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Review

Diastology for the clinician

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ABSTRACT

Diastolic filling of the heart is a complex sequence of multiple inter-related events consisting of processes such as ventricular relaxation, erectile coronary effect, visco-elastic forces of the myocardium, ventricular interaction, myocardial stress strain relationships, pericardial restraint, passive filling, and atrial contraction. However, in order to understand diastolic filling from a clinical aspect, a simplified foundation can be used which divides the cardiac cycle into contraction, relaxation, passive filling, and filling at atrial contraction. The mitral flow velocity curves are representative of the relative driving pressure between left atrium and left ventricle and allow one to grade the progression of diastolic dysfunction which occurs in disease states. Doppler tissue imaging is necessary as a surrogate of ventricular relaxation to further determine the stages of diastolic dysfunction in patients with preserved ejection fraction. These Doppler flow velocity curves can be applied to understanding diastolic filling of the heart in patients with both reduced ejection fraction and preserved ejection fraction.

Contents

Introduction

In the past, patients presenting with heart failure were diagnosed with a dilated or ischemic cardiomyopathy due to a reduction in systolic function of the left ventricle (LV). However, it has become clear over the past three decades that abnormalities of diastolic function of the heart importantly contribute to the signs and symptoms of heart failure, as much if not more than systolic dysfunction, resulting in a reduction in cardiac output and an elevation of LV filling pressures [1–3]. Over 50% of all patients now admitted with heart failure will have a preserved ejection fraction, in whom the pathophysiologic abnormalities are related in large part to diastolic dysfunction [4,5]. Abnormalities of diastolic filling are common even in the absence of heart failure, and it has been estimated that 70% of patients older than 75 years will have some degree of diastolic dysfunction [6,7]. Therefore, it has become increasingly important to be able to diagnose and manage patients

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with diastolic dysfunction. In this report, the following will be covered:

1) understanding how the heart fills with blood under normal circumstances and in patients with abnormalities of diastolic function
2) defining how Doppler echocardiography can be used to determine how the heart fills during diastole
3) applying this pathophysiologic and imaging information to patients in daily practice.

Pathophysiology of diastolic filling of the heart

Diastolic filling of the heart is a complex sequence of multiple interrelated events, consisting of processes such as ventricular relaxation, erectile coronary effect, visco-elastic forces of the myocardium, ventricular interaction, myocardial stress–strain relationships, pericardial restraint, passive filling, and atrial contraction [1–3]. These different interrelated events all contribute to how the ventricle fills with blood, both in the normal and the abnormal heart. There have been numerous publications which have attempted to define the individual components of diastolic filling of the heart, with multiple complex equations derived to measure the independent contribution from processes such as ventricular relaxation, the modulus of chamber stiffness, and pericardial restraint, as well as derivations from pressure–volume and stress–strain relationships. However, these complex equations are cumbersome to apply in the evaluation and management of patients in clinical practice.

Therefore, it is useful to have a simplified foundation for clinicians to use for the evaluation and management of patients with diastolic dysfunction. In this approach, the cardiac cycle can be divided into ventricular contraction, ventricular relaxation, early filling, passive filling, and then filling at atrial contraction (Fig. 1). During ventricular contraction, there is a rapid rise in LV pressure until it exceeds aortic pressure, resulting in opening the aortic valve and ejection of blood into the systemic circulation. During ejection there is a transition from contraction into ventricular relaxation in mid-to-late systole, with both processes occurring around the peak ventricular systolic pressure. As relaxation takes precedent, there is a rapid fall in ventricular pressure until the LV pressure falls below the left atrial (LA) pressure, leading to opening the mitral valve with a rapid flow of blood from left atrium to left ventricle. During early diastolic filling, ventricular relaxation will continue but overall filling of the LV will also be dependent on the passive filling properties of the LV, which are determined by myocardial stiffness, viscoelastic forces of the myocardium, and pericardial restraint. Thus, there will be a rise in LV pressure during early diastole which will meet or exceed LA pressure, decelerating the flow of blood from LA to LV. In normal hearts, ventricular relaxation is complete during the early one third of diastole. During mid-diastole there will be a continued low velocity flow from LA to LV due to continued inertial effects until equalization in LA and LV pressure causes the period of diastasis, when flow is absent. Finally, at the end of diastole, atrial contraction occurs, at which time there will again be an increase in the flow of blood from LA to LV. Thus, the determinants of diastolic filling are primarily (1) the rate of ventricular relaxation and (2) the concept of effective operative compliance, which is the rise in pressure per unit volume of blood.

It is important to understand the cardiac molecular signaling which affects contraction and relaxation [8], as this forms the basis for possible future therapies for patients with diastolic dysfunction [9–12]. The contraction and relaxation phases are active processes, dependent on calcium influx and the uptake and release of calcium from the sarcoplasmic reticulum, an ATP-driven process. During contraction, calcium binds to troponin C which alters the troponin–tropomyosin complex and allows interaction of myosin cross bridges with actin to initiate contraction. Dissociation of the filaments is also an ATP-requiring process, such that impairments in myocyte energy supply may promote an increase in diastolic tone by this mechanism.

