Evaluation of Diastolic Dysfunction Using Cardiac Magnetic Resonance Imaging

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Abstract

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.

Keywords

Diastolic function, cardiovascular magnetic resonance, left ventricle, congestive heart failure, magnetic resonance imaging

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Diastolic dysfunction and diastolic heart failure (DHF) have shown a steady increase in prevalence over the course of the last decade.[1] DHF is now regarded as a major public health concern. It shows an increasing trend with age and exceeds the incidence rate of systolic heart failure by the eighth decade of life.[2] In fact, it is estimated that approximately 25–30% of individuals 45 years of age in the general community have asymptomatic diastolic dysfunction.[3] Recent data show that the prevalence of DHF has increased from 38 to 54% of all heart failure (HF) cases.[4,5]

Unlike systolic HF, DHF has an unfavourable survival rate that has remained unchanged over the years.[5] New-onset symptomatic DHF is a lethal disease with a five-year mortality rate of approximately 50%.[6] Predisposing conditions for DHF are older age, female gender, diabetes and obesity, arterial hypertension and left ventricular (LV) hypertrophy.[7,8]

Terminology

Clinically, there is a distinction between diastolic dysfunction and DHF. While DHF refers to the clinical syndrome of HF in the setting of a normal ejection fraction (EF), diastolic dysfunction refers to an abnormality of diastolic function regardless of the clinical status of the patient.[9] It should, however, be noted that DHF is not exclusive to patients with normal EF (see 'Diagnostic Criteria' section). Both systolic and diastolic HF can co-exist in patients with DHF. Hence, in the recent literature the term HF with normal EF (HFNEF) has been used.[10] DHF and HFNEF will be used interchangeably in the rest of the article.

Diagnosis of Diastolic Heart Failure

Diagnostic Criteria

The diagnosis of DHF requires the following criteria: signs and symptoms of HF; normal or mildly abnormal systolic LV function; and evidence of LV diastolic dysfunction. However, unlike systolic HF, diagnosing DHF is not a simple process. This is related to both the complexity of the syndrome and the lack of a standardised method to confirm or exclude the diagnosis of DHF. Unlike HF with reduced EF (HFREF), in which one single parameter (i.e. EF <50%) is sufficient to confirm the diagnosis of the syndrome, in HFNEF different diastolic indices have been used to characterise the presence or absence of diastolic HF.[10]

Diagnostic Methods

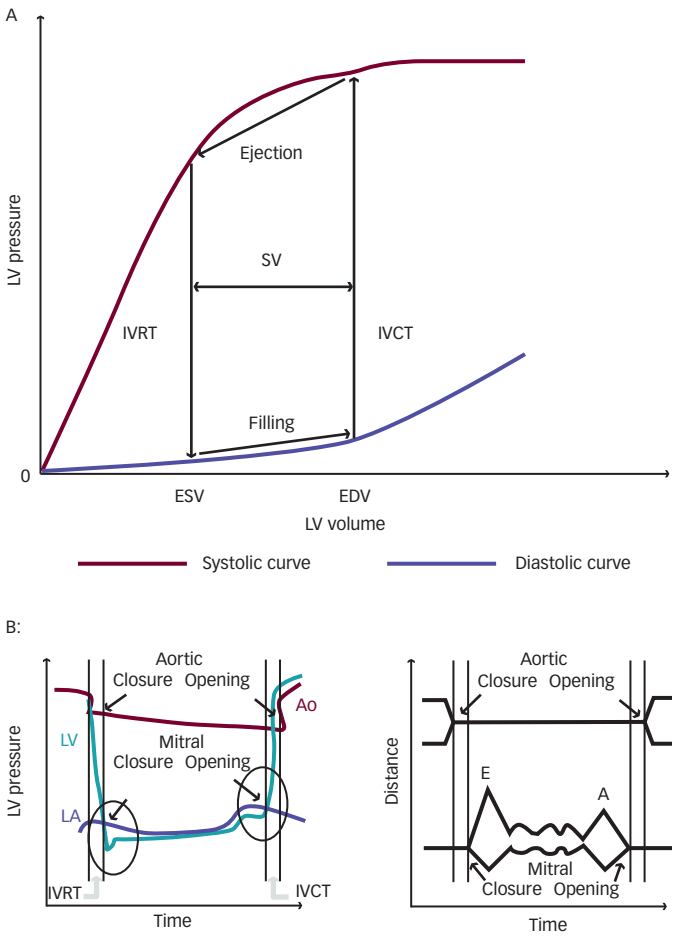
Invasive Methods

DHF can be diagnosed invasively by measuring: an elevated LV end diastolic pressure (>16mmHg); an elevated mean pulmonary capillary wedge pressure (>12mmHg); or an increased time constant of LV relaxation 'τ' (τ >48ms) or an increase in the constant for LV chamber stiffness (b >0.27).[11]

