Diastolic dysfunction and heart failure with a preserved ejection fraction: Relevance in critical illness and anaesthesia

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Epidemiological and clinical studies suggest that HF with a preserved ejection fraction will become the more common form of HF which clinicians will encounter. The spectrum of diastolic disease extends from the asymptomatic phase to fulminant cardiac failure. These patients are commonly encountered in operating rooms and critical care units. A clearer understanding of the underlying pathophysiology and clinical implications of HF with a preserved ejection fraction is fundamental to directing further research and to evaluate interventions. This review highlights the impact of diastolic dysfunction and HF with a preserved ejection fraction during the perioperative period and during critical illness.

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Keywords: Diastolic dysfunction, HF with preserved ejection fraction, Sepsis, Anaesthesia, Diabetes, Paediatrics, Renal

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Over five million people in the United States have chronic HF (HF) and about five hundred thousand new cases are reported every year [1–3]. Epidemiological and clinical studies have confirmed the trend of increasing incidence of chronic HF internationally [4]. HF remains largely a disease of the elderly and in patients older than 65 years it is the most common diagnosis at hospital discharge and the most frequent cause of readmission [3,5]. Diastolic dysfunction refers to abnormalities in left ventricular distensibility, filling or relaxation regardless of signs and symptoms of HF or left ventricular ejection fraction [6]. Diastolic dysfunction in the absence of symptoms is common in elderly hypertensive patients [7]. Heart failure with a preserved ejection fraction (HFpreEF), or diastolic HF, refers to the clinical syndrome of HF coupled with evidence of diastolic dysfunction and is estimated to occur in approximately 50% of patients with chronic HF [8–12]. In patients older than 70 years, the adjusted mortality rate for HFpreEF is equivalent to those patients with reduced systolic function [8–12]. It is projected that in the developed world the proportion of the population >65 years old and the number of surgical procedures in this group of patients will increase dramatically with at least one in two persons undergoing an operation in the remainder of their lifetime [13]. It is therefore imperative that anaesthetists and intensivists appreciate the impact of diastolic dysfunction and HFpreEF on the aging heart. Despite recent advances in the understanding of HF, there is little consensus about the definition, prognosis and treatment of HFpreEF and diastolic dysfunction. This review aims to describe the pathophysiological mechanisms for and highlight the clinical relevance of diastolic dysfunction and HFpreEF.

Methodology

The literature review was obtained from a computer search of the PUBMED®, MEDLINE® and EMBASE® databases from 1966 to December 2011. A number of different search strategies were used and articles were restricted to English language only. Search terms included ‘diastolic’, dysfunction, ‘heart failure’, ‘systolic’, ‘critical illness’, ‘paediatrics’, ‘pre-operative’, ‘post-operative’, ‘diabetes’, ‘renal impairment’ and ‘anaesthesia’. This is a narrative review as the broad spectrum of topics covered in this review prohibits a fully systematic approach. Abstracts were screened for relevance. Additional reports were identified from reference list screening and relevant systematic reviews were sought and their findings highlighted. Authors were not contacted for additional information.

Definition

The concept of HFpreEF was introduced by Kessler in 1988 [14]. Subsequently, there have been numerous attempts to develop diagnostic criteria; however there has been little consensus [15–19]. In 1998 Paulus et al. developed the European Criteria for HFpreEF [20]. This group suggested that there must be objective evidence of HF with a normal or mildly impaired systolic function (left ventricular ejection fraction (LVEF) > 45%) and abnormal left ventricular (LV) relaxation. All three criteria are required for the diagnosis of HFpreEF. Plasma levels of B-natriuretic peptide (BNP) are elevated in patients with HF, independent of the aetiology of HF [21,22]. An alternative and simpler definition of HFpreEF is an elevated BNP with a normal LVEF [23], however, there may be several limitations to this definition. Specifically elevated BNP levels have been found in patients with myocardial ischaemia in the absence of congestive heart failure (CHF) [24,25], renal failure, and obesity. The proposed mechanism by which ischaemia results in elevated BNP may be through regulation of the ventricular BNP expression or by transient increases in left ventricular wall stress [25,26]. The LVEF most widely accepted as a threshold value is >50%. Diastolic dysfunction refers to impaired LV filling capacity due to abnormalities in
relaxation or stiffness of the myocardium. This is characterized by the upward and leftward displacement of the end-diastolic pressure volume relationship (Fig. 1). However, these changes may occur in patients with diminished systolic function and in the absence of overt HF, and hence by themselves do not confirm a diagnosis of HF"preEF. The need for confirming evidence of diastolic dysfunction remains controversial particularly if there is evidence of hypertrophic remodeling [27,28]. Zile et al. examined 63 patients with a history of HF and an echocardiogram suggesting LV hypertrophy and a normal ejection fraction [28]. Ninety-two percent of these patients had some abnormality in LV relaxation, filling or diastolic stiffness. The updated consensus statement from the European Society of Cardiology is summarised in Table 1. This report considers an LV wall index >122 g/m² or an LV wall mass index >149 g/m², in the presence of symptoms, adequate evidence for the diagnosis of diastolic HF when other modalities such as Tissue Doppler Imaging (TDI) are inconclusive in the context of elevated BNP levels [29].

**Pathophysiology**

The four phases of diastolic function are depicted in Fig. 2. The optimal LV pressure curve would be rectangular allowing the maximal time for ventricular filling [30]. The structural, functional and molecular mechanisms involved in diastolic dysfunction can conceptually be divided in those that occur at the cardiomyocyte level and those that are extrinsic to the myocyte [28,29].

**Cardiomyocyte**

At the myocyte level, changes in calcium homeostasis result in an increased diastolic cytosolic calcium. This may be as a result of (1) abnormalities in the sarcoplasmic reticulum calcium (SR Ca²⁺) reuptake due to decreases in SR Ca²⁺ ATPase (2) abnormalities in the ionic channels responsible for calcium transport, and (3) changes in the state of phosphorylation of proteins such as phospholamban, calmodulin and calsequestrin that modify SR Ca²⁺ ATPase function [31,32]. Increased cytosolic calcium causes abnormalities in both active relaxation and passive stiffness [33].
Troponin I, T and C are bound to actin. Myocardial relaxation is an active process and ATP hydrolysis is required for actin-myosin separation, calcium dissociation from Tn-C and calcium sequestration by the SR [34]. The sensitivity of the myofilament to calcium has recently been reviewed by Kass et al. [35]. Current evidence supports a modified theory of excitation–contraction coupling that myosin cross bridges bind weakly to the actin filament in the relaxed state and creates a closed state [36]. In this closed state the cross-bridging interaction creates a non-force generating reaction [37]. Troponin I is necessary to tether the actin and maintain diastole. Altered troponin I function can produce diastolic dysfunction [38].

