LVH can readily be identified by CMR. Cine-imaging of heart function provides an assessment of ventricular function and can provide accurate assessment of the LVEF (**28**).

Delayed enhancement imaging 10-15 min after administration of a gadolinium contrast agent can be used to differentiate between different causes of cardiomyopathies which can result in diastolic dysfunction including amyloid cardiomyopathy, HCM, and sarcoid cardiomyopathy.41 CMR can also assess the presence of myocardial iron using T2* imaging aiding in the detection of iron overload cardiomyopathy (**29**).

Recently T1 mapping techniques have demonstrated an inverse correlation between the post contrast T1 and histological evidence of fibrosis in patients with heart failure. Cardiac magnetic resonance can also provide information about the rate and extent of LV filling. By segmenting the endocardial borders on each of the cine frames, volume-time curves can be generated to provide volumetric and rate parameters of diastolic filling similar to the methods described for SPECT. Improved segmentation algorithms are being developed which generate LV volume-time curves automatically, reducing the need for manual contouring of CMR images (**30**).

Recent Advances in Cardiac Magnetic Resonance for Evaluation of Diastolic Dysfunction:

1- Myocardial Tissue Velocity Imaging:

The CMR cine-phase contrast (CMR PC) sequence can also be used to evaluate the myocardial motion analogous to the myocardial tissue Doppler imaging by echocardiography. Using the CMR PC sequence, multiple oblique plane acquisitions, either in-plane or through-plane, are obtained. An initial study on cine-

phase contrast myocardial tissue velocity imaging generated interest as it demonstrated that lower early diastolic myocardial velocities are encountered in patients with myocardial infarction compared with controls and CAD patients without infarction. In another study, it was subsequently shown that the maximal myocardial long-axis velocity correlated with mitral inflow and colour Doppler echo parameters such as peak early filling velocity, early deceleration rate and E/A ratio. A pilot study by Paelinck and colleagues showed the feasibility of CMR tissue myocardial velocity measurement by comparing it with tissue Doppler and invasive measurements. They showed a strong relation between CMR-PC and Doppler-measured E/E'. For both techniques the correlation between the invasive peak capillary wedge pressure (PCWP) and E/E' was also strong. An E/E' <8 had a 100% positive predictive value (PPV) for PCWP <15mmHg and an E/E' >15 had a 100% PPV for PCWP >15mmHg (**27**).

2- Myocardial Tissue Tagging;

Myocardial tissue tagging aims to directly measure the diastolic properties of the myocardium, unlike transmitral flow and myocardial tissue velocity, which indirectly measure myocardial properties. Two myocardial properties are assessed: diastolic torsion recovery rate and LV strain rate recovery. In order to measure these properties, CMR radiofrequency tags are applied to the myocardium in a regular, grid-like pattern. As the heart contracts and relaxes, there is distortion of this regular grid pattern. Measuring the extent of myocardial deformation gives information in terms of diastolic torsion and strain rate recovery. **(27).**

3- Diastolic Torsion Recovery Rate:

Myocardium has oblique fibre orientation, which imparts angular momentum and results in systolic shearing or twisting of the heart during systole. This energy stored in the myocardium recoils in diastole, creating a suction effect that enables the opening of the mitral valve and ventricular filling **(27).**

The diastolic recoil or torsion recovery occurs in the isovolumetric relaxation time (IVRT) before the mitral valve opening and – unlike the mitral inflow parameters measured in late diastole – is not subject to pseudo-normalisation effects of LA contraction. Tau is a measure of the diastolic torsion recovery rate and has been shown to be independent of LA, ventricular or aortic pressure, thus representing a true measure of myocardial diastolic properties.38 A higher tau is expected in patients with impaired relaxation or with restrictive physiology **(27).**

4- Diastolic Strain Rate:

This strategy involves measuring the regional strain pattern of the myocardium. The complex 2D motion of the tagged LV tissue is computed with a previously validated tag-detection algorithm that measures the initial positions of the tags and their relative displacement as a function of the cardiac cycle. The data can be used to estimate the strain as the measure of underlying myocardial deformation at each point in the LV. However, due to several technical limitations this technique has not found widespread clinical use (**27**).

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