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REVIEW ARTICLE

Diastolic heart failure in anaesthesia and critical care

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Diastolic heart failure is an underestimated pathology with a high risk of acute decompensation during the perioperative period. This article reviews the epidemiology, risk factors, pathophysiology, and treatment of diastolic heart failure. Although frequently underestimated, diastolic heart failure is a common pathology. Diastolic heart failure involves heart failure with preserved left ventricular (LV) function, and LV diastolic dysfunction may account for acute heart failure occurring in critical care situations. Hypertensive crisis, sepsis, and myocardial ischaemia are frequently associated with acute diastolic heart failure. Symptomatic treatment focuses on the reduction in pulmonary congestion and the improvement in LV filling. Specific treatment is actually lacking, but encouraging data are emerging concerning the use of renin–angiotensin–aldosterone axis blockers, nitric oxide donors, or, very recently, new agents specifically targeting actin–myosin cross-bridges.

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Left ventricular (LV) diastolic dysfunction refers to abnormalities of diastolic distensibility, filling, or relaxation, regardless of whether LV ejection fraction (LVEF) is normal or abnormal and whether the patient is symptomatic or not.[8] If signs and symptoms of congestive heart failure (effort intolerance, dyspnoea, and pulmonary oedema) develop in a patient with normal or near normal systolic function, it is appropriate to classify this situation as diastolic heart failure. Chronic diastolic heart failure and decompensated diastolic heart failure are common entities, but their frequency is widely underestimated. Underestimation of diastolic heart failure might be related in part to the difficulties in obtaining the criteria defined by AHA-ACC guidelines,[52] requiring objective evidence using echocardiography. In addition, the poor sensitivity and specificity of echocardiography to recognize diastolic heart failure may aggravate this underestimation. There is increasing evidence that clinicians should differentiate systolic from diastolic heart failure since pathophysiology and management may differ greatly between the two entities.[110]

Since patients with diastolic heart failure are at high risk of decompensation in the perioperative period or during an ICU stay,[84] anaesthetists should be familiar with the pathophysiology of diastolic heart failure.

Epidemiology of diastolic heart failure

Between 30% and 50% of patients with chronic heart failure have preserved LVEF.[14 73 81 110] Two recent cohorts of patients hospitalized with decompensated heart failure showed that 35% had a preserved LVEF,[66] and that patients with preserved LVEF were 2–4 yr older than those with impaired ejection fraction and were mainly women (≈70%). Diastolic heart failure represents <15% of chronic heart failure in patients younger than 50 yr, and the proportion raises to 33% in 50–70 yr olds and to 70% in those aged >70 yr.[120] This prevalence in elderly subjects is related to alterations in the cardiovascular system frequently associated with ageing, namely, coronary artery disease, systemic hypertension, hypertrophic, and infiltrative cardiomyopathies that cause structural changes of the LV leading to chronic deterioration of LV diastolic properties.[3]

Diastolic heart failure is a condition that greatly affects patient outcome. Several authors have shown that the readmission rate and mortality rate were high in diastolic heart failure patients and might be similar to those observed in systolic heart failure.[14 55 93] Recent studies reported that 16–30% of patients with diastolic heart failure had to be readmitted within 6 months after hospital discharge for

chronic heart failure symptoms, a figure that is comparable with the 22% observed in patients with impaired LVEF.[2 95 120] Mortality rates in diastolic heart failure patients at 1 and 3 yr seem slightly lower than or comparable with those in systolic heart failure.[2 14 18 118]

Pathophysiology of LV diastolic dysfunction

LV diastolic dysfunction can be defined as the inability of the LV chamber to fill up at low atrial pressures. This dysfunction can result either from an impairment in LV compliance (passive mechanism) or from an alteration in LV relaxation (active process). Relaxation is usually the first to alter in LV diastolic dysfunction and relaxation abnormalities can occur abruptly, especially in the context of anaesthesia or critical care.

Physiology and pathophysiology of LV relaxation

Zile and Brutsaert[120] defined relaxation as 'the time period during which the myocardium loses its ability to generate force and shorten and returns to an unstressed length and force'. From a mechanical point of view, the transition between systole and diastole was described as the time of aortic valve closure. However, the transition between contraction and relaxation corresponds to the dissociation of actin–myosin cross-bridges that begins during the early phase of LV ejection, before aortic valve closure.[40]

The dissociation of actin–myosin cross-bridges follows the lowering of the intracellular calcium concentration (Fig. 1). The transfer of calcium from the cytosole into the sarcoplasmic reticulum requires energy. Phosphorylation of phospholamban that is needed to activate the ATPase-induced calcium sequestration into the sarcoplasmic reticulum, sodium/calcium exchanger-induced extrusion of calcium from the cytoplasm, release of calcium from troponin C, detachment of the actin–myosin cross-bridges, and return of the sarcomere to its resting length are all energy-consuming processes. Thus, alterations leading to diastolic dysfunction may involve phenomena that occur not only during 'classic' diastole, but also earlier in the cardiac cycle, at the time when intracellular calcium falls.

Functional factors are likely to occur during the perioperative period or in the ICU. Affecting LV relaxation, they may precipitate latent LV diastolic dysfunction.

Myocyte energy imbalance

Since relaxation is an energy-consuming process, it is adversely affected by myocardial ischaemia. Ischaemia precludes optimal calcium exchanges between the cytosole and sarcoplasmic reticulum, and is rapidly associated with impairment in LV relaxation.[100] Sepsis is also likely to alter myocytes energetic balance and, thus, to alter LV relaxation.[85]

Contraction–relaxation coupling

As described earlier, relaxation begins early during systole[40 98] indicating that relaxation and contraction are