The force and velocity of contraction and rate of relaxation are regulated by neurohormonal signaling pathways. It is the G protein-coupled receptors which are the foundation of cardiac molecular signaling for these processes. Activation of the beta-adrenergic receptor stimulates adenylate cyclase, leading to an increase in intracytoplasmic cAMP, which activates protein kinase-A signaling, resulting in an increase in contractility and relaxation. Activation of the guanylate cyclase, through nitric oxide or the natriuretic peptides, augments cyclic guanosine monophosphate – protein

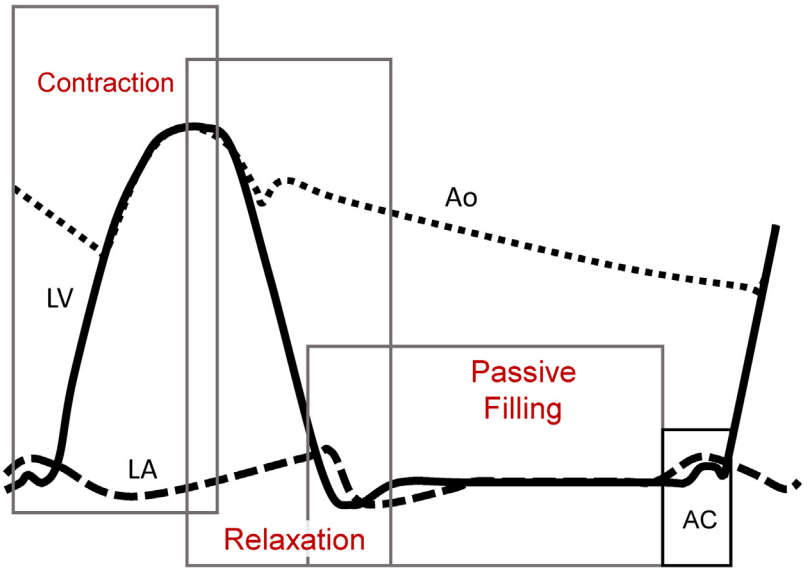

Fig. 1. Schematic diagram of the left ventricular (solid line), aortic (dotted line), and left atrial (dash line) during a cardiac cycle. The cardiac cycle can be divided into the phases of contraction, relaxation, passive filling, and atrial contraction. Note the temporal overlap between contraction and relaxation, as well as between relaxation and passive filling.

kinase-G signaling, which may reduce contractility but also enhance relaxation. Both cyclic nucleotide pathways are importantly regulated by the level and activities of phosphodiesterases (PDE).

PKA phosphorylates a number of cellular proteins involved in excitation–contraction coupling, including phospholamban, which then releases its inhibitory effect on sarcoplasmic reticulum calcium ATPase to increase the rate of calcium uptake by the sarcoplasmic reticulum. This serves to increase force of ventricular contraction by increasing the amplitude of the calcium transient with depolarization. Both PKA and PKG phosphorylate another cellular macromolecule known as titin, which functions like a bidirectional spring that importantly determines the tone of the cardiac myocyte, resulting in a decrease in myocyte stiffness.

The effective operative compliance of the LV is determined by multiple factors, including cellular stiffness as described above, LV muscle stiffness, the viscoelastic forces of the myocardium, as well as pericardial restraint [3,13]. Ventricular relaxation during filling will affect the operative compliance, particularly if it is prolonged. Myocardial stiffness is the major determinant of operative compliance and is affected by the composition of the extracellular matrix abnormalities, as well as changes in the cardiomyocyte itself, such as increased cardiomyocyte diameter, higher myofibrillar density, and increased cardiomyocyte stiffness. Interstitial fibrosis in association with myocyte apoptosis and degeneration are irreversible changes leading to increased myocardial stiffness.

In disease states there is usually a progression of changes in diastolic function [14–17]. In the very early stages of diastolic dysfunction, as may occur with hypertension or normal aging, there will be an abnormality of LV relaxation with slowing of the rate of pressure fall, usually present when systolic function is still preserved. This will result in a lower rate of early diastolic filling as the LV relaxation extends into mid-diastole. This will not necessarily result in an increase in the mean LA pressure at rest, as the slower early filling is compensated for by a large increase in flow at atrial contraction at the end of diastole. However, with exercise and a decrease in the diastolic filling period, there will be an increase in the LA pressure, causing symptoms of dyspnea on exertion. As disease progresses, or abnormal loads are imposed upon the heart, there will be an additional decrease in the effective operative compliance of the LV, promoting an elevation of the LA pressure at rest, reflected to the pulmonary circulation, resulting in the signs and symptoms of heart failure.