Data from explanted hearts and other models of HF show a shift towards higher intracellular Na⁺ [39–43]. The consequence of this high [Na⁺]i is cytosolic Ca²⁺ overload and alterations in cell growth and metabolism, which in turn result in selective abnormalities in diastolic function [39–43].

Abnormalities in myocardial phosphate metabolism also influence diastolic function. Normal diastolic function requires that the concentration of the products of ATP hydrolysis, ADP and inorganic phosphate [Pi], must remain low and produce the appropriate relative ADP/ATP ratio [23,44–47]. Diastolic dysfunction may occur if the absolute concentration of ADP increases or the [48] phosphocreatine/ATP ratio decreases. Studies in isolated heart models have also demonstrated diastolic dysfunction coupled to metabolic inhibition or ischaemia linked to increased free ADP [49].

The cardiomyocyte cytoskeleton is composed of microtubules, intermediate filaments (desmin), microfilaments and endosarcomeric proteins (titin, nebulin, alpha-actin, myomesin and M-protein) [50]. Changes in the cytoskeleton proteins may alter diastolic function [51–53]. The sarcomeric macromolecule titin has been recognized as a major determinant of both viscoelastic stiffness and relaxation [54]. Titins span the entire sarcomere extending from the Z-line to the centre of the sarcomere [55]. During contraction, potential energy is gained when titin is compressed. During diastole, titin acts like a spring and expends this potential energy, providing a recoiling force to restore the myocardium to its resting length [55,56]. Titin also protects the myocardium from being stretched beyond the resting length [52,55]. Titin is expressed in two isoforms: a smaller, stiffer N2B and a larger, more compliant N2BA. The ratio of N2BA to N2B is reduced in DHF [55,57]. The mechanisms involved in isoform switching are poorly understood but probably relate to chronic pressure overloading [55,57]. Pressure overload may increase microtubule density and distribution and increase myocardial stiffness.

A seminal paper by Selby et al. was amongst the first to use a LV biopsy sample obtained during coronary artery bypass surgery to examine tachycardia-induced relaxation abnormalities in patients with a normal ejection fraction [58]. Tissue samples obtained from patients with left ventricular hypertrophy (LVH) had some evidence of...
incomplete relaxation when paced a baseline of 60 beats/min that worsened when paced at 180 beats/min. The myocardial tissue samples from patients without LVH did not exhibit any evidence of relaxation abnormalities at baseline or 180 beats/min. The study also found a mechanistic explanation for this observation. In the LVH group they observed a higher resting tone, abnormalities in calcium actin-myosin cross bridge activation, and abnormalities in sarcolemmal calcium–sodium exchange with an increased cellular calcium load. Tachycardia is common during critical illness and in the perioperative period and this study helps explain the effects of tachycardia induced diastolic dysfunction.

Extracellular matrix

The myocardial extracellular matrix is a dynamic tissue that responds to environmental cues and tissue injury [59]. It is comprised of (1) fibrillar proteins such as collagen type I, collagen type III and elastin; (2) proteoglycans and (3) basement proteins such as collagen type IV, laminin and fibronectin. Changes in fibrillar collagen may be responsible for the development of diastolic dysfunction and diastolic HF [60–62]. Collagen homeostasis has three major determinants: transcriptional regulation, post-transcriptional regulation and enzymatic degradation [63]. Loading conditions, neurohormonal activation and growth factors influence collagen synthesis. Enzymes that influence collagen degradation include the collagenases, the matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs) [64,65]. Alterations in the activity of these enzymes may result in left ventricular remodeling [64]. Inhibition of MMPs may result in increased myocardial collagen with increased LV stiffness. Increased MMPs activity results in a 2-tiered response. Initially the myocytes respond to increased collagen destruction by myocardial hypertrophy and increased collagen production. Over a period of time, there is a decreased rate of pressure decrement during diastole [66]. Elevations of collagen turnover occur in patients with asymptomatic diastolic dysfunction as well as diastolic HF [67]. In addition, the magnitude of collagen turnover correlates directly with the severity of diastolic dysfunction [67]. There are four subtypes of TIMP in the normal myocardium [68,69]. The profile of

### Table 2. Studies comparing systolic and diastolic heart failure (na = not available from published data, NS = not significant).

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>EF (%)</th>
<th>Number of patients (%DHF)</th>
<th>Follow up</th>
<th>Mean age (years ± SD)</th>
<th>Mortality (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith [105]</td>
<td>2003</td>
<td>40</td>
<td>413 (48%)</td>
<td>6 months</td>
<td>70 ± 11</td>
<td>73 ± 11</td>
<td>21</td>
</tr>
<tr>
<td>Vasan [8]</td>
<td>1999</td>
<td>50</td>
<td>73 (51%)</td>
<td>5 yr</td>
<td>74 ± 7</td>
<td>72 ± 9</td>
<td>64</td>
</tr>
<tr>
<td>Cohn [106]</td>
<td>1990</td>
<td>45</td>
<td>623 (13%)</td>
<td>1 yr</td>
<td>58 ± 8</td>
<td>60 ± 7</td>
<td>19</td>
</tr>
<tr>
<td>Ansari [108]</td>
<td>2003</td>
<td>45</td>
<td>147 (44%)</td>
<td>22 months</td>
<td>69 ± 11</td>
<td>66 ± 11</td>
<td>12</td>
</tr>
<tr>
<td>Senni [258]</td>
<td>1998</td>
<td>50</td>
<td>59 (43%)</td>
<td>1 yr</td>
<td>74 ± 12</td>
<td>78 ± 12</td>
<td>42</td>
</tr>
<tr>
<td>Bhatia [109]</td>
<td>2006</td>
<td>50</td>
<td>2802 (30%)</td>
<td>1 yr</td>
<td>72 ± 12</td>
<td>75 ± 12</td>
<td>25</td>
</tr>
</tbody>
</table>