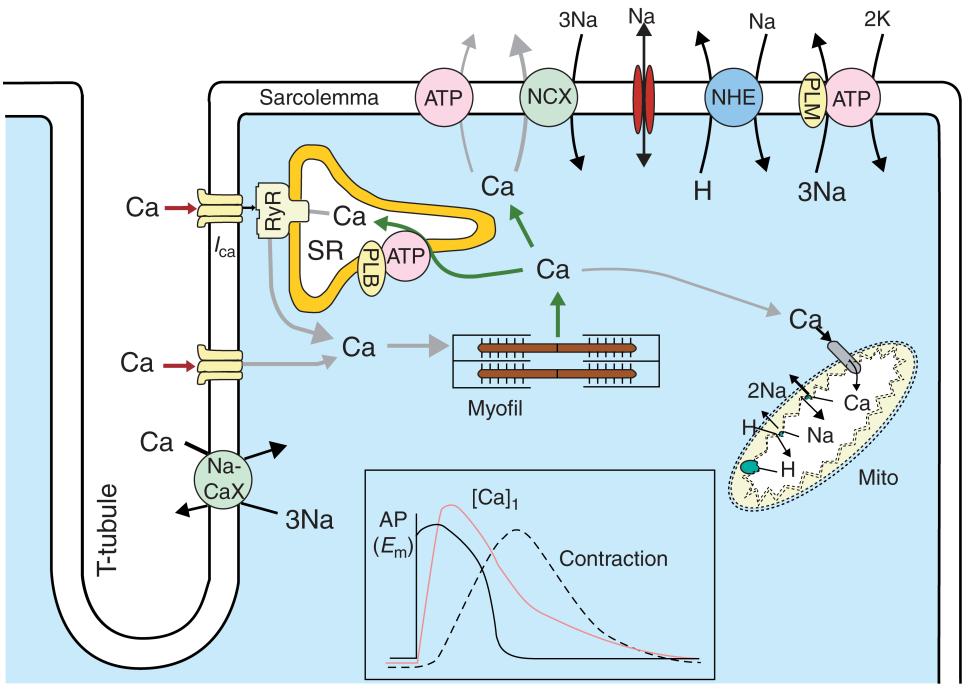

Fig 1 Calcium-induced calcium release in cardiac myocytes. After electrical stimulation, calcium influx through the calcium channels (I_{ca}) stimulates ryanodin receptors (RyR) to release more calcium from the sarcoplasmic reticulum (SR) into the cytosol. Calcium concentration falls (i) by reuptake in the SR via phospholamban (PLB) stimulation and (ii) by calcium efflux by Na^+/Ca^{2+} exchange (NCX). The inset summarizes the time course: action potential precedes calcium influx and the peak of myocyte contraction is seen while intracellular calcium concentration falls. From Bers and Despa[12] with permission.

intimately coupled. As a consequence, LV relaxation is greatly affected by the lack of homogeneity in LV contraction. Both LV segmental coordination and atrio-ventricular synchronization are essential to guarantee an efficient relaxation.[13 34] The loss of atrial contraction associated with atrial fibrillation not only alters LV filling but also results in a slowing of myocardial relaxation.

Several other factors known to alter contractile function, including changes in afterload and the use of inotropes, markedly affect relaxation. However, the effect of preload variations on relaxation is not clear.

Impact of afterload conditions on relaxation

Afterload dependency

In failing hearts, an increase in afterload induces a delay in the onset of relaxation and an increase in the time-constant of isovolumetric relaxation (τ, ms).[16 34 42] The afterload-dependence of τ has also been shown to be influenced by the inotropic state. Facing an increased afterload, beta-adrenoreceptor agonists help to keep τ constant, whereas antagonists (beta-blockers) markedly increased it.[15]

To describe better the relationship between load, contractility, and relaxation, the concept of relative load was defined experimentally as the ratio of peak systolic LV pressure to peak isovolumetric pressure.[38 40 58] The higher the relative load, the lower the contractile reserve (Fig. 2A). The contractile reserve quantifies the percentage force developed by the LV with respect to its maximum value. The consequences on relaxation of an elevation in LV afterload can range from a moderate acceleration to a marked deceleration, depending on the relative load. Up to a relative load of around 80%, the diastolic decline in LV pressure accelerates, but above this, LV pressure decline decelerates. Acceleration of the LV pressure decrease in response to a load elevation is observed in the normal heart, whereas slowing of the LV pressure decline is associated with impaired cardiac function.[31] This introduced the concept of afterload reserve which relates to the capacity of the normal LV to respond to elevation of afterload without changes in LV end-systolic volume and LV pressure decline.[38 39 58] Ventricles with altered contractile function consistently show a decreased 'afterload reserve'.[21 22 24 27 31] In such ventricles, even a small afterload elevation will cause a marked deterioration in LV relaxation and increase LV systolic and diastolic volumes.

An alternative concept: end-systolic volume dependency

Chemla and colleagues[17] recently proposed an alternative approach based on the suggestion that, at constant heart rate, relaxation might depend more on LV end-systolic volume than on afterload, namely LV systolic pressure. Indeed, recoiling forces are generated when the LV contracts below its equilibrium volume (usually slightly higher than LV end-systolic volume) and therefore recoiling forces act during early diastole. Thus, since a healthy heart is able to respond to increased afterload without any change in its LV end-systolic volume, relaxation remains unaffected. However, in failing dilated ventricles, LV end-systolic volume might exceed the equilibrium volume, which deprives the LV of recoiling forces and impairs the rate of isovolumetric relaxation.

Impact of preload conditions

Myocardial relaxation was initially considered not to be affected by preload conditions.[35] However, it has been suggested that marked preload variation can modify actin–myosin cross-bridge kinetics.[41] Indeed, in a patient with LV diastolic dysfunction, a leg elevation manoeuvre can result in a substantial increase in end-diastolic pressure (Fig. 2B). This case report suggests that LV diastolic dysfunction can be undetected in normo- or hypovolaemic patient. In contrast, any excess in fluid can induce a dramatic increase in LV end-diastolic pressure (LVEDP). Thus, preload reserve is reduced in patients with altered LV diastolic properties.

Analysis of diastole by cardiac catheterization

Diastolic heart failure is characterized by an elevated LVEDP (16–26 mm Hg) in 92% of patients,[108 121] whereas control patients had an average of 10 mm Hg. Using micromanometer catheters, it is possible to acquire high-fidelity instantaneous LV pressure curves. Such tools are used to plot pressure/volume loops and to assess the rate of LV pressure decline (dP/dt_{min}) and the time constant of isovolumetric relaxation (τ).

Pressure/volume loops

Systolic and diastolic functions are best described using the LV pressure/volume relationship, represented graphically as P/V loops (Fig. 3). In animals, a series of pressure/volume loops can be measured at baseline and after changes in preload (by inferior vena cava occlusion). The latter allow measurements of preload-independent variables as the end-systolic pressure/volume relationship and end-diastolic pressure/volume relationship.

In humans, pressure/volume tracings are usually performed only at baseline. In one study,[56] pressure/volume loops were performed at baseline and during a sustained handgrip manoeuvre (Fig. 4).