There is a triple control of ventricular relaxation which is important to understand and apply to clinical scenarios [3,13]. A decrease in the force generation during ventricular contraction will result in a slower rate of ventricular relaxation. A high load on the heart, clinically seen with severe hypertension due to arterial stiffening and wave reflections, will slow the rate of ventricular relaxation. Non-uniformity of relaxation, present with ischemic regional wall motion abnormalities or abnormal electrical conduction (i.e. left bundle branch block l or right ventricular pacing) will also slow the rate of ventricular relaxation. Clinically, in patients with an underlying abnormality of relaxation, the onset of ischemia or hypertension will further prolong relaxation to the extent that there will be a decrease in the effective operative compliance of the LV with an increase in the resting LA pressures. Due to the curvilinear diastolic pressure–volume relationship, an increase in preload will also decrease the effective operative compliance of the LV, particularly in patients with underlying myocardial disease. In many patients the progression of diastolic dysfunction is reversible, particularly if the changes in the operative compliance were due to ischemia, increased afterload, or increase in LV volume. However, at the end stage of cardiac disease, there will be severe irreversible muscle stiffness with a marked elevation of LA pressure.

Doppler echocardiography and diastolic filling

The transmitral Doppler flow velocity curves can be used to reflect the relative driving pressures from LA to LV and thus determine how the heart is filling during diastole [14–17] (Fig. 2). It is important to understand that these Doppler velocities represent diastolic filling of the LV but are not able to measure diastolic function, which requires intricate measures of pressure volume relationships. Nonetheless, the diastolic filling parameters can be useful in understanding the status of the LV in health and disease.

During ventricular relaxation, LV pressure will rapidly fall and when it drops below LA pressure with opening of the mitral valve, the transmitral Doppler flow velocity curve will show an increase in the early velocity, called the *E*-velocity (Fig. 2). After the LV pressure hits its nadir and begins to rise, it will meet or exceed LA pressure resulting in a deceleration of the transmitral flow. The deceleration time (measured as an extrapolation of the deceleration of flow to baseline) is a measure of the rate of deceleration and equates to the effective operative compliance of the LV, with decreased compliance reflected by a shorter deceleration time. During mid-diastole, passive flow will occur with a continued low velocity of flow. At atrial contraction, there will be active contraction of the atrium, re-accelerating flow across the mitral valve, resulting in the *A*-velocity on the transmitral flow velocity curve.

The progression of diastolic dysfunction can then be evaluated by these Doppler velocity curves (Fig. 3). In the normal patient between 30 and 60 years old, the transmitral flow velocity curve will consist of an *E*:*A* ratio which is slightly greater than 1.0 with a deceleration time between 180 and 220 ms (Fig. 3, left). In the early stages of diastolic dysfunction, when impaired ventricular relaxation occurs, the rate of ventricular pressure fall will be slowed, and there will be a decrease in the initial filling of the LV at the time of mitral valve opening resulting in a reduced initial *E*-velocity. Ventricular relaxation will continue to occur in mid-diastole resulting in a continued slower continued flow from LA to LV, seen as a prolonged deceleration time on the transmitral flow velocity curve. At atrial contraction, there will be an increase in the amount of blood from LA to LV, seen as a large *A*-velocity. The transmitral flow velocity curve with “abnormal relaxation” will thus show a reduced *E*-velocity, a prolongation of deceleration time, an increased *A*-velocity, and a low *E*:*A* ratio (Fig. 3, center).

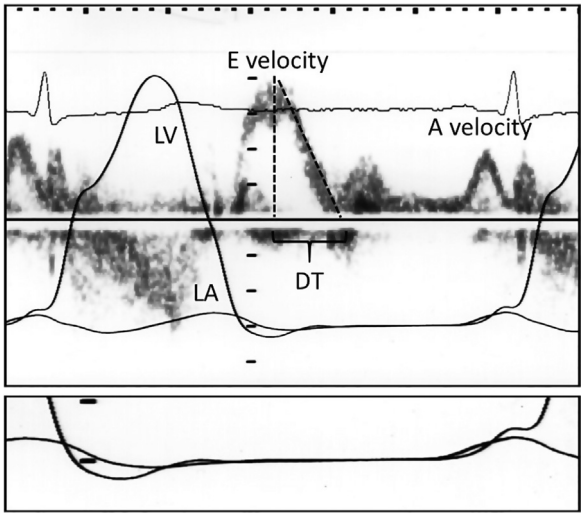

Fig. 2. The relationship of the driving pressures between left atrium and left ventricle during diastole and the transmitral flow velocity curve. LV, left ventricle; LA, left atrium; DT, deceleration time.