Non-invasive Methods

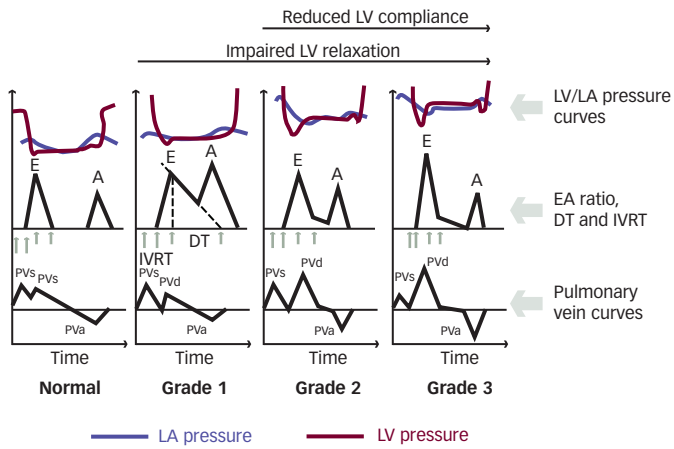
Conventional non-invasive diagnosis of DHF is obtained by echocardiography and tissue Doppler imaging (TDI). The most important parameter is the so-called E to E-prime ratio (E/E'). An E/E' >15 is considered abnormal and diagnostic of DHF. An elevated E/E' ratio (15 >E/E' >8) is suggestive of LV diastolic dysfunction, and requires additional echo variables for diagnostic evidence of LV

Figure 1: Normal Cardiac Physiology



A: The cardiac cycle consists of four phases. Note the pressure–volume changes during the cycle, in particular during isovolumetric relaxation time (IVRT) and ventricular filling. B: The pressure–time graph (left) shows the transmitral pressure gradient (TMPG, shown in the ovals) responsible for the ventricular filling. Note that normal ventricular filling takes place early (corresponding to the E-wave) and late in diastole during the atrial contraction (A-wave) (right). Ao = aorta; EDV = end diastolic volume; ESV = end systolic volume; LA = left atrium; LV = left ventricle; SV = systolic volume.

Figure 2: Interplay of Impaired Left Ventricular (LV) Relaxation and Reduced LV Compliance in the Pathogenesis of Diastolic Dysfunction



Top row demonstrates the left atrial (LA) and left ventricular (LV) pressure curves and changes in transmitral pressure gradient (TMPG) in the various stages of diastolic dysfunction. The middle row shows changes in EA ratio, deceleration time (DT) and iso-volumetric relaxation time (IVRT) corresponding to the changes in TMPG. The bottom row shows similar changes in the pulmonary wave systolic (PVs), diastolic (PVd) and A-wave reversal (PVa).

diastolic dysfunction. These include Doppler flow profile of mitral valve or pulmonary veins, measurement of LV mass index (LVMi) or left atrium volume index (LAVi), electrocardiographic (ECG) evidence of atrial fibrillation or high levels of B-natriuretic peptide (BNP).[11]

Cardiac Magnetic Resonance Imaging versus Echocardiography

While Doppler echocardiography is widely used and even considered a gold standard examination for evaluation of diastolic dysfunction, it has its own limitations: it is an operator-dependent exam with a limited field of view, and the flow measurements are indirectly calculated from velocities that depend on the placement of the sample volume and angle of ultrasound beam relative to the flow direction. Other limitations include patient-related factors such as body habitus and emphysema, which can result in a non-diagnostic exam. There is evidence that, compared with cardiac magnetic resonance (CMR) imaging, Doppler underestimates velocities and measurements such as the E/A ratio.[12]

CMR has inherent advantages over echocardiography. It can image in any desired plane and has a nearly unrestricted field of view, allowing visualisation of cardiac as well as extra-cardiac anatomy. Functional information, such as ventricular volumes, ventricular mass and measurements based on transvalvular flow, need no geometrical assumptions. Moreover, all major CMR techniques including volume, mass, viability and flow assessment have been shown to be highly accurate and very reproducible.[13–17]

