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Diastolic dysfunction and heart failure with preserved systolic function, till death do us apart

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Introduction

Diastolic dysfunction (DD) is best considered not as a distinct entity but as part of a continuum that also includes heart failure with preserved ejection fraction (HFpEF). This entity is the cause of heart failure in 50% of all patients presenting with decompensated heart failure.[1] It is associated with increased morbidity and mortality. Diastolic dysfunction refers to abnormalities of active myocardial relaxation and passive ventricular filling.[2]

Phenotypes

Literature looking at the profile of patients with diastolic dysfunction (DD) and HFpEF has shown that there are factors associated with this condition such as advanced age, hypertension, left ventricular hypertrophy and atrial fibrillation. Obesity has also emerged as a significant risk factor.[3]

Obesity clinical phenotype

Physiological changes seen in obesity, such as increase in cardiac filling pressures, ventricular remodelling and enhanced pericardial restrain, are contributing factors to DD. Visceral adiposity is related to impaired myocardial energetics. Increased metabolism of free fatty acids in obesity alters mitochondrial redox state and reduces mitochondrial efficiency. The diastolic phase is more sensitive to energetic depletion, due to higher energy demands of active calcium uptake via SERCA relative to myosin, with energy depletion, this process is impaired, leading to reduced relaxation during early diastole.[4]

Vascular stiffening

Vascular stiffening is seen with advanced age and hypertensive patients, and results in an increase in left ventricle (LV) afterload followed by LV hypertrophy leading to impaired LV early relaxation. During exercise, vascular stiffness and arterial wave reflections become more pronounced, unmasking decreased effort tolerance.[4]

Atrial fibrillation

As LV pressures rise, the physiological response is for the LA to increase pressure and size to maintain a pressure gradient during diastole; in so doing, the pulmonary vascular system is protected from the high pressures of the left heart. In patients who develop atrial fibrillation, this protective mechanism is lost, and these patients have worse outcomes such as increased risk of death, poor functional disability and developing right-sided failure.[4]

Pathophysiology

Diastole is made of two parts, passive and active phases. During the passive phase, the LV relaxes and blood flows passively from left atria to left ventricle down a pressure gradient; as the LV fills, the pressure within the LV rises and the flow begins to ebb. Then the active phase follows where the left atrium contracts, 'atrial kick' to force blood into the LV against rising ventricular pressures.

In LV DD, due to the remodelling changes of the ventricle, the compliance of the ventricle is decreased, resulting in an increase in the slope of the ventricular end-diastolic pressure-volume

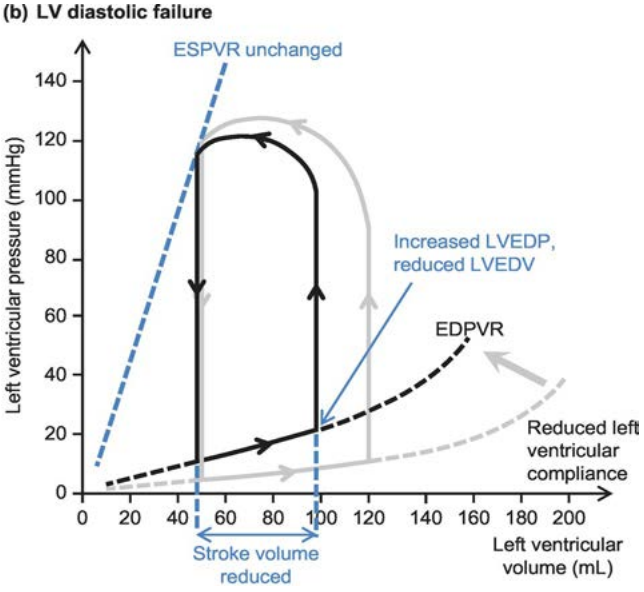

Figure 1: Left ventricle pressure-volume curve

relationship, leading to less ventricular filling and greater end-diastolic pressure, as seen in Figure 1. The ventricle cannot accept blood at low pressures and ventricular filling is slow or incomplete unless atrial pressure rises, and therefore there is increased dependence on filling through atrial contraction.[2,5]

Another cellular mechanism of DD is impaired lusitropy (ventricular relaxation), this is an active process. At the end of the cycle of excitation contraction coupling in the myocyte, the plasmic reticulum actively sequesters Ca^{2+} so that the concentration of Ca^{2+} in the vicinity of troponin C is reduced so that Ca^{2+} leaves its binding sites on the troponin C and thereby permits disengagement of actin from myosin. This is a necessary step to achieve rapid and complete relaxation of the myocyte; this process is impaired in DD which then reduces the extent of relaxation decreasing ventricular filling especially during the rapid phase.

