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Revalidation FOR ANAESTHETISTS RCA Revalidation matrix. Matrix reference 1A01, 2A06, 2C01, 3C00

*BJA Education*, 16 (9): 287–291 (2016)

**doi: 10.1093/bjaed/mkw007**
Advance Access Publication Date: 22 April 2016

# Diastolic dysfunction in anaesthesia and critical care

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**Key points**

- Diastolic dysfunction (DD) is associated with common comorbidities such as systemic hypertension, atrial fibrillation, and diabetes.
- "Heart failure with preserved ejection fraction" is destined to become the most prevalent cause of heart failure in the UK and extubation can provoke acute heart failure in these patients.
- DD predicts weaning failure in critical care and increased perioperative risk over a wide range of non-cardiac specialities and in previously asymptomatic patients.
- Perioperative diagnosis of DD has been facilitated by the increasing use of tissue Doppler imaging echocardiography.
- New treatment options are becoming available.

Ventricular function defined by systolic ejection is well recognized by clinicians due to its readily quantifiable and interpretable echocardiographic parameters. In contrast, ventricular function defined by its diastolic capacity to fill is less widely appreciated, perhaps because abnormal relaxation and reduced compliance are more challenging properties to demonstrate and correlate clinically. Both ventricles share these properties, but left ventricular (LV) dysfunction causes the greatest morbidity. Systolic and diastolic LV dysfunction may exist together or in isolation and any combination can lead to critically raised left atrial (LA) pressure, given the physiological challenges that anaesthesia, mechanical ventilation, and critical illness can bring.

This article will describe relevant pathophysiology of LV diastolic dysfunction (DD) and its relationship with perioperative risk and demonstrate why early recognition in perioperative and critical care medicine is important. It will also discuss diagnostic methods, current and emerging treatment options, and how the perioperative pathway can be optimized in this patient group.

## Pathophysiology of DD

The ventricle's ability to fill depends on its fixed viscoelastic stiffness and its variable capacity to relax. Diastole is classically divided into four stages—isovolumetric relaxation, early rapid filling, late slow filling, and atrial contraction. Isovolumetric relaxation refers to the rapid decrease in LV pressure with little or no change in volume and ends with the opening of the mitral valve and early LV filling. These early phases, sometimes referred to as LV suction, are characterized by a rapid decline in LV intracavity pressure and require energy in the form of ATP as substrate for sarcoplasmic/endoplasmic reticulum $Ca^{2+}$-ATPase to pump cytosolic calcium back into the sarcoplasmic reticulum and enable uncoupling of actin and myosin. This mechanism helps to explain why myocardial ischaemia can raise LV filling pressure so precipitously.

Filling later in diastole is more dependent on ventricular compliance and is affected by numerous factors, including the accumulation of cytoskeletal collagen, which increases with age, longstanding wall stress, and various neuro-humoral factors. Less common causes of impaired ventricular compliance are infiltrative diseases, pericardial constriction, and collection.

Any combination of the factors above can raise left ventricular end-diastolic pressure (LVEDP) with compensatory increases in LA pressure. Consequently, as pulmonary venous hydrostatic pressure increases, so does the potential for dyspnoea and pulmonary oedema.

DD is usually asymptomatic at rest, but as it progresses, it can become unmasked by exercise or when the cardiovascular system is stressed beyond its physiological reserve, for example, during episodes of uncontrolled systemic hypertension, fluid overload, or atrial fibrillation (AF).

## Tachycardia

Tachycardia shortens time for LV filling, so diastolic relaxation must occur more rapidly if stroke volume is to be maintained or increased. This is normally accomplished without an increase in LA pressure, demonstrating the normal ventricle's capacity to increase its diastolic properties under stress. However, in patients with DD, this capacity is markedly diminished and even a modest tachycardia can lead to overt heart failure.

## Atrial fibrillation

The relationship between AF and heart failure with preserved ejection fraction (HFpEF) is strong, but causality is not easy to establish as the two pathologies can be interdependent. Structural remodelling and LA dilatation resulting from DD and LA pressure overload is a common cause of AF, while longstanding AF can cause a tachycardia-induced myopathy, raised LV filling pressure, and LA dilatation. In patients with DD, new-onset AF causes loss of late LV filling with an immediate reduction in preload, systolic ejection, and cardiac output.

## Ventricular loading conditions

Loading conditions refer to the combination of preload and afterload acting on the ventricle at any one time. General anaesthesia, mechanical ventilation, and the surgical stress response affect LV loading conditions variably but in patients with DD, tracheal extubation carries greatest risk. The combination of tachycardia, increased ventricular preload (antecedent intravascular volume expansion, coughing with deep spontaneous inspiratory effort), and increased LV afterload (circulating catecholamines, systemic hypertension, zero PEEP) can combine to raise LA pressure high enough to precipitate acute pulmonary oedema.