Pathophysiology of Diastolic Heart Failure

The normal cardiac cycle consists of systole and diastole and is conventionally divided into four phases (see *Figure 1A*). Diastole is also divided into four phases: isovolumetric relaxation, early rapid diastolic filling, diastasis and atrial filling. A review of the pressure–time curve during diastole shows that the LV filling is essentially dependent on the transmitral pressure gradient (TMPG) (see *Figure 1B*). TMPG is largely dependent on two factors: LV relaxation and LV compliance. The various causes of diastolic dysfunction or DHF can therefore be grouped under the following categories.

- impaired relaxation – ageing, ischaemia and cardiomyopathy;
- reduced compliance – LV hypertrophy (hypertension and valvular and congestive heart diseases), myocardial fibrosis (infarction) and restrictive cardiomyopathy; and
- extrinsic compression – constrictive pericarditis and pericardial tamponade.

Note that extrinsic compression can also affect LV relaxation. The interplay of these two factors in various stages of diastolic dysfunction and the corresponding changes in the TMPG, mitral valve inflow and pulmonary vein flow are shown in *Figure 2*.

Cardiac Magnetic Resonance Evaluation of Diastolic Dysfunction or Diastolic Heart Failure

Parameters

On CMR, the following parameters can be used to evaluate diastolic dysfunction or DHF:

- mitral inflow – E/A ratio (ratio of peaks of mitral E and A waves) and deceleration time (DT);

- pulmonary vein flow – S/D ratio (ratio of the peaks of the pulmonary vein S and D waves) and A-wave amplitude and duration; and
- morphological evaluation – indexed left atrial (LA) volume and indexed LV mass.

Technique

Mitral Inflow

The CMR phase-contrast imaging technique is utilised for evaluation of mitral valve flow and velocity quantification. In phase-contrast CMR, protons moving through a magnetic field gradient produce a phase shift proportional to their velocity and direction. However, stationary protons produce no phase shift. Protons moving in the same direction as a magnetic field gradient, known as forward flow, create a positive phase shift in the MR echo signal that is proportional to their velocity. Protons flowing in the negative direction relative to the magnetic field gradient produce a proportional negative phase shift in the MR echo signal. Protons with zero velocity produce zero phase shift in the MR echo signal. The difference in phase shift between moving and stationary protons is measured. The calculated velocity is proportional to the measured phase difference between moving and stationary protons. Velocity equals the measured phase difference multiplied by the chosen velocity-encoding (VENC) factor (usually 100–200cm/second), divided by 180. The software calculates this during the flow analysis post-processing. First a cine-phase contrast ECG-gated CMR sequence is performed. The slice is carefully selected using multiplanar localisation to traverse the tips of the mitral valve leaflets and is placed perpendicular to the LV inflow (see *Figure 3A*). This generates short-axis cine-phase contrast images. A graphical contour of the mitral valve orifice is then drawn and automatically propagated (with manual override) to all time-frames of the cine loop in order to calculate the velocity, peak velocity and flow plots over time (see *Figure 3B*). Subsequently, the E-wave peak, A-wave peak, DT and E/A ratio are calculated (see *Figure 4A*).

Pulmonary Vein Flow

The cine-phase contrast technique described above is also employed to evaluate the pulmonary vein flow. Any pulmonary vein can be used for flow evaluation. In the experience of the authors, the right inferior pulmonary vein offers the most consistent visualisation and longest horizontal course, making it optimal for sampling. The VENC factor is usually 50–100cm/second. Again, automated contours with manual override are utilised to generate flow curves over time (see *Figures 3C* and *3D*). The S/D ratio, A-wave amplitude and A-wave duration are calculated (see *Figure 4B*).