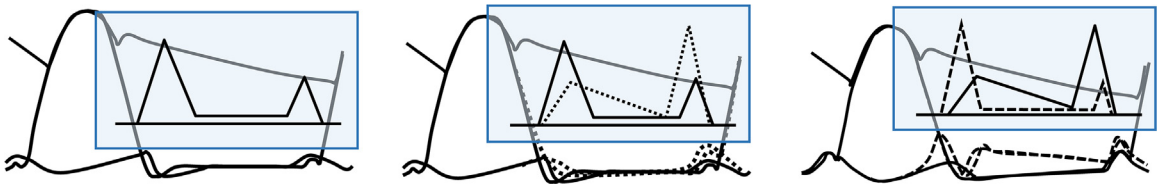

Fig. 3. Schematic diagram of the changes in the transmitral flow velocity curve in relationship to the changes in the left ventricular and left atrial pressure curves during the progression of disease. Left: Normal intracardiac pressures and normal transmitral flow velocity curve. Center: In the early stages of disease, there is abnormal relaxation. This results in a prolongation of the rate of left ventricular pressure fall and a decrease in the initial flow velocity from left atrium to left ventricle during early diastole. This results in less filling during early diastole and a compensatory increase in filling at atrial contraction. The normal baseline state is shown in the solid line and the abnormal relaxation pressures and transmitral flow velocity curves are shown in the dotted lines. Right: Elevated left atrial pressure from a decrease in the effective operative compliance of the left ventricle. This results in an increase in the left atrial pressure at the time of mitral valve opening, and increase in the initial driving pressure across the mitral valve. This will result in an increase in initial *E*-velocity on top of the reduced early diastolic filling from an underlying abnormality of relaxation. There will then be a rapid rise in left ventricular pressure exceeding left atrial pressure, resulting in a shortening of the deceleration time. With early rapid filling, there will be less filling at the time of atrial contraction. The solid line indicates the underlying abnormal relaxation in the pressure curves and transmitral curves, and the dotted line represents the changes that occur as left atrial pressure increases.

As diastolic dysfunction progresses, there will then be an abnormality of the effective operative compliance due to an increase in stiffness of the myocardium. With the abnormal compliance, there will be an increase in LA pressure so at the time of mitral valve opening there will be a more rapid increase in flow across the mitral valve in early diastole, resulting in an increase in transmitral *E*-velocity. The rate of LV pressure will then rise rapidly, exceeding LA pressure, resulting in a decrease in deceleration time. Thus, the initial abnormal relaxation pattern will show a higher *E*-velocity, shorter deceleration time, and higher *E*:*A* ratio. The resultant transmitral curve will be similar to a normal transmitral curve, which is now termed "pseudonormalization" (Fig. 3, right). As the disease progresses further with more compliance abnormalities and higher LA pressures, there will be an even higher *E*-velocity, lower *A*-velocity, and shorter deceleration time. This results in a high *E*:*A* ratio >2.0 and a short deceleration time <130 ms and is termed "restriction to filling".

This progression of disease exemplified by the Doppler velocity curves forms the basis for a grading scale of diastolic dysfunction (Fig. 4). Grade 1 is an abnormality of relaxation, in which there is a low *E*:*A* ratio and prolongation of deceleration time. As the disease worsens, there is a higher *E*:*A* ratio and shorter deceleration time with Grade 2 being the pseudonormal pattern. Grade 3 represents the restriction to filling pattern but with beneficial changes in load, reverse to Grade 2 or even Grade 1. Grade 4 indicates end-stage disease and irreversible restriction to filling.

In patients with systolic dysfunction, there will always be some degree of diastolic dysfunction. Therefore, in addition to staging the degree of diastolic dysfunction, the mitral flow velocity curves alone can be used to determine filling pressures as well as staging the severity of diastolic dysfunction. When the *E*:*A* ratio increases and the deceleration time decreases, progressive diastolic filling abnormalities are present.

More complexity emerges when applying the transmitral flow velocity curves to a patient who has preserved systolic function. In these patients, the concept of ventricular suction, or enhancement of ventricular relaxation, needs to be taken into consideration (Fig. 5). In young healthy individuals, there will be a rapid fall in LV pressure, resulting in a lower nadir of the LV pressure and "suction" of the blood from LA to LV. This results in early rapid filling and allows a greater filling of the LV so that there is enhancement of stroke volume without any increase in LV filling pressure. The transmitral velocity curve will show an increase in the *E*-velocity, a shortened deceleration time, and a high *E*:*A* ratio. Therefore, the "restrictive pattern" can indicate either very good diastolic filling or very poor diastolic dysfunction.

Thus, in a patient with preserved ejection fraction, additional information is required to fully interpret the mitral flow velocity curves. Doppler tissue imaging, which examines the velocity of myocardial motion is a widely available methodology to provide further insight into the transmitral curves [18]. If the Doppler tissue imaging is sampled at the annulus of the mitral valve, an estimate of the longitudinal contraction and relaxation of the myocardium is possible. During systole, there will be longitudinal contraction with movement of the myocardium toward the LV apex, resulting in a positive velocity (*S′*). During early diastole, there is lengthening of the myocardium away from the apex, resulting in a negative velocity as the annulus moves away from the transducer. The negative velocity (or *E′*) is directly related to the velocity of contraction (*S′*), the lengthening load of the ventricle (LA pressure) favoring re-expansion, and the rate of relaxation. As such *E′* is often used as a surrogate for the rate of ventricular relaxation. A higher *E′* velocity is associated with a faster rate of ventricular relaxation and good diastolic filling. As diastolic function worsens, and relaxation gets slower, the *E′* velocity will get lower. Thus, the ratio of the transmitral *E*-velocity to the Doppler tissue *E′* velocity can be used for further assessment of diastolic filling. The *E*/*E′* ratio will be inversely related to the severity of diastolic dysfunction (Fig. 6).