### Table 3. Criteria used to define diastolic dysfunction (modified from Nageuh et al. [30] and Gabriel et al. [259].

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Normal adult</th>
<th>Impaired relaxation (stage 1)</th>
<th>Pseudonormal (stage 2)</th>
<th>Reversible restrictive (stage 3)</th>
<th>Irreversible restrictive (stage 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/A ratio</td>
<td>1–2</td>
<td>&lt;1</td>
<td>1–1.5 (reverses with Valsalva maneuver)</td>
<td>&gt;1.5</td>
<td>1.5–2 (no change with Valsalva maneuver)</td>
</tr>
<tr>
<td>Deceleration time (ms)</td>
<td>150–240</td>
<td>&gt;240</td>
<td>150–200</td>
<td>&lt;150</td>
<td>&lt;150</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>70–90</td>
<td>&gt;90</td>
<td>&lt;90</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>PV S/D ratio</td>
<td>&gt;1</td>
<td>&gt;1</td>
<td>&lt;1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PV Arev-MV wave (ms)</td>
<td>&lt;0</td>
<td>&lt;0 or &gt;30</td>
<td>&gt;30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Arev velocity (cm²)</td>
<td>&lt;35</td>
<td>&lt;35</td>
<td>&gt;35</td>
<td>&gt;35</td>
<td>&gt;35</td>
</tr>
<tr>
<td>Vp</td>
<td>&gt;55</td>
<td>&gt;45</td>
<td>&lt;45</td>
<td>&lt;45</td>
<td>&lt;45</td>
</tr>
<tr>
<td>E' velocity</td>
<td>&gt;8</td>
<td>&gt;8</td>
<td>&lt;8</td>
<td>&lt;8</td>
<td>&lt;8</td>
</tr>
<tr>
<td>LA volume index</td>
<td>&lt;34 ml/m²</td>
<td>&lt;34 ml/m²</td>
<td>&gt;34 ml/m²</td>
<td>&gt;34 ml/m²</td>
<td>&gt;34 ml/m²</td>
</tr>
</tbody>
</table>
TIMP is altered in HF. TIMP-1 is downregulated in myocardial ischaemia. TIMP-4 is upregulated in hypertension. A deficiency in TIMP-3 may be directly related to cardiac remodeling and the evolution of HF [70]. The specific contribution that TIMP makes to diastolic dysfunction is unresolved and a better understanding of this complex protein in HF is warranted.

Age related changes in diastolic function

During aging, changes related to increased myocardial and ventricular stiffening and diminished β-adrenergic receptor responsiveness are highly significant. At the myocyte level, age-related reductions in SERCA2 levels and activity result in abnormal diastolic sequestration of calcium [71–74]. An increase in activity of phospholamban also impairs diastolic function. Aging is associated with a β-adrenergic associated signal dampening [75,76]. This may be due to receptor down-regulation or due to reduced receptor coupling to adenyl cyclase via Gα proteins. There is some evidence that the adrenergic receptor density changes with age with a decrease in high affinity β-receptor [77,78]. There is also an age related increase in myocyte size but decrease in myocyte number [79]. At the extracellular matrix level there is an age-related interstitial fibrosis as a result of increases in fibrin, fibronectin and collagen. Age related degeneration of the conducting system makes elderly patients prone to arrhythmia and further compromises diastolic function [80]. Aging is associated with systolic-ventricular and arterial stiffening [81–84], which may influence diastolic function in several ways. Arterial stiffening increases myocardial oxygen consumption for a given stroke volume and ventricular systolic stiffening exacerbates this effect. Energy costs are predicted to be >50% higher in patients with HfpreEF than controls [85]. The increased arterial stiffness results in ventricular hypertrophy to preserve systolic function at the expense of left ventricular compliance and filling [84,86].

Assessment of diastolic function

Echocardiography

The ideal method to assess diastolic function should be widely available, easy to interpret and accurate. Unfortunately this remains elusive and all existing methods have limitations. Invasive techniques have largely been replaced by echocardiography. The reference ranges for the echocardiography variables used have been derived from studies employing transthoracic echocardiography (TTE). However in the perioperative and critical care context TTE is often technically challenging. This may be due to difficulties with patient positioning, or a reduction of the acoustic window by high levels of positive end expiratory pressure, the presence of injuries, drains or dressings on the precordial area [87,88]. Transoesophageal echocardiography (TEE) has been recommended to overcome these limitations [89]. The reference ranges are derived from awake patients undergoing TTE in the lateral decubitus position. This is in contrast to the supine anaethetised patient receiving mechanical ventilation under dynamic haemodynamic conditions influenced by anaesthetic drugs [90–93]. A comprehensive review on the perioperative assessment of diastolic function has recently been published and the reader is referred here [93]. A summary of the criteria commonly used to define diastolic dysfunction is presented in Table 3 [30]. The mitral inflow velocity is one of the early echocardiographic indices used to define diastolic dysfunction. Early transmitral inflow is denoted as E velocity and depends on left atrial compliance, left ventricle compliance, the rate of left ventricle relaxation and the suction effect created by the base to apex intraventricular pressure gradient atrial contraction is represented by the A velocity and is influenced by left atrial contractility and left ventricular compliance. The deceleration time (DT) is the time interval between the peak of the E wave to baseline and represents the time for equalization of pressure between the left atrium and ventricle (Fig. 2). While mitral inflow velocities are easily obtained, they are highly preload dependant and problematic in patients with atrial fibrillation. Diastolic dysfunction results in delayed transfer of blood from atrium to ventricle. The atrium responds by emptying more vigorously and soon accounts for the dominant component of left ventricular filling. In response to chronic increased left atrial impedance, the atrium undergoes enlargement. As diastolic dysfunction evolves further the atrial pressure increases and the DT decreases, the E/A ratio and the DT appear normal (grade II). With further deterioration of diastolic function the E/A ratio may exceed 2 and the DT < 150 ms. Haemodynamic manipulation such as the Valsalva maneuver will distinguish between severe irreversible diastolic dysfunction (grade IV) from less severe reversible (grade III) disease.

The pulmonary vein has a systolic (S wave), a diastolic (D wave) and an atrial reversal (Arev
Innovation to strain analysis is speckle tracking myocardial deformation and is expressed as Lagrangian strain. Strain rate is the rate of strain and magnetic resonance imaging measured historical time interval [101]. TDE measures natural strain and magnetic resonance imaging measures Lagrangian strain. Strain rate is the rate of myocardial deformation and is expressed as change of strain per unit time. A more recent innovation to strain analysis is speckle tracking [102]. This involves a computer algorithm using routine greyscale imaging that contain unique speckle patterns. Within a user-defined area on the myocardial wall, the image processing algorithm to track frame by frame changes in the speckle pattern to velocity vectors [103]. These advances have well described in recent publications and are beyond the scope of this review [89,93,96,102].

Prognosis

There is a clear association between diastolic HF, asymptomatic diastolic dysfunction, and mortality that is influenced by several variables, including the population being studied, the threshold EF used to define DHF and the influence of co-morbidities. Several variables have been identified as independent clinical predictors of mortality in patients with HF. These include age, New York Heart Association Class IV symptoms, CAD, Diabetes, peripheral vascular disease and the presence of valvular heart disease. Whether patients survive longer after a diagnosis of systolic HF than a diagnosis of systolic HF is still debated [104–109] (Table 2). Hospital readmission rates and length of hospital stay for patients with HFpreEF are similar to SHF and the former have a higher likelihood of functional limitations or labile symptoms on follow-up [110,111]. When outcome from HF is adjusted for the contribution of co-morbidities, there is a uniformly poor prognosis regardless of the ejection fraction.