Using this mechanical approach, diastole begins at the closure of the aortic valve and lasts until the closure of the mitral valve. Diastole can be divided into two phases. The first corresponds to the LV pressure decline at constant volume, isovolumetric relaxation, which lasts from closure of the aortic valve to opening of the mitral valve. The second, auxotonic relaxation, corresponds to LV chamber filling and lasts until the closure of the mitral valve. LV filling mainly depends on the pressure gradient between the left atrium (LA) and LV, which is mainly

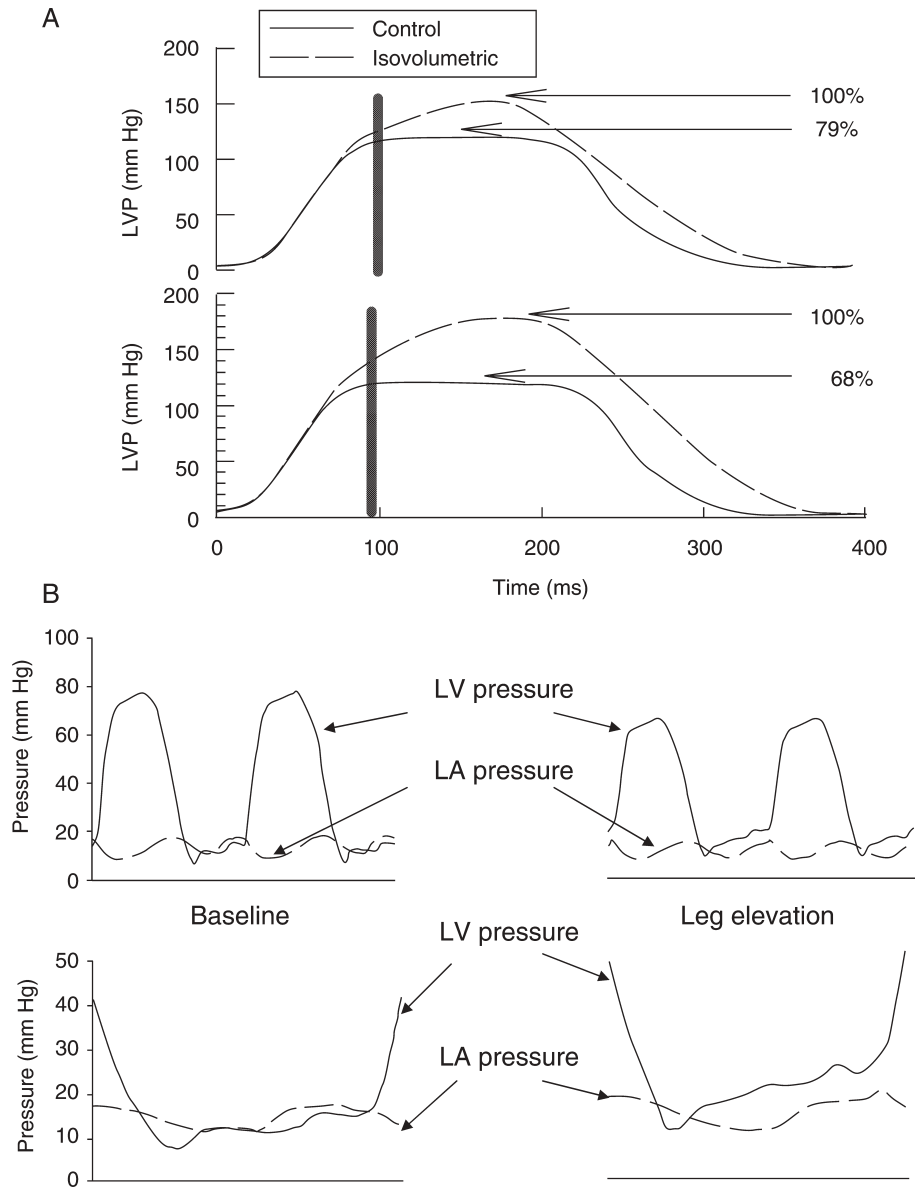

Fig 2 (A) Effect of afterload. Each panel displays two superimposed heartbeats, control (solid line), and isovolumetric (dotted line). The isovolumetric heartbeat was experimentally obtained in dogs by occluding the ascending aorta during diastole. Relative load is defined as the ratio of baseline to isovolumetric systolic LV pressure (LVP) expressed as a percentage. Top, isovolumetric pressure elevation is limited (32 mm Hg) and relative load is 79%. Bottom, isovolumetric pressure elevation is fair (56 mm Hg) and relative load is 68%. Relative load is the main determinant of load dependence of LVP fall. This dependence is related to the timing of the transition from contraction to relaxation. This transition occurs when 81% to 84% of peak isovolumetric pressure is reached, or the equivalent timing during early ejection. The transition occurs precisely at the time indicated by a vertical line in both panels. From Gillebert and colleagues[40] with permission. (B) Effect of preload. On the upper part, LV (solid lines) and LA (dotted lines) pressure tracings in a cardiac surgical patient at baseline and after leg elevation; on the lower part, amplification of the diastolic phase. In baseline conditions, LV filling is already impaired. With leg elevation, diastolic failure develops with further slowing of the myocardial relaxation and a marked increase in LVEDP, exceeding the left atrial pressure (LAP) resulting in an impaired filling of the LV during diastole.

influenced by passive chamber properties (compliance), active relaxation, and, at end-diastole, by atrial contraction. Thus, impairment of LV compliance (decreased LA–LV pressure gradient), or the loss of atrial contraction, directly impair diastolic filling. Structural modifications (i.e. myocardial hypertrophy, fibrosis) mainly affect the passive, late phase of diastole and are more likely to develop chronically, whereas functional factors (i.e. ischaemia, sepsis) adversely affect active relaxation during early diastole. In LV diastolic dysfunction, the diastolic portion of the pressure/volume loop (compliance curve) is shifted to the left and upward (Fig. 3). Consequently, for a given LV end-diastolic volume (LVEDV), LVEDP is increased and may result in pulmonary congestion.