Morphological Evaluation

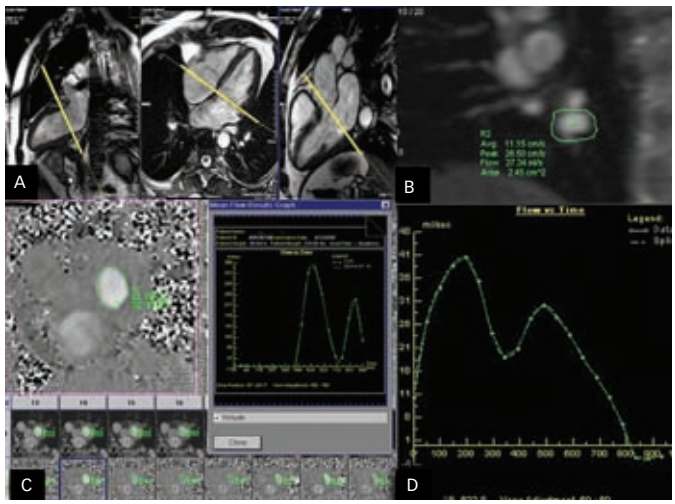
Left Atrial Volume

The bi-plane area length method is the most frequently used technique for evaluation of the LA volume. LA area and length are measured in two- and four-chamber views using planimetry (see *Figures 5A* and *5B*). The volume is given by the following formula:

LA volume = (0.85 x A1 x A2)/L

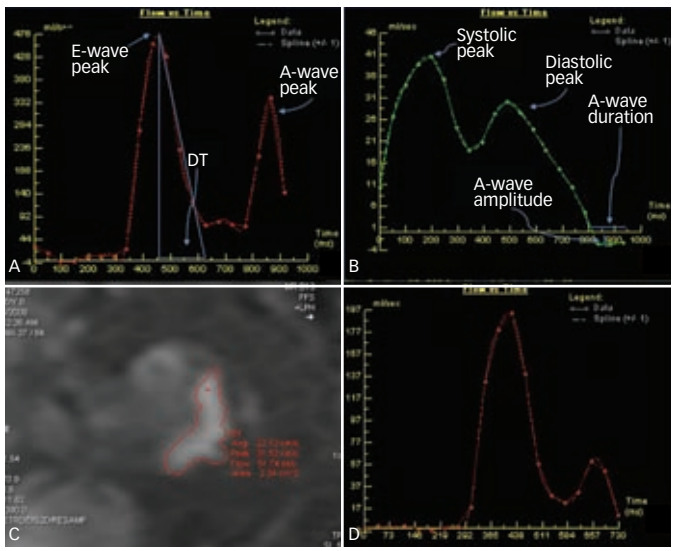
where L = LA length (the shorter of the LA lengths in two-chamber and four-chamber views), A1 = LA area in two-chamber view and A2 = LA area in four-chamber view (see *Figures 5A* and *5B*). The resultant LA volume divided by the body surface area (BSA) yields the indexed LA volume.

Figure 3: Cardiac Magnetic Resonance Evaluation of Mitral Valve and Pulmonary Vein Flow



A and B: The position of the slice across the mitral valve plane in all three of the left ventricular (LV) long-axis views, as shown by the yellow lines (A, top left), ensure imaging of the true short axis of the mitral orifice. On the resultant cine-phase contrast images (B, bottom left), contours are drawn across the valve orifice to generate a mitral inflow curve. Similarly, contours across a cross-section of the pulmonary vein cine-phase contrast sequence (C, top right) yield a pulmonary wave curve on cardiac magnetic resonance (CMR) imaging (D, bottom right).