Information regarding the prognosis in asymptomatic diastolic dysfunction is sparse. A community based study of 2042 patients 45 years and older found that patients with diastolic dysfunction without a history of cardiac failure have a significant risk of death [112]. Compared with normal diastolic function, those with mild diastolic dysfunction have a hazard ratio of 8.31 (p < 0.001, 95% CI 3.00–23.10) and those patients with moderate to severe diastolic dysfunction have a hazard ratio of 10.17 (p < 0.001 95% CI 3.28–31.00) for 5 year mortality [112]. This observation has been confirmed by other reports [9113]. Wang et al. performed one of the earliest studies evaluating the relationship between TDI-derived mitral annular velocities and outcome [114]. A total of 518 patients were recruited for this study (353 with cardiac disease and 165 normal subjects) with the endpoint of mortality at 2 years. This study found that if the Ea or S peak velocities were between 3 and 5 cm/s then the hazard ratio for death was 12.8 (95% CI 2.9–56) [114].
Anaesthetic implications

Pre-operative assessment

The American College of Cardiology and the American Heart association (ACC/AHA) as well as the European Society of Cardiology and European Society of Anesthesiology (ESC/ESA) guidelines recommend the use of risk indices for pre-operative cardiac evaluation for non-cardiac surgery [115,116]. The Goldman, Detsky and Revised Cardiac Risk Index (RCRI) all identify HF as a predictor of perioperative cardiovascular events [117-119]. A limitation of these risk indices is that they do not account for the patient with decompensated HF who improves both symptomatically and functionally on medical therapy. When this patient presents for elective surgery several months later, the patient's perioperative risk calculated by the original Goldman Index does not appreciate the history of HFHF and the RCRI does not appreciate the patient's clinical improvement. There is no specific risk model for predicting perioperative risk in patients with HfpreEF.

When planning surgical procedures in patients with stable HF, it is important to identify those patients that are unlikely to survive long enough to accrue benefit from the procedure. Data from studies describing the clinical profile of cardiac transplant patients have highlighted the difficulties in predicting survival in patients with advanced HF. Several prognostic models have been developed to identify those patients with advanced HF with a high risk of death needing urgent transplantation. These include the Heart Failure Survival Score (HFSS), the Seattle Heart Failure Model [120], and more recently the MUSIC Risk Score [121,122]. None of these scores were specifically intended for pre-operative risk stratification, but may offer some guidance in making difficult decisions in patients with HF that may require surgery.

There is limited data on perioperative risk stratification for isolated diastolic dysfunction. Patients requiring vascular surgery have been shown to frequently have asymptomatic isolated diastolic dysfunction that is associated with a significantly higher rate of major adverse cardiovascular events (MACE). The study by Flu and colleagues found about 50% of vascular surgical patients to have isolated diastolic dysfunction and 80% of these patients were asymptomatic. The study found an OR 2.3 (95% CI 1.4–3.6) for 30 day MACE in all patients with diastolic dysfunction compared with no ventricular abnormalities, abnormalities. The OR for MACE in symptomatic HF was 1.8 (95% CI 1.1–2.9). This study highlights the importance of looking beyond HF symptoms and advocates for the use of echocardiography in patients undergoing high-risk surgery. A similar study by Matyal and colleagues found 43% of patients to have isolated diastolic dysfunction and a strong association in these patients with a prolonged length of stay and higher rates of post-operative HF. Interestingly the study did not find an association with perioperative outcomes and systolic dysfunction. The association was between isolated diastolic dysfunction and perioperative MACE in cardiac surgical patients. Isolated diastolic dysfunction has been shown to increase the risk for postoperative atrial fibrillation in cardiac surgical patients [123]. These observations make a compelling case for the routine assessment of perioperative diastolic function.

Exercise capacity and diastolic dysfunction

Exercise capacity is a useful pre-operative screening test. A self-reported limitation in exercise capacity has a negative predictive value of 95% and a positive predictive value of about 10% for a major perioperative cardiovascular event [124,125]. Exercise intolerance is often the earliest clinical presentation of diastolic dysfunction and is a major determinant of quality of life [126].

Recent evidence suggests diastolic dysfunction may impair the Starling mechanism during exercise [127,128]. The tachycardia that occurs during exercise reduces ventricular filling time. In healthy individuals ventricular filling is maintained by progressive acceleration of the IVRT and an increased suction effect by a more rapid fall in early diastolic LV pressure [129]. In patients with diastolic dysfunction this compensatory mechanism fails [129]. These patients are unable to augment their cardiac output by increasing their end diastolic volume. Left ventricular end diastolic pressure and pulmonary venous pressure rises, reducing the pulmonary compliance and increasing the work of breathing [129].

Patients with diastolic dysfunction have an associated reduction in chronotropic, vasodilator and cardiac output reserve compared with patients without diastolic dysfunction [123,130]. It is thought that these factors may also contribute significantly to the observed limitations in functional capacity.

Implications in the perioperative period

Asymptomatic diastolic dysfunction is frequently underappreciated in the elderly surgical population. Phillip et al. conducted a prospective
study of 251 patients with at least one risk factor for cardiac disease determining the prevalence of diastolic dysfunction in the geriatric surgical patient. [131]. The mean age of the patients was 72 ± 7 years and diastolic filling abnormalities were discovered in 61.5% of the patients. A major limitation of this study was that no outcome measurement was performed so the clinical significance of the findings was not established. Similarly observations have been reported in patients undergoing elective vascular surgery [132]. It is highly likely that elderly patients with vascular disease or hypertension would have some degree of diastolic dysfunction.

Induction of anaesthesia results in significant alterations in ventricular filling in patients with diastolic dysfunction [133]. This may be due to positive pressure ventilation, reduced venous return and reduced right atrial contractility. In patients having aortic surgery, application of the aortic cross clamp worsens diastolic performance that returns to baseline upon release of the cross clamp [134]. In patients requiring cardiac surgery, diastolic dysfunction has been shown to be a better predictor of haemodynamic instability than systolic dysfunction [135,136]. Moderate and severe diastolic dysfunction is also independently associated with difficulties with separation from cardiopulmonary bypass [135,137]. Pre-operative diastolic dysfunction is associated with a range of adverse outcomes including higher mortality, worse mitral regurgitation and longer hospital stay in patients requiring surgical ventricular restoration, mitral valve annuloplasty or elective vascular surgery [132,138,139].