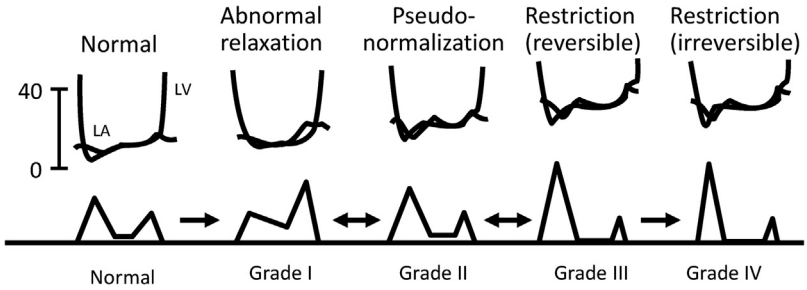

Fig. 4. Schematic diagram of the left ventricular and left atrial pressure curves, as well as the transmitral curves demonstrating the progression of disease. A grading scale is assigned from Grade 1 to Grade 4 as the disease worsens, with a higher *E*:*A* ratio and shorter deceleration time.

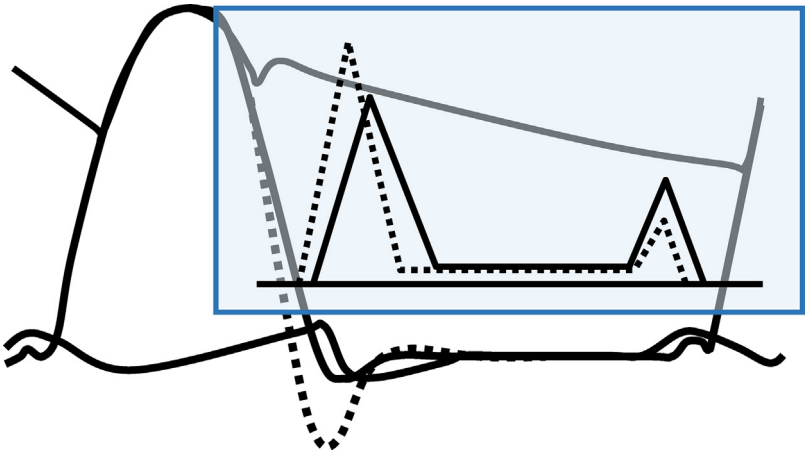

Fig. 5. The pressure curves and transmitral curve in a patient with preserved systolic function and enhancement of ventricular relaxation. With the faster rate of ventricular relaxation, there is a lower nadir of the early left ventricular pressure before the onset of rapid filling. This will "suck" blood from left atrium to left ventricle causing an increase in the early filling and an increase in *E*-velocity on the transmitral flow curve with a shortened deceleration time. The baseline pressures and transmitral curves are shown in the solid line and enhanced relaxation is shown in the dotted line.

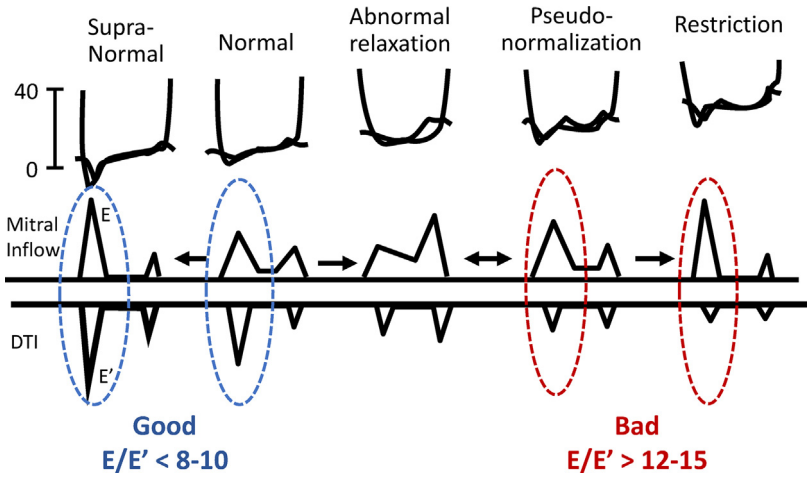

Fig. 6. The pressure curves, transmitral curves, and Doppler tissue imaging are now shown demonstrating the parabolic nature of the mitral flow velocity curves in patients with preserved systolic function. The initial *E*′ velocity on the Doppler tissue imaging will gradually decrease with a progression of disease. Thus, the *E*/*E*′ ratio is necessary to show the extent of disease in patients with preserved ejection fraction.

At the present time, current measurements of Doppler tissue imaging are made in a one-dimensional plane. However, there is a complex series of inter-related cross-fibers which result in contraction and relaxation of the LV. This results in a "twisting and untwisting" of the ventricle to allow optimal contraction and relaxation sequences. Ongoing studies are evaluating whether speckle tracking and myocardial strain analyses may allow greater understanding of the contraction and relaxation patterns of the LV.