Figure 4: Measurement of Mitral Valve and Pulmonary Vein Flow Parameters

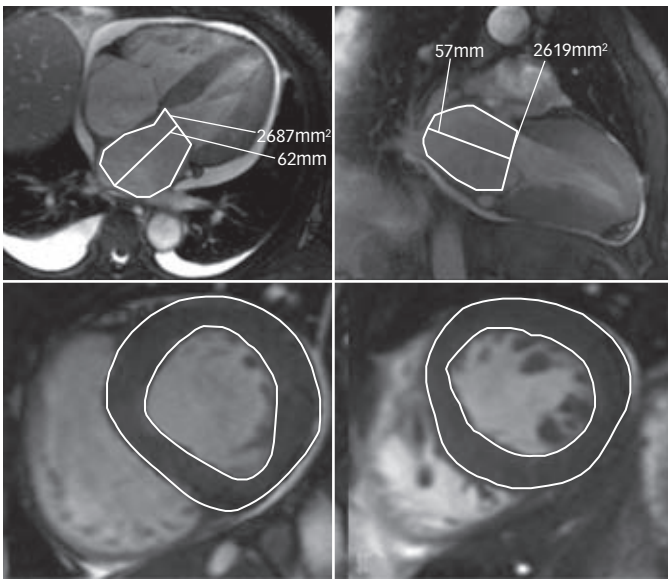


A: Mitral inflow trace obtained from the cine-phase contrast sequence shows various inflow parameters such as E-wave peak, deceleration time and A-wave peak. B: Pulmonary vein flow curve shows the pulmonary vein systolic wave (PVs), diastolic wave (PVd) and A-wave (PVa) and calculation of A-wave amplitude and duration. C: Phase-contrast short-axis image through the mitral valve showing mitral valve contour in a case of diastolic dysfunction. D: Mitral inflow curve from the same case shows abnormal, highly elevated, restrictive pattern of the E–A ratio (>2:1).

Left Ventricular Mass

For calculation of LV mass, epicardial and endocardial contours are drawn on the cine short-axis views in end-diastole from base to apex. These are multiplied by the slice thickness to obtain LV volume, which is multiplied by the myocardial density (1.05) to obtain the LV mass. In practice, the myocardial contours are drawn manually and the LV mass is automatically calculated by the computer software (see *Figures 5C* and *5D*). The resultant LV mass divided by the BSA yields the indexed LV mass.

Figure 5: Morphological Evaluation of Left Atrial Volume and Left Ventricular Mass on Cardiac Magnetic Resonance Imaging



A and B: Bi-plane area-length method used for magnetic resonance evaluation of left atrial volume on cine-true fast imaging with steady-state precession (FISP) four- and two-chamber views. Left atrial (LA) volume = (0.85 x A1 x A2)/L, where L = LA length, A1 = LA area in two chamber view and A2 = LA area in four-chamber view. C and D: Epicardial and endocardial contours for calculation of myocardial mass. These contours are drawn from the base to the apex in the cine two-chamber short-axis views.

Importance of the Various Cardiac Magnetic Resonance Parameters

Mitral Inflow

Mitral inflow is quantified by measuring the E-wave, the A-wave, the E/A ratio and the DT:

- the E-wave represents early mitral inflow velocity and is influenced by the relative pressures between the LA and LV;
- the A-wave represents the atrial contractile component of the left ventricular filling and is influenced by LV compliance and LA contractility; and
- DT represents the interval from E-wave peak to a point of intersection of the deceleration of flow with the baseline. It correlates with time of pressure equalisation between the LA and LV. As the early LA and LV filling pressures either evolve toward or away from equivalence, the DT either shortens or lengthens, respectively.

The major advantage of mitral inflow parameters is that they can be obtained in all patients; these provide diagnostic and prognostic information and have been validated to be consistent across modalities. However, mitral inflow parameters are highly preload-dependent, can be difficult to obtain in patients without good ECG tracing and hence can be problematic in patients with high heart rates, atrial fibrillation or heart blocks.[9]

Pulmonary Vein Flow

The normal pulmonary vein pattern consists of the:

- S-wave, occurring during LV systole, and dependent on atrial relaxation and mitral annulus motion;
- D-wave, occurring during LV diastole and reflecting LV filling; and
- A-wave, which is below the baseline as opposed to the S and D waves, occurs during atrial contraction, and reflects changes in LV compliance.

Pulmonary vein flow measurements complement mitral inflow parameters, especially if E and A waves are fused (differentiating normal versus pseudo-normal patterns). Also, the relationship of the pulmonary vein A-wave reversal (PVAR) duration with mitral A-wave duration is the only marker specific for elevation in LV end-diastolic pressure. Like mitral inflow, this parameter is dependent on the myocardial rhythm.

Left Atrial Volume

The LA volume can be viewed not only as a morphological expression of LV diastolic dysfunction but also as a biomarker of the chronicity of diastolic dysfunction. Its role in diastolic dysfunction and heart diseases in general is considered somewhat analogous to that of glycated haemoglobin (HbA_{1c}) in diabetes. This simple measure of LA volume provides significant insight into an individual's risk of the development of adverse cardiovascular events, including myocardial infarction, stroke, atrial fibrillation and heart failure.[18–20] In echocardiographic literature, LA volume is graded relative to risk as mild (28–33ml/m^2), moderate (34–39ml/m^2) or severe (>40ml/m^2) enlargement. These severity scales determine clinical outcome.[19] However, measurement of LA volume has a potential pitfall: the LA may be enlarged in other medical conditions, including chronic anemia, athletic heart and chronic valvular disease, without an increase in LV filling pressure.