Perioperative atrial fibrillation in patients with diastolic dysfunction results in a significant reduction in left ventricular filling and cardiac output due to loss of atrial kick. Atrial fibrillation may be precipitated by hypovolaemia, hypervolaemia with atrial overdistension, electrolyte abnormalities, particularly hyper and hypokalaemia, anaemia, abrupt withdrawal of beta-blockers or calcium channel blockers, and ischaemia. The onset of atrial fibrillation has been shown to precipitate HF in patients with pre-existing diastolic dysfunction [140]. The presence of pre-operative diastolic dysfunction is a strong independent predictor for developing post-operative atrial fibrillation after cardiac surgery [141]. Diastolic dysfunction also predicts long term rhythm after intraoperative ablation for atrial fibrillation [142]. The dominant mechanism is probably inflammatory mediated though the exact etiology for the development of atrial fibrillation in these patients is unknown. This may explain the observation that statins may reduce the rate of atrial fibrillation after cardiac surgery [143].

Myocardial ischaemia results in significant impairment in LV relaxation and increases the risk of rhythm disturbances as already discussed. The earliest abnormality induced by epicardial occlusion is a reduced ventricular compliance. This precedes regional wall motion abnormalities, electrocardiographic changes or chest pain [144]. There are two mechanism by which acute myocardial ischaemia induces diastolic dysfunction [145]. The first mechanism is by arterial hypoxaemia and occurs within 2 min, The second mechanism is by perfusion ischaemia and occurs at about 20–30 min. Diastolic dysfunction is commonly associated with LVH. Increases in intra-cavitary pressure together with increased left ventricular mass result in malperfusion of the left ventricle. LVH may be eccentric or concentric. Each geometric pattern is associated with a particular pressure or volume stimuli, contractile efficiency and prognosis. The concentric pattern carries the worse prognosis compared with eccentric hypertrophy [146]. In patients with right HF, increased right atrial pressure impairs postcapillary blood flow resulting in coronary venous engorgement [33]. Right ventricular dilatation may also impede LV filling by ventricular interdependence.

There is limited clinical data on the effect of anaesthetic drugs on diastolic function. The choice of anaesthetic technique has been shown to influence diastolic properties in patients with pre-existing diastolic dysfunction [91,147]. In a small randomised study of 24 patients, the use of sevoflurane during spontaneous ventilation preserved early diastolic function better than propofol. However during a balanced anaesthetic technique with positive pressure ventilation, no difference between sevoflurane and propofol on diastolic function was observed [91]. These findings are consistent with other studies [147]. The mechanism by which propofol affects diastolic function are similar to volatile anaesthesia [148,149]. There is impaired calcium reuptake by the sarcoplasmic reticulum and modulation of phosphorylation of the contractile proteins [150]. More recently a comparisons between isoflurane, desflurane and sevoflurane found no significant effect on diastolic performance in healthy subjects and no difference between these agents in patients with diastolic dysfunction [151]. Morphine and midazolam do not appear to have any effect on diastolic performance [152,153]. Similarly, remifentanil has been
shown to not to impair diastolic function in healthy volunteers [154].

Diastolic dysfunction and sepsis

The occurrence of myocardial dysfunction in patients with sepsis carries a significant burden of mortality (70%) compared with those patients that do not have myocardial dysfunction [155]. Both systolic and diastolic dysfunction have been described. Parker et al. demonstrated the relationship between diastolic dysfunction and sepsis in 1984 [156] comparing haemodynamic and radionuclide cineangiographic data between a group of 20 patients with septic shock and a control group of 32 critically ill patients with negative blood cultures, not in shock. The patents with septic shock were volume resuscitated to a PAWP of 12–15 mmHg and inotropes were added as required. Survivors of septic shock (n = 13) had high left ventricular volumes (mean left ventricular end diastolic volume index (LVEVPI) 159 ± 29 mL/m²) that returned to normal by about 10 days. Non-survivors had normal mean LV volumes (mean LVEDVI 81 ± 9 mL/m²) that did not change during the 10 day period. Unfortunately, no ventricular volume data was reported for the control group. The same group of investigators evaluated 39 patients with septic shock again using haemodynamic and radionuclide angiographic studies [157]. Survivors (n = 22) displayed simultaneous biventricular dilatation that returned to normal after recovery. Non-survivors (n = 17) displayed less severe dilatation but did not improve on subsequent evaluation. Changes in right ventricular volumes paralleled changes in the left ventricle [157].

Using both haemodynamic and radionuclide measurements, in a group of 56 patients admitted to ICU, Ognibene et al. was able to show higher PAWP with a trend towards higher LVEDVI in patients with septic shock compared with controls [158]. The pre-enrollment fluid resuscitation in the septic shock group was more aggressive than the controls making the data difficult to interpret.

More recent studies have used echocardiography to evaluate diastolic performance. Jafri et al. observed that Doppler parameters of LV filling were abnormal in a subset of 46 septic patients with or without shock [159]. The clinical significance of the study is unclear as there was a statistically significant difference in the heart rate between the control group and the sepsis group (116 ± 15 beat/min septic shock, 110 ± 26 beat/min, sepsis without shock vs. 73 ± 12 beat/min controls, p < 0.05) and the echocardiography modality used does not account for patients with pseudonormal filling pattern. Subsequently, Munt et al., have demonstrated similar abnormalities in diastolic performance in a group of 24 critically ill patients [160]. This report also identified abnormalities of LV filling as being independently predictive of mortality [160]. Non-survivors of severe sepsis had more abnormal Doppler parameters of diastolic relaxation, as measured by E/E VT and deceleration time (DT). In a multivariate analysis, DT was the only echocardiographic parameter that independently predicted mortality. All patients were studied within 24 h of presentation and after volume resuscitation. There was no difference in mean pulmonary artery occlusion pressure or heart rate between survivors and non-survivors. This study has several limitations that deserve comment. Although patients with pre-existing cardiac disease were excluded, there was no control group and systolic function was not assessed making it difficult to draw meaningful conclusions. Mortality was significantly associated with advanced age and also with abnormal Doppler parameters of diastolic relaxation. It is impossible to determine whether sepsis induced an abnormality of LV relaxation in non-survivors, or whether there was pre-existing diastolic dysfunction in this subgroup of patients. Interestingly, cardiac output was actually higher in non-survivors than in survivors in this study [160].