Assessment of diastolic dysfunction

Noninvasive echocardiography is the commonly used tool for assessing the presence and severity of DD. Some of the commonly used parameters:

1. **Transmitral flow velocity:** the early diastolic peak filling velocity when the transmitral pressure gradient is greatest generates the E wave velocity on the echocardiogram. The late diastolic peak filling velocity associated with atrial contraction generates the A wave. Because the normal atrial contribution to total diastolic filling is only 30%, a normal A wave is smaller than the mitral E wave, with an E/A ratio of 1. DD initially produces a low E wave and a high A wave velocity, with reversal of the E/A ratio. As disease progresses and LV compliance is reduced further, LA pressure progressively increases to maintain a transmitral pressure gradient. The E wave increases until E/A ratios are 1.5. During the process of this transition, the E/A ratio will temporarily normalise, despite the presence of moderately severe disease. This is referred to as pseudonormalisation and highlights a limitation to the sole use of E/A ratios for diagnosis.
2. **Deceleration time (DT):** the rate of dissipation of the transmitral pressure gradient is also a function of LV compliance. Normal DT is 180–240 ms. Again, the prolongation of the DT seen in early DD is reversed in moderate to severe disease, as there is a progressive compensatory increase in left atrial pressure (LAP).
3. **Tissue doppler:** this uses Doppler shifts of ultrasound waves to calculate the velocity of myocardial tissue movement in a similar way to that of blood flow. It can be used to assess the extent and timing of diastolic wall motion. As the cardiac apex is relatively fixed, the mitral valve ring moves towards the apex during systole. During diastole, the annulus initially moves away from the apex (e′) and then back towards the apex during atrial contraction (a′). These waves reflect the same events as the E-wave and A-wave respectively.
4. **Left atrial volume index:** left atrial volume over body surface area, measured at end-systole.

The severity of DD is divided into four grades (Table I). A combination of parameters is used to make the assessment; no single parameter can accurately determine the severity of DD.

Diagnosis

Patients with DD who are not in failure are difficult to identify clinically. In the advanced stages of DD, grade III/IV symptoms of failure may manifest. The diagnostic approach to HFpEF should include the following: (i) Symptoms and signs of HF, (ii) an LVEF ≥ 50%, (iii) objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised biomarkers. ESC guidelines put forward recommendations for the

Table I: Grades of diastolic dysfunction as categorised by echocardiography[6]

	Normal	Grade I: abnormal relaxation	Grade II: pseudonormal	Grade III: restrictive (reversible)	Grade IV: restrictive (fixed)
NYHA		I–II	II–III	III–IV	IV
Mitral inflow (PW)	0.75 < E/A < 1.5 150 < DT < 240 ms IVRT 70–90 ms	E/A ≤ 0.75 DT > 240 ms IVRT > 90 ms	0.75 < E/A < 1.5 150 < DT < 200 ms IVRT < 90 ms	E/A > 1.5 DT < 150 ms IVRT < 70 ms	E/A > 1.5 DT < 15 ms IVRT < 70 ms
Mitral inflow on Valsalva	ΔE/A >0.5	ΔE/A ≤0.5	ΔE/A ≥0.5	ΔE/A ≥0.5	ΔE/A <0.5
Mitral annular motion (TDI)	E/e′ < 10 e′ > 8	E/e′ < 10 e′ < 8	E/e′ ≥ 10 e′ < 8	E/e′ ≥ 10 e′ < 8	E/e′ ≥ 10 e′ < 8
Vp (Colour M-mode)	Vp > 55	Vp > 45	Vp < 45	Vp < 45	Vp < 45
Pulmonary venous flow (PW-Doppler)	S ≥ D AR_{dur}-Adur < 0 ms	S > D ARdur-Adur < 0 ms	S < D or ARdur-Adur ≥ 30 ms	S < D or ARdur-Adur ≥ 30 ms	S < D or ARdur-Adur ≥ 30 ms
LV relaxation (tau)	Normal	Impaired	Impaired	Impaired	Impaired
LV compliance	Normal	Normal to ↓	↓↓	↓↓↓	↓↓↓↓
LA pressure	Normal	Normal	↑↑	↑↑↑	↑↑↑↑
LV blood filling	Normal	↓	↓↓	↓↓↓	↓↓↓
LV volume index	< 34 ml/m²	< 34 ml/m²	> 34 ml/m²	> 34 ml/m²	> 34 ml/m²