Left Ventricular Mass

LV mass is influenced by haemodynamic factors including high blood pressure and stroke work, as well as constitutional factors such as body size and gender.[21] The LV mass is considered inappropriate (iLVM) in cases where the degree of LV hypertrophy (LVH) is excessive – considering haemodynamic and constitutional factors – and is represented by the percent ratio of the observed LV mass to the predicted LV mass by height, gender and stroke work. iLVM has been reported to be an independent cardiac prognostic factor, regardless of the presence or absence of LVH. Inappropriately or excessively increased LV mass is associated with metabolic abnormalities, systolic dysfunction and concentric geometry of the LV, which is independent of the presence of hypertension.[22,23] Recently, it has also been shown that iLVM is an independent predictor of diastolic dysfunction.[24,25] Echocardiography can overestimate LV mass.[26] Magnetic resonance imaging (MRI) offers a reliable alternative to echo, as it does not involve geometrical assumptions for cube calculation of LV mass.[27,28] MRI measurements of LV mass have also been anatomically validated.[29] On MRI, the normal range of LV mass indexed to BSA is 50–86g for males and 36–72g for females.[30] Recent data show that inappropriateness of LV mass is independently associated with increased E/E', an important parameter to assess diastolic dysfunction.[24] E/E' is, however, an echocardiographic parameter, and so far this observation has not been validated using CMR imaging. This is largely due to the fact that a tissue Doppler equivalent on CMR has not been reliably established. Further studies are needed to investigate the use of LV mass as a useful CMR parameter in the evaluation of diastolic dysfunction.

Recent Advances in Cardiac Magnetic Resonance for Evaluation of Diastolic Dysfunction

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.[31] 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.[32] 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.[33] 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.[34]

Myocardial Tissue Tagging

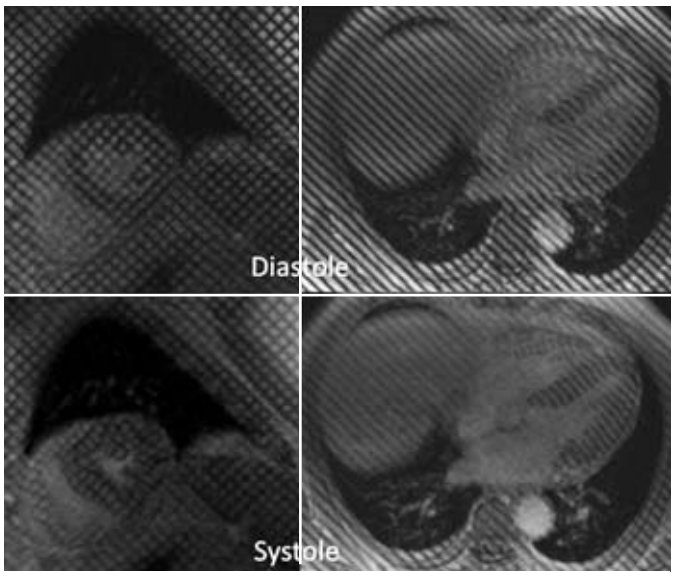
Myocardial tissue tagging aims to directly measure the diastolic properties of the myocardium, unlike transmitral flow and myocardial tissue velocity, which indirectly measure myocardial properties. Two myocardial properties are assessed: diastolic torsion recovery rate and LV strain rate recovery. In order to measure these properties, CMR radiofrequency tags are applied to the myocardium in a regular, grid-like pattern (see *Figure 6*). 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.[35,36]

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.[37]

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.

Figure 6: Myocardial Tissue Tagging



Myocardial tissue tagging: radiofrequency tags in the form of a grid or lines are applied on the heart during cine image acquisition. The deformation of these patterns from systole (bottom row) to diastole (top row) provides a means to measure the strain rate and diastolic torsion recovery rate.

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.[31]

Conclusion

Diastolic dysfunction and DHF are important causes of cardiovascular morbidity and mortality; it is therefore essential to diagnose these important conditions reliably and in a timely manner. While echocardiography has been the mainstay of diagnosis, CMR has shown increasing potential to define diastolic properties of the heart. Using CMR it is now possible to measure the conventional mitral inflow, velocity and morphology parameters similar to echo. CMR can also study the actual torsion and recovery of the myocardium and throw insight into hitherto unknown features of myocardial function. ■

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