Baitugaeva et al. examined diastolic performance in 59 patients between the ages of 18–24 years with sepsis, severe sepsis and septic shock and noted a significant relationship between diastolic dysfunction and pro-inflammatory cytokines [161]. The patients in this age group are unlikely to have pre-existing diastolic dysfunction. The findings in these studies are consistent with a growing body of evidence from experimental studies that supports the concept of sepsis or endotoxin induced abnormalities in LV compliance [162,163]. The majority of these studies have shown a reduction of ventricular compliance by pressure–volume analysis early (within hours) into the course of sepsis without ventricular dilation. Over a period of days and with the administration of intravascular volume, the left ventricle dilates. Measured compliance at this stage may still be reduced, or may return toward normal, and it has been proposed that ventricular compliance in sepsis may be volume dependent [2]. It is estimated that about 20% of patients with septic shock will have some impairment of left ventricular relaxation [164]. The spectrum of cardiac
abnormalities ranges from isolated diastolic abnormalities to HFpreEF and systolic HF.

Ventricular dilation seen in early studies in both human and animal studies has been implicated in the maintenance of cardiac output in the face of impaired contractility [165].

Animal models have confirmed both systolic and diastolic dysfunction related to the ability of inotropes to restore diastolic function [166,167]. Dobutamine improved systolic function but did not improve diastolic dysfunction in animal models of sepsis.

There are several confounding issues that make evaluation of diastolic performance in critical illness particularly challenging. These include the potential effects of inotropes, volume resuscitation and the lack of well-established reference ranges for diastolic parameters in critical illness. It is hoped that the use of more standardised methods for evaluating diastolic function such as TDI and strain rate will overcome some of these difficulties and provide insight into the interrelation of sepsis and ventricular diastolic function and its implications for patient survival.

Pediatric patients with cardiac disease

It is important to understand the maturation of diastolic function before we can appreciate diastolic dysfunction in the pediatric patient. Data from 238 healthy neonates suggests that at birth there is impaired left ventricular relaxation characterized by a prolonged isovolumic relaxation time and limited early diastolic filling predominantly dependent on atrial contraction [168]. In the first week of life there are improvements in left ventricular relaxation. By two months of age the pattern of transmitral flow changes dramatically with early mitral flow velocities increasing by about 80% from newborn values [168,169]. The effect of heart rate on early filling appears to be negligible and does not account for the observed differences [168]. In contrast, during the same period, there are no significant improvements in tricuspid diastolic annular motion or inflow velocities, implying that the right ventricle has delayed improvement in diastolic function [169]. In pre-term infants the maturation of diastolic function is prolonged and at two months there is still a predominance of diastolic filling during atrial contraction [170]. The maturational process of diastolic performance takes about three months and limits tolerance to preload stressors [171]. A study of cardiac growth in healthy children using TDI showed a correlation between diastolic function and age [172].

In children with congenital heart disease, diastolic dysfunction has historically been under-recognised. The use of transcatheter techniques have advanced the understanding of diastolic dysfunction in children. TDI and strain rate and strain imaging studies have revealed no significant increase in left sided pressure after closure of an atrial septal defect (ASD) [173–176]. In contrast, ASD closure in adult patients is characterised by an increase in left ventricular dimensions, elevations in N-terminal proBNP, delayed improvement in exercise tolerance and even HF [177]. This makes a convincing case for early closure of ASD [178].

Following repair of a patient with Tetralogy of Fallot (TOF), several acute and chronic complications have been shown to have a significant impact on the post-operative course. In these patients, biventricular systolic function is usually well preserved with restrictive right ventricular physiology [179]. Right ventricular restriction is characterised by anterograde diastolic pulmonary flow, implying that the right ventricle has become a stiff conduit in late diastole [180–185]. Restrictive filling following repair of a TOF is associated with increased inotropic requirements, prolonged mechanical ventilation time, higher doses of diuretics and longer hospital stay as well as poor exercise capacity and symptomatic arrhythmias [182]. Recent studies using TDI and strain rate and strain, after complete repair of TOF, have found significant systolic and diastolic dysfunction of the right ventricle. These patients have a significant risk of late right ventricular failure, and pulmonary insufficiency [183–185]. TDI and strain rate may provide invaluable information about the need for pulmonary valve replacement. These reports provide further evidence that complete repair of TOF should be performed during infancy as delayed repair exposes the myocardium to chronic hypoxaemia and hypertrophy [186,187].

Diastolic dysfunction and medical disease

Renal disease

There appears to be a consistent relationship between diastolic dysfunction and chronic renal disease in both paediatric and adult patients [188]. There are two parallel pathophysiological mechanisms that underlie the development of diastolic dysfunction in patients with chronic renal insufficiency [188]. The first is that cardiac remodeling results in left ventricular hypertrophy (LVH). Pressure overload results in concentric LVH whereas eccentric LVH may be related to volume...
overload. Over a period of time, the maladapta-
tion phase of LVH results in decreased capillary
density, coronary reserve and subendocardial per-
fusion. Myocardial fibrosis with systolic and dia-
static dysfunction result.

The second mechanism involves vascular injury. Chronic renal disease and cardiac disease share
many common risk factors. These include athero-
sclerosis and vascular calcification.

Chronic renal dysfunction is frequently associ-
ated with diastolic HF and has been shown to
independently increase mortality [189–194].
Ahmed and colleagues conducted a post hoc pro-
pensity-matched study of patients in the Digoxin
Investigation Group (DIG) trial to determine the
impact of LVEF, chronic renal insufficiency (CRI)
and mortality in a cohort of 7788 ambulatory pa-
tients in sinus rhythm [195]. DHF was present in
988 patients (defined as LVEF > 45%). Interest-
ingly, this study concluded that mortality associ-
ated with chronic renal insufficiency (CRI) was
higher in patients with diastolic HF compared
with SHF [195,196]. Additionally, there was a
graded relationship with higher CRI-associated
mortality occurring with increasing LVEF. There
are several potential explanations for this observa-
tion. The mean age of patients with DHF was
3 years older than patients with systolic HF
(P < 0.0001) and there were more patients
>75 years of age with CRI and DHF than systolic
HF. Renal impairment in DHF may represent
intrinsic renal disease in advanced age. Thirdly,
the influence of medical therapies needs to be ex-
plored. Patients with DHF do not show the same
prognostic improvement when commenced on
medical therapy when compared with matched
patients with HF and low EF [197]. Lastly, there
may be unmeasured co-variables that may ac-
count for these observations.