## Heart failure with preserved ejection fraction

Between one-quarter and a half of all patients presenting with classical symptoms of heart failure have a syndrome known as 'HFpEF' in which symptomatic pulmonary congestion is associated with a systolic ejection fraction in excess of 50%. Its prevalence is increasing due to our ageing and increasingly comorbid population and in a decade, HFpEF is destined to become the most prevalent form of heart failure.[1]

Several large, community, and inpatient-based observational studies from Europe and North America have demonstrated that, when compared with patients with heart failure with reduced ejection fraction (HFrEF), patients with HFpEF tend to be older, female, have less ischaemic heart disease (IHD) but more AF and more non-cardiac comorbidities, including diabetes, obesity, peptic ulcer disease, cancer, chronic obstructive pulmonary disease, and anaemia.[1] While HFpEF is thought to include heterogenous aetiologies such as ventricular dyssynchrony, LA dysfunction, and abnormalities of global and longitudinal strain, DD can be found in at least 70% of cases.[2] Furthermore, this value is likely to be an underestimate as most HFpEF patients are diagnosed using resting echocardiography and some may develop detectable DD only when stressed or exerted.

Surgical patients with HFpEF should be identifiable by their preoperative history and clinical signs. However, those with subclinical DD can pass easily through preoperative assessment with the potential to decompensate in the operating theatre in the presence of unfavourable LV loading conditions.

## Increased perioperative risk

The association between DD and perioperative complications is increasingly apparent and identification of DD appears to be important in pre-assessment for a wide range of surgical specialities.

In cardiac surgical patients, evidence of DD has been shown to predict difficulty in weaning from cardiopulmonary bypass and other postoperative complications.[3–5]

In high-risk vascular patients, the presence of DD (with or without preserved ejection fraction) was independently associated with postoperative adverse events ($P$=0.002) and increased hospital length of stay [7 days (range 5–10) *vs* 5 days (range 4–6), $P \leq 0.001$].[6]

In patients undergoing low- and intermediate-risk surgery, a preoperative diagnosis of DD (with or without preserved ejection fraction) was independently predictive of postoperative pulmonary oedema [odds ratio (OR) 4.6, 95% confidence interval (CI) 2.9–7.2, $P \leq 0.001$] and major cardiac events (OR 4.0, 95% CI 2–7.9, $P \leq 0.001$).[7]

In patients undergoing vascular surgery, even the presence of asymptomatic DD has been shown to be independently associated with postoperative 30 day cardiovascular events (OR 1.8, 95% CI 1.1–2.9) and long-term cardiovascular mortality (OR 3.0, 95% CI 1.5–6).[8]

## Failure to wean from mechanical ventilation

Weaning from mechanical ventilation coupled with discontinuing sedation can lead to adrenergic stimulation, hypertension, and tachycardia, which may provoke overt heart failure in at-risk patients.

The periodic withdrawal of ventilatory support to assess an intensive care unit (ICU) patient's potential for successful extubation is known as a 'spontaneous breathing trial' (SBT). In an observational study of patients being weaned from mechanical ventilation, including a variety of physiological and comorbidity-related variables, echocardiographic evidence of DD was found to be the most powerful independent predictor of failed SBT (OR 6.6, 95% CI 1.2–27, $P$=0.03).[9] These findings were supported by another study which demonstrated that LV DD was predictive of weaning failure, whereas LV systolic dysfunction was not.[10]

## Sepsis

A recent meta-analysis of patients with sepsis, severe sepsis, and septic shock found that DD was present in 48% and was significantly associated with mortality (RR 1.82, 95% CI 1.12–2.97, $P$=0.02).[11] Interestingly and in contrast, systolic dysfunction was present in only 30% and this was not associated with mortality. Future treatments for septic shock may be directed towards potential DD and the β-blocker esmolol is currently under evaluation in this patient group [ESMOSEPSIS trial (ClinicalTrials.gov identifier: NCT02068287)].

## Diagnosis of DD

Specific echo measurements are necessary to make a formal diagnosis of DD. However, there are simpler, more accessible ways to recognize when patients either have the condition or may be at-risk of it.

History taking, clinical examination, bloods, ECG, and basic two-dimensional (2D) echo information at the preoperative visit can help detect the structural abnormalities associated with either its cause (left ventricular hypertrophy, LVH) or effect [atrial enlargement, pulmonary hypertension (PH) and RV dysfunction].

## History

Early in the disease, recognition of DD can be difficult, especially at the preoperative visit. However, clinical suspicion of DD should be heightened by a history of several cardiac and non-cardiac risk factors.

Cardiac risk factors include LVH, systemic hypertension, and coronary artery disease. Non-cardiac risk factors include increasing age, female sex, diabetes, and renal impairment.

As the disease progresses, breathlessness, reduced exercise tolerance, and orthopnoea ensue, even in the presence of a normal LV ejection fraction.

## Associated structural abnormalities

### Left ventricular hypertrophy

All patients with LVH, regardless of its cause, will have some degree of DD. Voltage criteria for LVH are satisfied when the combined ECG voltages of the V2 S wave and V5 R wave exceed 35 mm, but LVH is then quantified in the TTE parasternal long axis (PLAX) view.