Systolic dysfunction also affects the pressure/volume loop: the end-systolic pressure/volume slope is shifted

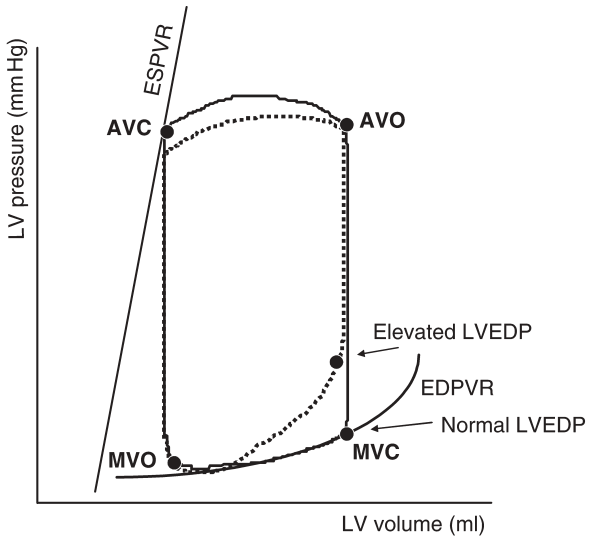

Fig 3 Pressure/volume loop. The solid line represents a normal heart. The dotted line represents an isolated LV diastolic dysfunction. In patients with diastolic heart failure, the main alteration in the P/V loop is a shift in the end-diastolic pressure/volume relationship (EDPVR), whereas the end-systolic pressure/volume relationship (ESPVR) remains unaltered. AVO, aortic valve opening; AVC, aortic valve closure; MVO, mitral valve opening; MVC, mitral valve closure; LVEDP: left ventricular end-diastolic pressure.

downward and to the right, indicating a reduction in contractility, whereas end-systolic and end-diastolic LV volumes are increased, which may also lead to upstream congestion. Patients with heart failure can have combined systolic and diastolic dysfunction. In such cases, modest increases in LVEDV may result in large increases in LVEDP. Kawaguchi and colleagues[56] recently demonstrated that, in patients admitted with heart failure but with preserved LVEF, the diastolic portion of the pressure/volume loops, although apparently normal at rest, altered on exertion. Indeed, manoeuvres such as sustained isometric handgrip markedly impaired LV diastolic properties, increased LVEDP, and could reveal diastolic heart failure (Fig. 4).

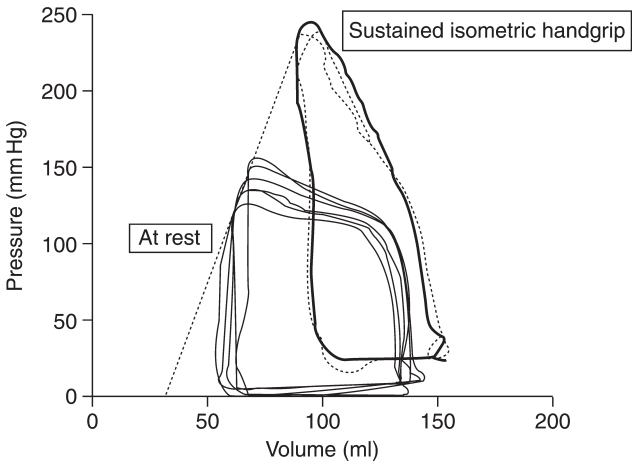

Fig 4 Decompensation of LV diastolic dysfunction during exertion. Pressure/volume relationship before (dotted line) and after (dark solid line) sustained isometric handgrip in a patient with chronic class II NYHA heart failure admitted for rapid-onset pulmonary oedema and LVEF >50%. Handgrip was used to assess LV diastolic properties in response to increase systolic blood pressure and LV afterload. In a patient with normal LV diastolic function, relaxation and filling are unaltered by increased LV afterload. Handgrip-induced upward shift of the PV loop induced a parallel increase in the filling curve strongly suggesting that the LV wall is stiff without relaxation reserve. From Kawaguchi and colleagues,[56] with permission.

Pressure decline analysis

In diastolic heart failure patients, LV pressure decline analysis reveals a significant increase in the time constant of isovolumetric relaxation, τ.[108 121]

A recent multicentre, prospective study, using cardiac catheterization and echocardiography to assess LV diastolic properties in 47 patients with diastolic heart failure and 10 normal controls,[119] demonstrated that insight into the respective roles of active relaxation and compliance could be gained using a detailed analysis of the LV diastolic pressure curve. The following measurements are of particular interest:

(i) τ, the time constant of the isovolumetric relaxation;
(ii) P_{min}, LV minimal pressure after the opening of the mitral valve;
(iii) $P_{Pre\text{-}A}$, LV pressure just before atrial contraction;
(iv) LVEDP, LV end-diastolic pressure, just after atrial contraction.

This study showed that in patients with diastolic heart failure, in contrast to the control subjects, isovolumetric relaxation was incomplete at the time of P_{min}. Thus, τ was prolonged and P_{min} increased, resulting in a positive correlation between τ and P_{min}. Incomplete relaxation accounted for 7 (1) mm Hg of the measured increase in P_{min}. In these patients, LV compliance was also significantly altered with an increase in LVEDP, despite a reduced LVEDV.

Assessment of LV diastolic function in clinical practice

There are differences between heart failure with reduced and preserved ejection fraction with regards to symptoms, physical examination, echocardiographic and ECG abnormalities, and X-ray findings (Table 1).

Echocardiography

The combination of several ultrasound modalitieses is useful in the assessment of diastolic function in patients with possible diastolic heart failure. These modalities include: 2-D echo, pulsed-wave Doppler, M-mode colour Doppler, and tissue Doppler imaging. In the presence of acute pulmonary oedema, echocardiography is suggestive of diastolic heart failure, if preserved LV systolic function is associated with indirect signs of elevated LA pressure.

Table 1 Characteristics of heart failure with preserved or reduced LVEF

	Altered ejection fraction	Preserved ejection fraction
Dyspnoea	Chronic	Transient mainly
Heart rate	Increased	Increased
Mitral regurgitation	Present	Rare
S3/S4 gallop	S3>S4	S4 mainly
Rales	Present	Present
Peripheral oedema	Present	Rare
Cardiomegaly	Constant	Inconstant
LV dilatation	Nearly constant	Absent
ECG abnormal	Constant	Inconstant
BNP	Markedly increased	Often mildly increased

LV systolic function can be assessed by 2-D echo and global performance estimated qualitatively ('eye-balling') and, if possible, quantitatively (measurement of ejection fraction). These measurements should be performed as soon as possible after the onset of symptoms, as a low ejection fraction can return to normal within 24–48 h after treatment of decompensated heart failure. Ejection fraction values ranging between 0.4 and 0.5 are not strictly 'normal', but cannot explain *per se* the occurrence of acute pulmonary oedema. Therefore, the criterion generally required to define 'preserved LVEF' is a value >0.5. However, Petrie and colleagues[82] showed that 'heart failure with preserved LVEF' could be associated with subtle LV systolic dysfunction, yet recognizable using new measures of LV systolic function (measurement of LV systolic atrio-ventricular plane displacement). Another study,[9] however, concluded that even if 'subtle abnormalities in regional systolic function' might exist in diastolic heart failure, they are 'unlikely to be responsible for clinical signs of heart failure'.