Clinical applications

With this background of understanding, the pathophysiology of the diastolic filling of the heart, as well as the ability to interpret the noninvasive Doppler velocity curves, a simplistic clinical approach can be used for the diagnosis and management of patients with cardiac disease. It will be important to categorize patients according to the clinical scenario as well as the underlying cardiac structure and function as determined by a two-dimensional echocardiogram. These categories consist of the following:

A) Patients with reduced ejection fraction
B) Patients with heart failure and preserved ejection fraction at rest
   i. Heart failure with preserved ejection fraction
   ii. Myocardial restrictive disease
   iii. Constrictive pericarditis
C) Patients with heart failure and preserved ejection fraction with symptoms exclusively during exercise

Patients with reduced ejection fraction

In a patient with systolic dysfunction, the transmitral flow velocity curves alone can be used to determine the degree of diastolic filling abnormalities as well as filling pressures [14,16,19]. Since patients with systolic dysfunction will have some degree of diastolic dysfunction (and thus will not have a truly "normal" mitral flow curve), the higher the *E*:*A* ratio and shorter the deceleration time, the higher the filling pressure indicating more decompensation. Grade 1 patterns indicate well-compensated ventricles with low to normal filling pressures. As decompensation occurs and filling pressures increase, the *E*:*A* ratio increases and deceleration time decreases. In many patients, there is a reversible component of diastolic filling, so that a Grade 3 diastolic dysfunction pattern can become a Grade 1 diastolic dysfunction pattern simply by diuresis to reduce preload, since the

left atrial pressure and E wave velocity are reduced with decongestion. However, at the end stages of disease, Grade 4 irreversible diastolic dysfunction occurs when the myocardial stiffness of the ventricle becomes so severe that the restriction to filling will not be able to be reversed by changes in load. Interstitial fibrosis with myocyte degeneration and myofiber stiffness are present at this end stage. These are the patients who have the worse prognosis and are the hardest to treat. In the echocardiographic laboratory, the differentiation between Grade 3 and Grade 4 diastolic dysfunction can be made by lowering preload, either during the strain phase of the Valsalva maneuver, upright posture, or the use of sublingual nitroglycerin.

Patients with preserved ejection fraction and heart failure at rest

Heart failure with preserved ejection fraction

Over half of all patients hospitalized for heart failure maintain a preserved ejection fraction [4,5]. Most of these patients will have what is termed heart failure with preserved ejection fraction (HFpEF) [1,2,5,20]. There is a typical phenotype for HFpEF patients consisting of older women with a history of hypertension, diabetes, obesity, and sleep disordered breathing. They will usually be compensated during daily life but intermittently will develop severe heart failure requiring hospitalization. Hypertension and fluid overload is a prominent finding upon admission.

These patients have a markedly abnormal dynamic response to loading conditions. In the normal heart, LV filling pressures will remain normal even with an elevation of blood pressure or fluid overload. Patients presenting with HFpEF have underlying abnormalities of relaxation, usually well compensated without symptoms of heart failure at rest. However, an increase in afterload, a sodium load, or myocardial ischemia will markedly affect the relaxation to the point of decreasing the effective operative compliance of the LV, resulting in severe elevation of filling pressures leading to the signs and symptoms of severe heart failure. This concept is referred to as abnormal ventricular vascular coupling (Fig. 7). Even when compared to matched controls with hypertension, arterial stiffening can be brought out during exercise stress in patients with HFpEF, and the degree of impaired arterial vasodilation is correlated with the magnitude of elevation in LV filling pressures [21].

The underlying pathophysiology of patients with HFpEF is likely related in part to low-grade systemic inflammation and endothelial dysfunction [5]. Many of these patients will have co-morbid conditions including hypertension, diabetes, obesity, smoking, and obstructive sleep apnea. These are pro-inflammatory conditions that lead to systemic microvascular endothelial inflammation. This then leads to increased oxidative stress, muscle inflammation, decreased nitric oxide cyclic GMP signaling, microvascular dysfunction, and eventually results in interstitial fibrosis, myocyte degeneration, and myofiber stiffness. There is adverse cardiac remodeling, impaired coronary reserve, as well as impaired oxygen delivery uptake and utilization. Obesity is also a common finding that likely plays a role in HFpEF, by causing greater volume overload, more severe inflammation, heightened pericardial restraint, and more abnormal right ventricular-pulmonary artery coupling [22].

Therefore, in these patients with HFpEF there is an underlying myocardial problem exacerbated by abnormal load usually associated with an abnormal vasculature. When they present with heart failure there will generally be high blood pressure, often with a history of increased sodium intake, noncompliance with medications, or other precipitating factors such as ischemia or hypoxia. The mitral flow velocity curve in this setting will reveal a restrictive pattern, reflecting the high filling pressures, which are reflected back to the pulmonary circulation. By simply decreasing preload and afterload on the heart or relieving ischemia, the mitral flow velocity curve can be taken from a severe restrictive pattern to a pseudonormal pattern and even an abnormal relaxation pattern.