Diabetes

Although diabetes is a well recognized risk fac-
tor for the acceleration of ischaemic heart disease
and hypertension, the relationship between dia-
abetes and cardiac disease independent of these
diseases is less well understood. Diabetic patients
without significant coronary artery disease may
develop features of abnormal LV relaxation with
normal systolic function [198–201]. The severity
of the diastolic dysfunction correlates indepen-
dently with the derangement in glycaemic control
as manifested by elevated glycosylated haemoglo-
bin [199–201]. A nationwide case control study
showed that diabetes was independently associ-
ated with idiopathic cardiomyopathy [202]. The
pathophysiological mechanisms that underly the
relationship between diabetes and diastolic dys-
function are probably mediated through the
microcirculation. Intra vascular ultrasound studies
have shown impaired coronary flow reserve in
both type 1 and type 2 diabetic patients [203,204].
A reduced coronary flow reserve indicates coro-
nary microvascular dysfunction, in the absence
of epicardial coronary stenosis [205]. This micro-
vascular dysfunction may lead to myocardial cell
injury, fibrosis or apoptosis [206]. Other possible
mechanisms of microcirculatory dysfunction in-
clude autonomic dysfunction, endothelial dys-
function and insulin resistance [207–209]. The
 cellular mechanisms that underly diabetic dia-
static dysfunction are probably due to three char-
acteristic metabolic abnormalities that are
observed in diabetes [201]. These are (1) hyper-
glycaemia which generates reactive oxygen spe-
cies causing mitochondrial dysfunction (2.)
hyperinsulinaemia which promotes myocyte
hypertrophy and (3) elevations in non-esterified
fatty acids which are thought to induce insulin
resistance and myocardial apoptosis [210–215].

The clinical features of the cardiovascular changes
induced by both type 1 and type 2 diabetes are
similar [216–218].

Chronic obstructive airways disease (COPD)

The cardiovascular consequences of COPD in-
clude impaired left ventricular filling, arterial stiff-
ness, cor pulmonale and chronic HF [219]. The
Multi Ethnic Study of Atherosclerosis (MESA)
Lung is a population based study that explored
the relationship between emphysema, airflow
obstruction and left ventricular filling in 2816 sub-
jects [220]. Magnetic resonance imaging was used
to measure left ventricular structure and function,
CT scanning was used to define the severity of
emphysema and spirometry was performed
according to the American Thoracic Society guide-
lines. The study found a linear relationship be-
tween both severity of emphysema and airflow
obstruction with impairment of left ventricular
filling, reduced stroke volume and cardiac output
without significant reductions in ejection fraction.
These findings are consistent with other work
which has highlighted the presence of both right
and left ventricular diastolic dysfunction early in
the course of COPD, without overt cardiovascular
disease [221]. The mechanisms by which COPD
causes impaired left ventricular filling include
pulmonary vascular changes, pulmonary hyperin-
flation, arteriolar hypoxia and ventricular interde-
pendence. Other less well understood
### Table 4. Summary of intravenous therapy for a hypertensive crisis [240,241].

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clevidipine</td>
<td>Third generation dihydropyridine</td>
<td>Starting dose 1–2 mg/h, doubled every 90 min until target BP reached.</td>
<td>Specifically arteriole dilator. Rapid onset 2–4 min. Agent contains phospholipids that support microbial growth and vial must be changed every 4 h</td>
</tr>
<tr>
<td></td>
<td>CCB</td>
<td>No more than an average of 21 mg/hr over a 24 h period</td>
<td></td>
</tr>
<tr>
<td>Enalaprilat</td>
<td>ACE inhibitor</td>
<td>1.25 mg every 6 h over a 5 min period. 50% dose reduction for patients with creatinine clearance &lt;30 ml/min</td>
<td>Onset of action 15–30 min. Peak effect at 4 hours and duration of effect 12–24 h. Not easily titrated due to long duration of effect</td>
</tr>
<tr>
<td>Fenoldopam</td>
<td>Peripheral dopamine type 1 agonist</td>
<td>Starting dose 0.1–0.3 μg/kg/min, increased by increments of 0.05–0.1 μg/kg/min every 15 min. Maxumin rate 1.6 μg/kg/min</td>
<td>Onset of action within 5 min. Duration of effect 30 min. Avoid in patients with glaucoma, increased ICP or sulphur allergy</td>
</tr>
<tr>
<td>Esmolol</td>
<td>β₁ adrenergic antagonist</td>
<td>Loading dose 0.5–1.0 mg/kg over 1 min then 50 μg/kg/min infusion increased by 50 μg/kg/min up to maximum 300 μg/kg/min</td>
<td>Onset of action within 1 min. Duration of effect 10–20 min. Metabolized by erythrocyte esterases</td>
</tr>
<tr>
<td>Labetolol</td>
<td>Combined α₁ and non-selective β adrenergic antagonist</td>
<td>20 mg iv bolus followed by 20–80 mg iv bolus every 10 min or infusion 1–2 mg/min</td>
<td>Duration of effect with infusion or repeated bolus dose is 2–4 h</td>
</tr>
<tr>
<td>Sodium nitroprusside</td>
<td>Nitric oxide donor</td>
<td>Starting dose 0.3–0.5 μg/kg/min increased by 0.5 μg/kg/min. avoid dosed &gt;2.0 μg/kg/min</td>
<td>Concern about cyanide, toxicity and meth-haemoglobinemia</td>
</tr>
</tbody>
</table>

CCB = calcium channel blocker, ACE = angiotensin-converting enzyme, ICP = intracranial pressure.
mechanisms involve systemic inflammation, oxidative stress, connective tissue degradation and vascular dysfunction. Retrospective pharmacoepidemiologic studies have hinted at the possible benefit of statins combined with low dose inhaled corticosteroids at reducing the acute coronary events and hospitalizations in patients with COPD [222–224]. Randomized control trials are awaited.

Cirrhotic cardiomyopathy

The cardiac dysfunction noted in patients with liver cirrhosis is greater than what is accounted for based on alcohol alone and has been termed cirrhotic cardiomyopathy [225]. The term refers to spectrum of cardiac abnormalities that include systolic and diastolic dysfunction, electrophysiological changes such as prolonged QT interval and a diminished response to catecholamines. The mechanism by which cirrhosis causes diastolic dysfunction is a combination of myocardial hypertrophy, fibrosis and sub-endothelial oedema [226]. Increased sodium intake may induce myocardial hypertrophy and may in itself be responsible for some of the diastolic dysfunction observed in these patients [227]. The severity of diastolic dysfunction observed is more pronounced in patients with ascites. This may be a consequence of the mechanical effects of ascites or reflect the severity of liver cirrhosis [228]. Patients with diastolic dysfunction are very sensitive to the volume changes that occur with transjugular intrahepatic portosystemic shunts (TIPS) procedures [229]. Portal decompression by TIPS results in rapid shifts of large blood volumes from the splanchnic circulation to the heart. The persistence of diastolic dysfunction after TIPS has been found to be a strong independent predictor of mortality [229]. Diastolic dysfunction has been associated with a slower mobilisation of ascites [230]. Liver transplantation improves/reverses diastolic dysfunction though the evidence is sparse [231]. The time course for the changes that occur after transplantation are not completely understood. Some authors have reported a persistence of hyperdynamic circulation for up to two years after transplantation and others report an immediate amelioration to the cardiac and circulatory disturbance.