LA pressure cannot be directly measured using echocardiography. Pulsed-wave Doppler measures the velocity of blood at a precise location: the Doppler 'window'. This velocity is proportional to the pressure gradient. Thus, if the Doppler window is placed at the tip of the mitral valve, the diastolic flow velocity profile will reflect the pressure gradient between the LA and the LV.[4] The mitral blood flow is composed of an E (early) wave for passive diastolic filling followed by an A (auricular) wave for atrial systole. Mitral blood flow profile is affected by LV relaxation, LV compliance, and LA pressure. Normal diastole is characterized by a predominant E wave (peak and area under the curve), implying that most of the LV filling is occurring during the early phase of diastole. Mitral blood flow abnormalities are of three types:

(i) in mild diastolic dysfunction, only relaxation is impaired and atrial contraction contributes relatively more to ventricular filling; thus, peak of A wave >peak of E wave, with prolonged E wave deceleration time (usually >240 ms);
(ii) in moderate diastolic dysfunction, relaxation is impaired, LV compliance is decreased, and atrial pressure increased; a pseudo-normal pattern with a predominant E wave is observed, but the E wave deceleration time is shortened;
(iii) in severe diastolic dysfunction, LV compliance is extremely low; a restrictive pattern is observed with a high peak E wave velocity, usually more than twice the peak A wave velocity.

However, Zile and colleagues reported a lack of sensitivity of the mitral blood flow analysis for the diagnosis of diastolic heart failure. In their study,[121] the E/A ratio was abnormal in only 48% of the patients presenting signs of heart failure with a normal ejection fraction. The E wave deceleration time was found to be more sensitive (abnormal in 64% of the patients).

If the Doppler window is located within a pulmonary vein, the flow velocity will reflect the pressure gradient between the vein and the LA throughout the cardiac cycle. A markedly increased LA pressure (>18 mm Hg) will generate characteristic alterations in the velocity profiles. Pulmonary vein flow is composed of two waves, one systolic and one diastolic. The elevation of the LA pressure impairs atrial filling, and the pulmonary vein diastolic wave becomes predominant. Nevertheless, pulmonary vein flow abnormalities cannot discriminate between systolic and diastolic heart failure.

Tissue Doppler Imaging directly measures myocardial velocity and allows wall movements to be directly analysed.[28] Tissue Doppler has been validated for the evaluation of cardiac function.[43 67 101 107] The myocardial portion commonly studied is above the mitral annulus. Three waveforms are visualized: peak systolic wave, early diastolic wave (Ea), and end-diastolic wave related to atrial contraction. Systolic velocities have been shown to be good predictors of contraction.[46] The Ea wave[97] is relatively independent of loading conditions and is therefore used to assess LV relaxation.[28] A cut-off of $8\ cm\ s^{-1}$ for Ea measurement is now widely accepted as a sign of diastolic dysfunction. The E (early mitral inflow velocity)/Ea ratio is considered a useful indicator of LV filling pressures.[70 71] Although influenced by LVEF, E/Ea measurement performed on the lateral mitral annulus can reliably be used to evaluate filling pressures in patients presenting with a preserved ejection fraction.[90] More recently, the delay from onset of Ea to onset of E has been shown to correlate strongly with invasively acquired relaxation indices.[89]

None of these Doppler indices is 100% sensitive or specific and a combination of indices is usually required to ascertain high LA pressure.

Natriuretic peptides

Brain natriuretic peptide (BNP) is recognized as a specific marker of heart failure in patients presenting with acute dyspnoea.[69] Maisel and colleagues[62] measured BNP in 1586 patients presenting with acute dyspnoea. Of the 452 patients with a final diagnosis of heart failure, 165

(36.5%) had preserved LV function on echocardiography, whereas 287 (63.5%) had systolic dysfunction. Patients with non-systolic heart failure had significantly lower BNP concentrations than those with systolic heart failure (413 *vs* 821 pg ml^{-1}, $P<0.001$). When comparing patients with acute diastolic dysfunction with those with non-cardiogenic dyspnoea, a BNP concentration $\geq$100 pg ml^{-1} had a sensitivity of 86%, a negative predictive value of 96%, and an accuracy of 75% for detecting abnormal diastolic dysfunction.[63] Mildly elevated values of BNP may not differentiate between systolic and diastolic heart failure and BNP may be normal in some cases of acute hypertensive pulmonary oedema in patients with preserved LV systolic function.[60]

Diastolic heart failure in clinical practice

Many factors including uncontrolled hypertension, atrial fibrillation, myocardial ischaemia, anaemia, renal insufficiency, and non-compliance with treatment may precipitate overt systolic and diastolic heart failure.[106] However, uncontrolled hypertension is involved in more than 50% of the cases of acute (decompensated) diastolic heart failure.[36 118] Anaesthetists may have to deal with acute decompensated diastolic heart failure during the perioperative period, in the ICU or in the emergency department.

Perioperative setting

The perioperative period carries a risk of decompensation of chronic diastolic heart failure or induction of acute diastolic dysfunction. Therefore, it is important to identify high-risk patients and situations and drugs likely to adversely affect LV diastolic function and be able to prevent and treat acute decompensations.

Preoperative screening should focus on the detection of:

(i) history of diastolic heart failure or structural factors potentially associated with an impaired LV diastolic function: LV hypertrophy (except in young athletes) and atrial arrhythmia affecting LV 'active filling';
(ii) factors carrying a higher risk of diastolic heart failure: female, age more than 70 yr old, history of untreated hypertension, ischaemic heart disease, or diabetes mellitus;
(iii) clinical signs of heart failure, especially dyspnoea on exertion;
(iv) specific measures from echocardiography: LV hypertrophy, impairment of diastolic function, preserved LVEF.

Different guidelines have been published in order to clarify the definition and the diagnosis of diastolic heart failure.[52 87 111] Vasan and Levy[111] produced pragmatic criteria that are widely used in the cardiology. They separated the diagnostic procedure into three sequential steps: (1) diagnosis of heart failure, (2) preserved systolic LV function (LVEF >0.5), and (3) documentation of LV diastolic dysfunction if feasible (Table 2).