A – late diastolic mitral velocity, A_{dur} – duration of A wave, AR_{dur} – peak pulmonary venous atrial reversal flow velocity duration, D – a diastolic wave in pulmonary vein flow, E – early diastolic mitral velocity, e′ – peak early diastolic mitral annulus velocity, IVRT – isovolumic relaxation time, NYHA – New York Heart Association, PW-Doppler – pulse-wave Doppler, S – a larger systolic wave in pulmonary vein flow, TDI – tissue Doppler imaging, Vp – colour M-mode Doppler

Table II: Objective evidence of cardiac structural and functional abnormalities[8]

Parameter	Threshold	Comments
LV mass index	≥ 95 g/m² female ≥ 115 g/m² male	Although the presence of concentric LV remodelling or hypertrophy is supportive, the absence of LV hypertrophy does not exclude the diagnosis of HFpEF
Relative wall thickness	0.42	
LA volume index	> 34 ml/m²	In the absence of AF or valve disease, LA enlargement reflects chronically elevated LV filling pressure (in the presence of AF, the threshold is > 40 ml/m²)
E/e' ratio at rest	> 9	Sensitivity 78% specificity 59% for the presence of HfpEF by invasive exercise testing
NT-proBNP	> 125(SR) or > 365(AF) pg/ml	Up to 20% of patients with invasively proven HfpEF have NPs below diagnostic threshold particularly in the presence of obesity
BNP	> 35(SR) or > 105(AF) pg/ml	
PA systolic pressure	> 35 mmHg	Sensitivity 54%, specificity 85% for the presence of HFpEF by invasive exercise testing
TR velocity at rest	> 2.8 m/s	

diagnosis of HFpEF (Table II). Of the commonly used echographic diastolic function parameters, only four (mitral E velocity, septal e' velocity, septal E:e' ratio and LAVi) have shown a clear association with increased cardiovascular-related mortality.[7,8]

Management

Despite all we know about the disease process of DD and HfpEF, no treatment has convincingly shown a reduction in morbidity and mortality.[8] However, we know the predisposing factors to developing DD, and once it is established, it may progress to HFpEF. Therefore, treatment should target screening for risk factors and addressing them to prevent development of DD. Secondly, once DD has been established, prevent progression to HFpEF.[9]

Prevention of development of diastolic dysfunction

Current data shows that risk factors for DD include hypertension, diabetes, obesity and peripheral vascular disease; optimisation of these conditions may prevent the development of DD. Wachtell et al. showed that antihypertensive therapy resulting in LV mass or relative wall thickness regression is associated with significant improvement of diastolic filling pressures.[10]

In type 2 diabetes, glycaemic control has a direct correlation to the development of DD; tight glucose control is yet another window of opportunity to prevent the development of DD.[11]

Several good quality studies have been conducted to determine the best treatment for HFpEF, sadly, thus far, results have not been impressive and the ideal treatment still eludes us. Pitt et al. investigated the effects of spironolactone in patients with HFpEF. They found no significant reduction in the incidence of mortality, aborted cardiac arrest and hospitalisation for heart failure.[12] The I-PRESERVE study looked at the effects of irbesartan on patients with HFpEF and found no improvements in outcome.[13]

We may understand the disease process a little better, have validated echo parameters for the diagnosis of this entity, **but** the management still eludes us. There is a gap in our knowledge in this area and more scientific work still needs to be done.

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