Treatment of these patients usually consists of vasodilators, angiotensin-converting enzyme (ACE) inhibitors, and diuretics which work primarily on the abnormal load imposed upon the LV, although clinical trials have shown that even as these medicines lower blood pressure, they do not improve heart failure-related outcomes as compared to placebo. Thus far, there has not been any medical therapy that has been shown to directly improve the underlying abnormal diastolic function. Randomized trials evaluating the effect of medical therapy that has been shown to be effective in patients with systolic dysfunction (beta blockers, ACE inhibitors, angiotensin receptor blockers, aldosterone antagonists) have not shown benefit in patients with HFpEF in terms of mortality benefit or reduction in hospitalizations. Drugs that target the nitric oxide pathway such as the PDE5 inhibitors and the addition of nitrates theoretically should improve the adverse cardiac signaling but have not been effective in randomized trials thus far. Newer agents such as neprilysin inhibitors do show promise in terms of regression of hypertrophy and improvement in diastolic function and the results of a large randomized trial are pending.

The most effective treatments may be those targeting the underlying pathophysiology of HFpEF, including aggressive treat-

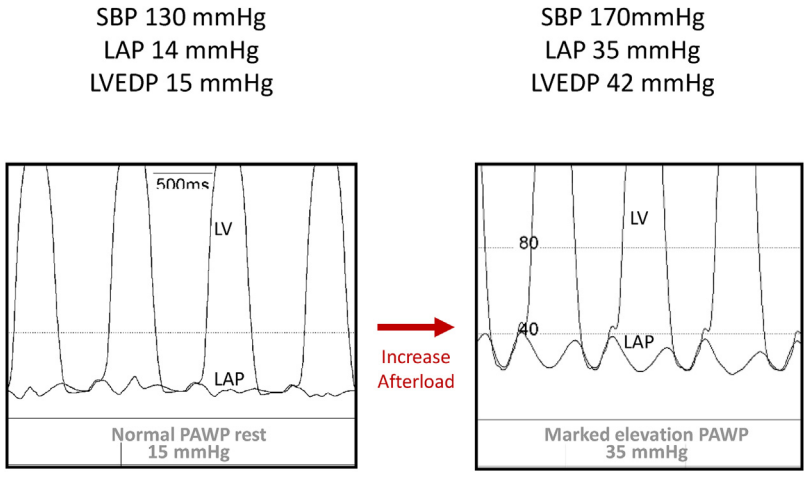

Fig. 7. Left ventricular, pulmonary artery, and pulmonary artery wedge pressures in a patient with underlying impaired relaxation. In the baseline state (left panel), the left ventricular diastolic filling is compensated with only a mild elevation of the pulmonary artery wedge pressure. However, as the systolic blood pressure increases (center and right panel), there is a marked elevation of pulmonary artery wedge pressure. This is an example of ventricular vascular coupling.

ment of the comorbid conditions, such as hypertension, diabetes, and obesity.

Severe myocardial restrictive disease

Patients with "garden variety" HFpEF must be differentiated from a group of patients who present with severe heart failure and preserved ejection fraction in the absence of hypertension or ischemia. These are the patients whose primary problem is severe muscle stiffness that is not necessarily related to systemic processes such as aging, metabolic stress, obesity, or hypertension. They present with severe heart failure signs and symptoms, often at rest or minimal activity, and as opposed to patients with HFpEF they will have marked elevation of venous pressure in the presence of low to normal blood pressure. Their echocardiogram may show a normal ejection fraction and no significant valvular disease but they will have a Grade 4 diastolic dysfunction pattern on the transmitral flow velocity curve with a markedly reduced *E′* velocity. These patients usually have the true restrictive or infiltrative cardiomyopathies, such as amyloid heart disease, sarcoidosis, or hemochromatosis. These patients require further evaluation with magnetic resonance imaging scanning, pyrophosphate scanning, free light-chain analysis, and endomyocardial biopsy.

Constrictive pericarditis

It is of critical importance to diagnose another disease which presents with heart failure and preserved ejection fraction. Constrictive pericarditis is due to a rigid pericardium which prevents the expansion of the myocardium during diastolic filling and is one of the only reversible causes of heart failure. These patients will present primarily with right-sided heart failure with symptoms of progressive edema and ascites. Echocardiography will reveal a normal ejection fraction, absence of valvular heart disease, and normal pulmonary pressures, but will have a very dilated inferior vena cava indicating elevation of right atrial pressure and a septal bounce and septal shift from the enhancement of ventricular interaction. The transmitral flow velocity curves will show a restriction to filling pattern, but there will be respiratory changes with a decrease in *E*-velocity during inspiration and hepatic vein reversals during expiration. The treatment is complete pericardiectomy, which has excellent outcomes.

Patients with heart failure with preserved ejection fraction that is only apparent during the stress of exercise

A subtler presentation of patients with HFpEF are those who do not have obvious signs and symptoms of heart failure at rest, but experience dyspnea on exertion. These patients are usually well compensated at rest with normal or only mild elevation of filling pressures. However, with exercise, they will develop a significant increase in filling pressures, causing limiting symptoms of dyspnea (Fig. 8). With exercise, the increase in venous return to the heart augments preload, while the increase in afterload on the LV may prolong relaxation and elevate the early diastolic LV pressure nadir. Together with obligate shortening of the diastolic filling period, these perturbations result in marked elevation in the LV filling pressures. These patients are difficult to diagnose, as there may be multiple other etiologies for exertional symptoms including pulmonary disease, deconditioning, and other non-cardiac problems.