Table 2 Definition of definite, probable, and possible DHF.[111] SAP, systolic arterial pressure; DAP, diastolic arterial pressure; BP, blood pressure

Diagnosis	Criteria	
	Clinical	**Echocardiography**
Definite	Clinical evidence of heart failure	Preserved LVEF within 72 h of the heart failure events+documented diastolic dysfunction
Probable	Clinical evidence of heart failure	Preserved LVEF within 72 h of the heart failure events but no documentation of diastolic dysfunction
Possible	Clinical evidence of heart failure	Preserved LVEF but not at the time of the heart failure events without documentation of diastolic dysfunction
Upgrade from possible to probable diastolic heart failure	SAP >160 mm Hg or DAP >100 mm Hg during the episode of heart failure, which may include the following: tachyarrhythmia precipitation of event by the infusion of a small amount of i.v. fluid clinical improvement in response to therapy directed at the cause of diastolic dysfunction (such as lowering BP, reducing heart rate, or restoring the atrial booster mechanism)	Concentric LV hypertrophy without wall-motion abnormalities

Zile and colleagues[121] prospectivly compared cardiac catheterization and echocardiography in patients suspected of diastolic heart failure (heart failure symptoms and LVEF >0.5) and concluded that 'objective measurement of LV diastolic function is useful to confirm rather than establish the diagnosis of diastolic heart failure. The diagnosis of diastolic heart failure can be made without measurement of parameters that reflect LV diastolic function'.[121]

On the basis of this, and using the criteria proposed by Vasan and Levy,[111] a specific algorithm can be proposed for the preoperative risk stratification of LV diastolic function impairment (Fig. 5). Particular attention should be paid in patients with potential LV diastolic dysfunction to avoid a further deterioration of diastolic function, especially hypovolaemia, tachycardia, and rhythms other than sinus. For elective surgery, patients with definite diastolic heart failure group would benefit from a cardiologist opinion and their treatment checked to optimize diastolic function before surgery.

Perioperative period

During the perioperative period, haemodynamic changes and anaesthetic agents can adversely affect LV diastolic function.

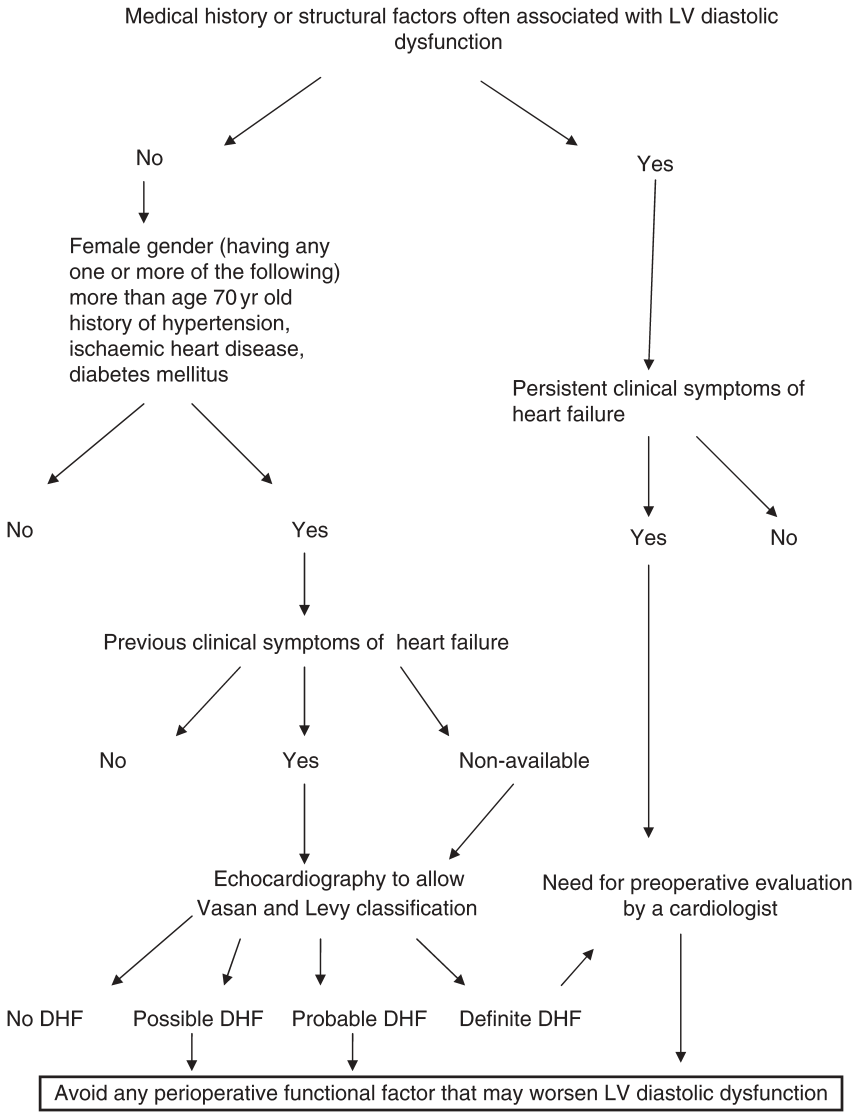

Fig 5 Algorithm for preoperative risk stratification of patients with suspected diastolic heart failure.

Haemodynamic changes affecting diastolic time, such as arrhythmia and myocardial ischaemia, are likely to decompensate further pre-existing diastolic dysfunction. Tachycardia shortens diastole and is likely to impair LV filling. Rhythm disturbances can be precipitated by hypo- or hyper-kalaemia, anaemia, or hypovolaemia. Treatment with beta-blockers or non-dihydropyridine calcium-channels blockers has been proposed to prevent tachycardia and improve LV filling.[6 94]

Myocardial ischaemia or acute increases in cardiac loading (volume loading or changes in position) (Fig. 2B) may result in a significant slowing of myocardial relaxation. Myocardial ischaemia may also induce rhythm disturbances that will further aggravate LV diastolic dysfunction. Thus, prevention of ischaemic episodes should remain a major objective for anaesthetists dealing with suspected diastolic heart failure. Beta-blockers still remain the best drug to achieve a safe reduction in myocardial oxygen consumption. Indeed, perioperative use of beta-blockers has been shown to reduce overall mortality due to cardiac events.[64 113] Whether this strategy is still applicable to diastolic heart failure remains to be determined. Finally, the use of regional or general anaesthesia is still debated, but no study has found benefit of one technique over the other.