Is diastolic heart failure a precursor to the evolution of systolic heart failure or a syndrome on its own?

Whether HF is a single syndrome with HFpreEF preceding HF with systolic impairment or whether HF is two distinct syndromes: one with concentric remodeling and diastolic dysfunction (DHF) and the other with eccentric remodeling and systolic-diastolic dysfunction (SHF) is unclear.

The evolution of our understanding of ventricular function has led to various models of cardiovascular performance each with its own set of defining variables. If the myocardial performance is defined as a haemodynamic pump then LVEF is an important measure [55,218,232–234]. The haemodynamic performance of the heart is influenced by factors outside the myocardium, such as preload and afterload. LVEF is usually derived by radial measurements of the LV. During the early period of systolic dysfunction, there may be radial compensation for longitudinal impairment and this does not reflect changes in regional and temporal abnormalities in cardiac muscle [232,233,235]. In this context, a normal ejection fraction does not equate with preserved systolic function. If myocardial performance is viewed as a muscle pump then indices of longitudinal function and non-uniformity define ventricular performance [55,232–235]. These include TDI derived mitral annular velocity and strain and strain rate indices than by LVEF [232,233,235]. Advocates for the two-syndrome model cite the lack of prognostic improvement in recent therapeutic trials with DHF as compared to the success in SHF. This would imply different disease processes. The presence of ultrastructural changes in the cardiac myocyte, and changes in matrix metalloproteinase also support the latter view [236–238].

Treatment

The key targets for therapy are active relaxation, passive LV relaxation and myocardial fibrosis [239]. The management of acute decompensated diastolic HF should focus on correcting the precipitating factors such as myocardial ischaemia, hypertensive crisis, acute rhythm disturbances, hyperglycaemia and hyperinflation as well as therapy to relieve pulmonary congestion. The steep gradient of the diastolic pressure-volume relationship means that a small change in a LVEDV results in a significant change in LVEDP, diuretics or nitrates should therefore be carefully
considered when attempting to reduce LVEDV. Hypertensive crisis are frequently encountered in these patients. There have been several exciting developments in the pharmacotherapy available and the choice should be based on individual patient characteristics (Table 4) [240,241]. The use of non-invasive ventilation is an effective therapy for acute exacerbations of diastolic HF reducing hospital mortality and the need for endotracheal intubation [242,243]. Less recognized factors may also play a role. For example obesity is a surrogate for obstructive sleep apnoea (OSA). The cardiovascular abnormalities associated with OSA include LV hypertension, paroxysmal atrial fibrillation and sympathetic activation. NIV will reverse these abnormalities [244].

Beta blockers have been proposed for the treatment of HFPreEF based on the assumption that the rate lowering effect of prolonging diastole would result in better LV filling [6]. There is data from observational studies suggesting a differential benefit for beta blockers in HFPreEF compared with patients with systolic impairment [245,246]. The sinus node I, blocker Ivabradine offers the potential to reduce heart rate without any effect on contractility and may find a niche in patients with HFPreEF [247]. Aldosterone is known to promote ventricular fibrosis and collagen deposition. The aldosterone antagonist spironolactone has been shown to limit myocardial fibrosis [248]. Canrenone is a spironolactone metabolite. In a small randomized study, canrenone improved LV diastolic performance without altering blood pressure of LV mass significantly [249]. The trials evaluating angiotensin receptor blockers candesartan (CHARM PRESERVED trial), ibesartan (I-PRESERVED trial), and the angiotensin-converting enzyme inhibitor perindopril (PEP CHF trial) did not show any survival benefit when compared with placebo [250–252].

The management of circulatory failure related to diastolic dysfunction in critical illness is largely supportive. Adequate fluid resuscitation is often followed by drugs with a positive lusitropic effect. In practice systolic and diastolic dysfunction often co-exist and phosphodiesterase inhibitors and calcium channel sensitisers are invaluable. Levosimendan is a calcium-sensitizing agent that mediates effect through binding to Troponin C. This results in increased myocardial contractility with minimal increases in oxygen consumption. In this study, levosimendan improved both systolic and diastolic function in LPS treated animals and controls. Levosimendan detaches from troponin C at low calcium concentrations so its effect on diastole is unexpected. It is probable that Toponin C may have some effect on Troponin I even during hyperphosphorylation [166]. The use of levosimendan septic shock was first described in 2005 and since then there have been two randomised clinical trials in this group of patients [253–255]. The first trial compared levosimendan with dobutamine in 28 patients with septic shock [255]. In both groups norepinephrine was used to maintain mean arterial pressure. There were significant improvements in cardiovascular performance and organ function in the levosimendan group (end-diastolic and end-systolic volume index and left ventricular stroke work index) The second trial involved thirty-five patients with septic shock, ARDS and right ventricular failure [254]. Magnetic resonance imaging showed an improved right ventricular end diastolic volume index as well as an improved right ventricular end systolic volume index and right ventricular ejection fraction. These were small studies not powered to show any mortality benefit and there is insufficient evidence to recommend the routine use of levosimendan in sepsis induced diastolic dysfunction. A meta-analysis by Landoni et al. evaluated the role of levosimendan in critically ill patients [256]. The study concluded a mortality benefit in favour of levosimendan (OR 0.74, 95% CI 0.62–0.89). This methodically rigorous analysis pooled 27 studies involving patients with decompensated HF, elective cardiac surgery, acute myocardial infarction and elective abdominal aortic aneurysm repair. The heterogeneity of patients included in this meta-analysis makes it difficult to extrapolate its findings to severe sepsis.

Future trials should focus on the specific structural and functional abnormalities that occur in HFPreEF patients. These include cardiomyocyte hypertrophy, alterations in myocardial extracellular matrix metabolism, the shift in myocyte metabolism from glucose to free fatty acids, and the higher expression and phosphorylation titin isoforms [257].

**Conclusion**

Diastolic dysfunction and HF remain underappreciated in the peri-operative and critical care environment. Epidemiological data predict that diastolic HF will become the more frequently encountered type of HF encountered in clinical practice. Advances in echocardiography technology have been instrumental in our understanding of ventricular function. Currently, therapeutic
options specific to this group of patients is limited and mortality has remained unchanged. In contrast to patients with reduced EF, the prognosis for those with HTPreEF has failed to improve in the last three decades. The potential public health burden should make diastolic dysfunction and diastolic HF a priority.

Conflict of interest

The authors have no conflicts of interest to declare.

References