The gold standard for the diagnosis of HFpEF in these patients is a right heart catheterization with exercise [23]. The pulmonary artery wedge pressure may be normal or only mildly elevated at baseline (over 40% with HFpEF have a normal resting wedge pressure), but will rise to over 25 mmHg with exercise, accompanied by a blunted cardiac output response. Pulmonary hypertension will occur, which is usually secondary to the elevation of pulmonary artery wedge pressure and not intrinsic pulmonary vascular disease. Both the American Society of Echocardiography and the European Association of Cardiovascular have provided criteria for the diagnosis of HFpEF using the combination of

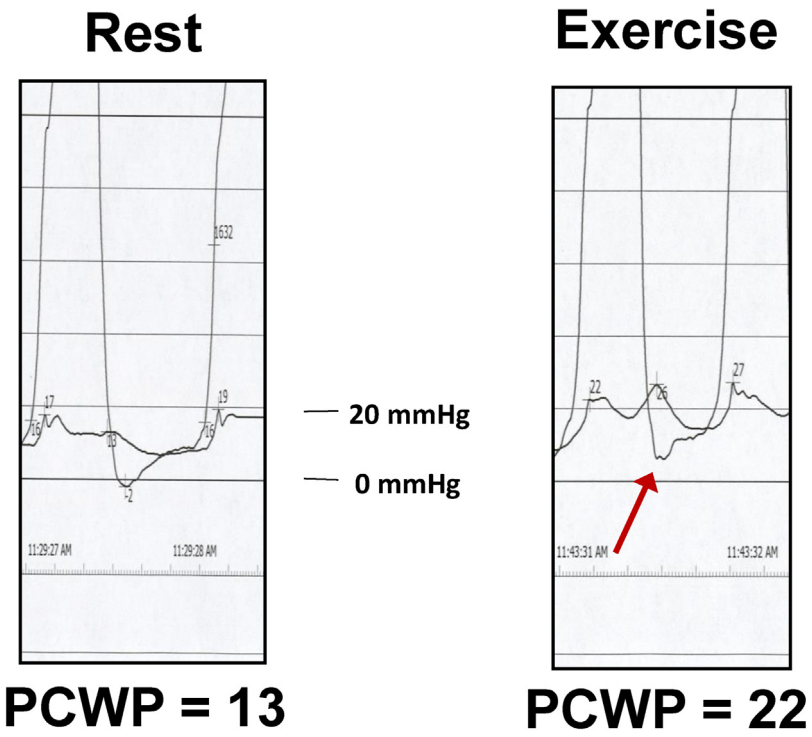

Fig. 8. In this patient with impaired relaxation at rest, the left ventricular filling is compensated with a normal pulmonary artery wedge pressure. However, with exercise, there is a shortening of the diastolic filling and further impairment of relaxation. The nadir of the early diastolic left ventricular pressure is increased (arrow) and there is a significant increase in pulmonary artery wedge pressure.

parameters from two-dimensional and Doppler echocardiography [24]. However, based upon a direct comparison with invasive exercise hemodynamics, 40–70% of patients will have a misleading diagnosis using these noninvasive criteria for HFpEF [25].

It is useful in these patients to determine when there is completely normal LV systolic and diastolic function. This can be reliably diagnosed when there is normal LV size and ejection fraction, normal LA size, and an E/E' ratio < 8 on Doppler imaging. These patients are less likely to elevate their filling pressures with exercise, and non-cardiac causes of the dyspnea should be pursued first, although a significant minority (20%) of patients with HFpEF will display a resting E/e' ratio in this range. Alternatively, a high E/E' ratio >15 at rest indicates a high filling pressure and thus HFpEF is likely, particularly if there is an enlarged LA on the two-dimensional echocardiogram.

In the absence of all these findings, it is more difficult to rule in or rule out HFpEF. Exercise with measurement of the E/E' ratio at peak exercise has been suggested to further aid in diagnosis. However, the relationship between the actual measurement of the pulmonary artery wedge pressure and E/E' ratio changes during exercise; absolute unit increases in the E/E' ratio during exercise are much lower than the unit changes in pulmonary artery wedge pressure, indicating a lower dynamic range for the E/E' ratio. A high E/E' ratio with exercise can be seen in both patients with HFpEF and patients whose pulmonary artery wedge pressure did not significantly rise. If the E/E' ratio remains <10 during peak exercise at a time the patient needs to stop due to symptoms, and the signal quality of the Doppler and tissue Doppler spectra are of excellent quality, then the patient can be deemed unlikely to have HFpEF. All other patients require a right heart catheterization to confirm or rule out HFpEF as a cause for exertional symptoms.

Conclusion

Diastolic dysfunction is a complex sequence of multiple interrelated events. However, a simplistic approach can be taken to understand the mechanism of filling in the normal and abnormal heart, using non-invasive Doppler parameters can be used to determine the stage and extent of diastolic filling. Understanding these underlying pathophysiologic mechanisms will then aid in proper diagnosis and treatment of these patients.

Conflict of interests

None.

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