The effect of anaesthetic agents on LV diastolic properties has been extensively studied for volatile agents, but less for i.v. agents (Table 3). The volatile agents, sevoflurane and desflurane, as well as opioids and muscle relaxants do not appear to affect LV diastolic properties.

In high-risk diastolic heart failure patients, anaesthetists should pay particular attention to the choice of monitoring and to avoiding acute perioperative changes in load conditions, heart rate, and myocardial oxygen balance.

Table 3 Effects of volatile and i.v. anaesthetic agents on diastolic function. Experimental models were either animal models[29 44 51 65 68 72 75 76 96 109 116] or cellular models. [45 47–49 59 88 112] Human models were either healthy[33 74] or patients with underlying cardiac impairment[10 20 23 26 50]

	LV relaxation	LV compliance
Enflurane		Decrease[116]
Experimental model	Impairment[51 116]	
Human	No data	
Halothane		
Experimental model	Impairment[29 47 48 51 75 112]	No change,[44 109] decrease[68 75 116]
Human	No change,[33] impairment[50]	
Isoflurane		
Experimental model	No change,[48 49 112] impairment[51 75]	No change[75 116]
Human	No change,[74] impairment[50]	
Sevoflurane		
Experimental model	No change[48 49]	No change[116]
Human	No change,[10 20 23 33] impairment[26]	
Nitrous oxide		
Experimental model	Impairment[65]	Decrease[65]
Propofol		
Experimental model	No significant change,[33 59 72 96] impairment[88]	Decrease[76]
Human	Impairment,[10 23 20] no change[37]	
Ketamine		
Experimental model	Impairment[76]	Decrease[76]
Midazolam		
Human	No change[37]	
Morphine		
Experimental model		No change[68]

There are no good clinical data on the action of anaesthetic drugs in LV diastolic dysfunction.

Recovery room, ICU, and emergency room

Hypertensive crisis

Gandhi and colleagues[36] compared the echocardiographic findings on admission and after 2–3 days of treatment in patients presenting with acute pulmonary oedema as a consequence of severe arterial hypertension. Although transient LV systolic dysfunction due to the hypertensive crisis was expected, no difference in LVEF and regional wall motion was found between the acute episode and after 24 and 72 h of treatment. Around 50% of the patients admitted with an acute pulmonary oedema had preserved ejection fraction and 89% of the patients who had a preserved ejection fraction after treatment also had no sign of systolic dysfunction during the acute episode. Similarly, in patients with an impaired ejection fraction, no differences were found within the first 72 h, suggesting that acute diastolic failure might also be the major mechanism of decompensation in patients with baseline systolic dysfunction. Acute diastolic dysfunction during hypertensive crisis remains poorly understood. In diastolic heart failure at rest, it is understandable that a small increase in LVEDV will lead to a marked elevation in LVEDP. However, this is less clear in patients without diastolic dysfunction at rest. It has been proposed that a hypertensive crisis leads to a marked increase in coronary perfusion pressure and thus in coronary turgor.[114] Nevertheless, it is unlikely that an increase in coronary blood volume can cause a significant increase in wall thickness.

Myocardial ischaemia

Myocardial ischaemia is one of the main mechanisms of LV diastolic dysfunction in the early postoperative period, and several factors, including pain-induced sympathetic activation (tachycardia, hypertension), shivering, anaemia, hypovolaemia, and hypoxia, may alter myocardial oxygen balance.

In a rabbit model,[80] the early and late haemodynamic consequences of a circumflex artery ligation were analysed by echocardiography and Doppler. One hour after experimental infarct, the rabbits exhibited a significant alteration of the LV filling pattern; decrease in E and A waves, A wave reversal velocities and increase in the mean pulmonary venous systolic-to-diastolic ratio. Three weeks after coronary ligation, the rabbits still exhibited significant abnormalities in filling pattern. Stugaard and colleagues[100] assessed LV diastolic function in 20 patients during coronary angioplasty and in eight anaesthetized dogs during experimental coronary occlusion. Diastolic function was explored using M-mode Doppler, which determines the time difference between the peak velocity in the apical region and in the mitral tip. The authors reported a significant increase in time difference in both patients and dogs, and the time difference evolution correlated significantly with the variation in the time constant of isovolumetric relaxation. Pacing tachycardia, volume loading, and vena cava restriction did not significantly alter the time difference.

Nitric oxide (NO) metabolism seems to play a controversial role in acute diastolic dysfunction following episodes of ischaemia–reperfusion. A beneficial role for NO has been suggested since pre-treatment with cGMP donors or with NO donors protects myocytes from relaxation failure in experimental models of hypoxia-reoxygenation.[30 92] However, excessive NO production during reperfusion appears to alter diastolic function due to an excess of peroxynitrite formation.[115]

Sepsis

Increasing evidence suggests that both systolic and diastolic functions are affected in severe sepsis and septic shock.[85] We recently showed, using pressure/volume tracings in anaesthetized endotoxaemic rabbits, that LV diastolic properties are altered; prolonged relaxation, decreased LV compliance leading to increased end-diastolic pressure.

In a transmitral Doppler analysis of 13 patients in septic shock,[54] 10 in sepsis without shock, and 33 controls patients with septic shock and sepsis without shock had a

significantly altered LV filling pattern in comparison with controls. More recently, in a study of systolic and diastolic function using transoesophageal echocardiography and pulmonary artery catheters in 25 consecutive patients in septic shock,[83] 8 of the 25 patients had no regional wall motion abnormality and a normal LV filling pattern (transmitral E/A waves ratio >1; pulmonary veins systolic/diastolic waves ratio >1); 11 had evidence of abnormal left auricular filling (systolic/diastolic waves ratio <1) but with a preserved systolic function and E/A waves ratio. According to the investigators, transmitral flow in this group could be considered as 'pseudo-normalized'. Finally, 6 of the 25 patients exhibited both systolic and diastolic dysfunctions. The authors concluded 'cardiac effects of septic shock can be expressed in various degrees, ranging from a normal pattern, through diastolic dysfunction up to both poor LV systolic and diastolic functions resulting in combined cardiogenic-septic shock'. Mechanisms of sepsis-induced systolic and diastolic dysfunctions are complex and described elsewhere.[85] Delayed relaxation and impaired compliance are likely to be related to nitration of contractile proteins rather than alterations in calcium homeostasis. We and others showed that calcium influx is unaltered in papillary muscle and cardiac myocytes from endotoxaemic or septic animals.[102–104] Increased free radical production, especially peroxynitrite overproduction, seems to play a major role in the nitration and therefore the deterioration of protein function in septic patients.[57 86] In the myocardium of patients who died of septic shock, contractile proteins such as myosine appear to be specifically nitrated by peroxynitrite.[86]

The effects of the three most commonly used inotropes (dobutamine, enoximone, and levosimendan) were recently studied in normal and endotoxaemic rabbits (personal data). Together with the improvement in the indexes of LV systolic function, the inotropes generally improved relaxation or LV compliance in normal rabbits. In endotoxaemic rabbits, however, only levosimendan improved both relaxation and LV compliance. The effects of two vasopressors, norepinephrine and vasopressin, were also studied in endotoxaemic rabbits,[32] and for a similar increase in systolic blood pressure (15%), norepinephrine induced no change in the index of LV systolic function dP/dt_{max} nor in cardiac output whereas vasopressin induced marked deterioration in these measurements. The effect of inotropes and vasopressors on LV diastolic function in septic patients requires further investigation.

Management of diastolic heart failure

Initial management of acute decompensated diastolic heart failure

The management of acute decompensated diastolic heart failure is based on a reduction in pulmonary congestion and a correction of the precipitating factors, such as a hypertensive crisis, myocardial ischaemia, acute rhythm disturbances, and sepsis. Specific treatment of precipitating factors should always be considered: vasodilators for hypertensive crisis, coronary revascularization, restoration of sinus rhythm, and haemodynamic optimization in septic shock.

A hypertensive crisis can be managed by i.v. calcium-antagonists such as nicardipine or nitrendipine (sublingual nifedipine is not recommended). High-dose nitrates i.v. can decrease both preload and afterload. Sodium nitroprusside can also produce balanced vasodilatation, but may result in severe unloading or hypotension in these non-dilated ventricles. Angiotensin converting enzyme inhibitors are not useful in the acute phase because of their slower onset of action. Beta-adrenergic blockers or diltiazem may be used in acute heart failure related to rapid atrial fibrillation or severe myocardial ischaemia.

Pulmonary congestion can be reduced by controlling blood volume or improving LV filling. Because of the steepness of the LV diastolic pressure/volume relationship, a small decrease in LVEDV can lead to a marked decrease in LVEDP. The reduction in the blood volume can be achieved either by nitrates or by diuretics, in order to reduce venous return and decrease LVEDV. Nevertheless, diuretics should be carefully considered in the context of acute hypertensive crisis, as blood volume is often already decreased by chronic hypertension or the long-term use of diuretics. As contractile function is preserved, the role of sympathomimetic inotropes is limited. Digoxin is useful only to slow the heart rate in rapid atrial fibrillation.

Continuous positive airway pressure seems to be effective in the treatment of diastolic dysfunction.[11]

Future treatments for acute diastolic heart failure

Future approaches will probably focus on the optimization of LV relative load at the cardiac level and cardiac myocytes calcium homeostasis at the cellular level.

As mentioned earlier, drugs that may decrease LV relative load are of interest. The decrease in the relative load can be obtained either by decreasing cardiac load or by improving systolic function, or by the combination of both. Thus, levosimendan may be a candidate for acute diastolic heart failure treatment as it combines a vasodilator effect, by opening ATP-sensitive K^+ channels, and a positive inotropic effect, by modulating the interaction between troponin and calcium.[105] Despite a 'calcium sensitizer' effect that is expected to worsen diastolic properties of the heart, levosimendan has been recently shown to improve LV diastolic properties.[77 99]

The effect of NO donors on LV diastolic function has been studied in animals and humans.[78] They have been shown to induce an early relaxation and a decrease in basal tone both related to a reduction in cardiac myofilament

responsiveness to Ca^{2+}, within seconds of administration *in vitro*. Similarly, intracoronary injections of the NO donor, sodium nitroprusside, in normal hearts caused an earlier onset of LV relaxation, a decline in LV minimum and end-diastolic pressures, an increase in LVEDV, and a down and rightward shift of the LV diastolic pressure/volume relationship, within minutes of administration.[79] These results are consistent with a direct NO-induced improvement in diastolic function. A direct beneficial effect of NO donors on diastolic dysfunction has not been shown in patients in the acute/early phase of acute diastolic heart failure. Of note, two other vasodilators, urapidil and nicardipine, seem to have no effect on relative load or directly on the diastolic properties of the LV.[25] In addition, another endogenous cardiovascular mediator, endothelin, has no effects on diastolic properties in normal or chronic heart failure patients.[61]

Long-term management of chronic LV diastolic dysfunction

Myocardial remodelling over months or years is essential to restore adequate LV filling conditions. Several approaches have been proposed to control LV structural abnormalities. Because the renin–angiotensin–aldosterone system plays an important role in the development of diastolic heart failure and particularly in myocardial remodelling and fluid retention, angiotensin-converting enzyme inhibitors, angiotensin receptors antagonists, and aldosterone antagonists have been proposed in the treatment of diastolic heart failure.[19] Spironolactone has recently been shown to limit the evolution of cardiac muscle fibrosis.[53 91] A study of enalapril on diastolic heart failure in elderly patients with prior myocardial infarction[7] reported a benefit in terms of exercise capacity. The CHARM-preserved study is a multicentre, randomized, double-blinded study comparing in diastolic heart failure the effects of a selective angiotensin-receptors blocker (candesartan) and placebo.[117] This showed a significant reduction in hospitalization rate after 36 months follow-up in the candesartan group. Losartan has been shown to improve echocardiography and exercise tolerance.[5]

Of note, cardiac resynchronization therapy affects LV loading conditions and has recently been shown to improve LV filling.[1]

Conclusion

Although frequently underestimated, diastolic heart failure is a common pathology. Diastolic heart failure is recognized as the mechanism involved in heart failure with a preserved LV function, and LV diastolic dysfunction can also account for acute heart failure occurring in critical care situations. Hypertensive crisis, sepsis, and myocardial ischaemia are frequently associated with acute diastolic heart failure. Symptomatic treatment focuses on the reduction in pulmonary congestion and the improvement in LV filling. Specific treatment is actually lacking, but encouraging data are emerging concerning the use of renin–angiotensin–aldosterone axis blockers, NO donors or very recently new agents specifically targeting actin–myosin cross-bridges.

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