### LA enlargement

LA enlargement indicates remodelling due to chronic atrial pressure/volume overload and in the absence of significant structural heart disease, this is likely to be caused by DD. A broad (>120 ms) and sometimes notched (or 'bifid') P-wave in lead II with deepening (>1 mm) of the negative P-wave segment in V1 is known as 'P mitrale'. LA diameter can be measured in the TTE PLAX view or 'eyeballed' in relation to the size of its neighbouring aortic root. LA area can be measured in the apical four-chamber (A4C) view.

### Pulmonary hypertension

In the absence of obvious structural heart or chronic lung disease, PH should invite suspicion of DD. A formal diagnosis of PH requires Doppler interrogation, but associated RV dilatation and/or systolic impairment seen in the 2D TTE A4C view can provide supportive evidence.

### Right atrial enlargement

Right atrial (RA) enlargement indicates chronic RV pressure or volume overload and in a patient without significant valvular or chronic lung disease, this is also likely to be the result of DD of either or both ventricles. An abnormally tall P-wave in lead II (>2.5 mm) and positive segment of the P-wave in V1 (>1.5 mm) is known as a 'P pulmonale'. RA size is best eyeballed or measured in the 2D TTE A4C view.

## Biomarkers

Brain natriuretic peptide (BNP) and its inactive N-terminal fragment pro-BNP (NTproBNP) are released by the ventricles during periods of excessive myofibrillar stretch associated with high filling pressure. Their half-lives are 20 min and 1–2 h, respectively, so both can be used to screen for heart failure in symptomatic patients with strong negative predictive value at thresholds of 35 pg $ml^{-1}$ for BNP and 125 pg $ml^{-1}$ for NTproBNP.[12] Elevated levels can be found in other conditions such as renal disease.

## Doppler assessment

In patients with sinus rhythm, conventional pulsed wave (PW) Doppler of trans-mitral bloodflow reveals a biphasic waveform. The initial (E) wave represents early, passive LV filling and the following (A) wave results from active atrial contraction (Fig. 1A and B). The relationship of these peak velocities is known as the E/A ratio and, varies according to LV diastolic properties and the pressure gradient between the LA and LV.

Previous American Society of Echocardiography (ASE) guidelines for the evaluation of LV diastolic function recommended a variety of PW measurements to grade severity of DD including E/A ratio, E wave deceleration time, and pulmonary venous flow analysis.[13] However, these measurements are challenging for the non-cardiologist to interpret, poorly validated, and often difficult to obtain in critically ill patients. Furthermore, all conventional Doppler measurements are strongly influenced by loading conditions that, as described previously, are highly variable in this patient group. In addition, pathology that alters normal trans-mitral flow, such as mitral valve disease or AF, will render interpretation of diastolic function inaccurate or impossible from these measurements. In April 2016, the ASE published updated, and considerably simplified, guidelines that recommend the use of just four variables: E/A ratio, LA volume index, tricuspid regurgitation velocity (a surrogate measure of PA pressure), and data derived from Tissue Doppler at the mitral annulus.[14]

## Tissue Doppler imaging assessment

Tissue Doppler imaging (TDI) uses a low-pass filter to exclude blood flow and measure tissue velocity, and it can be used to measure the velocity of longitudinal displacement of the LV basal wall as it relaxes and fills in diastole.

TDI at of the mitral annulus reveals a waveform that is similar in shape to the PW trans-mitral (inflow) E and A waves but, only in the opposite direction, and the corresponding peak velocities are known as e prime (e′) and a prime (a′) (Fig. 1C and D). Measurements should ideally be taken from both the septal and lateral annulus, and then averaged (Fig. 1).

If E is conceptualized as LA/LV driving pressure and e′ is the increase in LV volume, then E/e′ represents the relationship between LV pressure and volume change—or, known as elastance, with its reciprocal being compliance. Therefore, the higher E/e′ are the more likely there is to be higher the likelihood of DD. E/e′ has been shown to reflect LV filling pressure in patients with both preserved and reduced ejection fraction HFpEF and HFrEF.

TDI data are important because they are independent of loading conditions and are easy to obtain so they have considerable utility in critically ill patients. Furthermore, e′ can be measured in AF, when there is no A wave, and also in sinus tachycardia, when E and A waves are often fused, precluding conventional Doppler assessment. Importantly, accuracy of TDI can be affected by abnormalities of basal LV motion, for example, such as mitral annular disease or basal regional wall motion abnormalities.

The updated ASE guidelines have a greater emphasis on TDI to confirm or refute the presence of DD, particularly for patients with normal ejection fraction (Fig. 2), and this makes them much more applicable to patients in the perioperative and critical care setting.

## Management strategies

### Chronic heart failure

Disease-specific therapies aimed at the underlying pathogenic mechanisms of HFpEF have been largely unsuccessful so far.

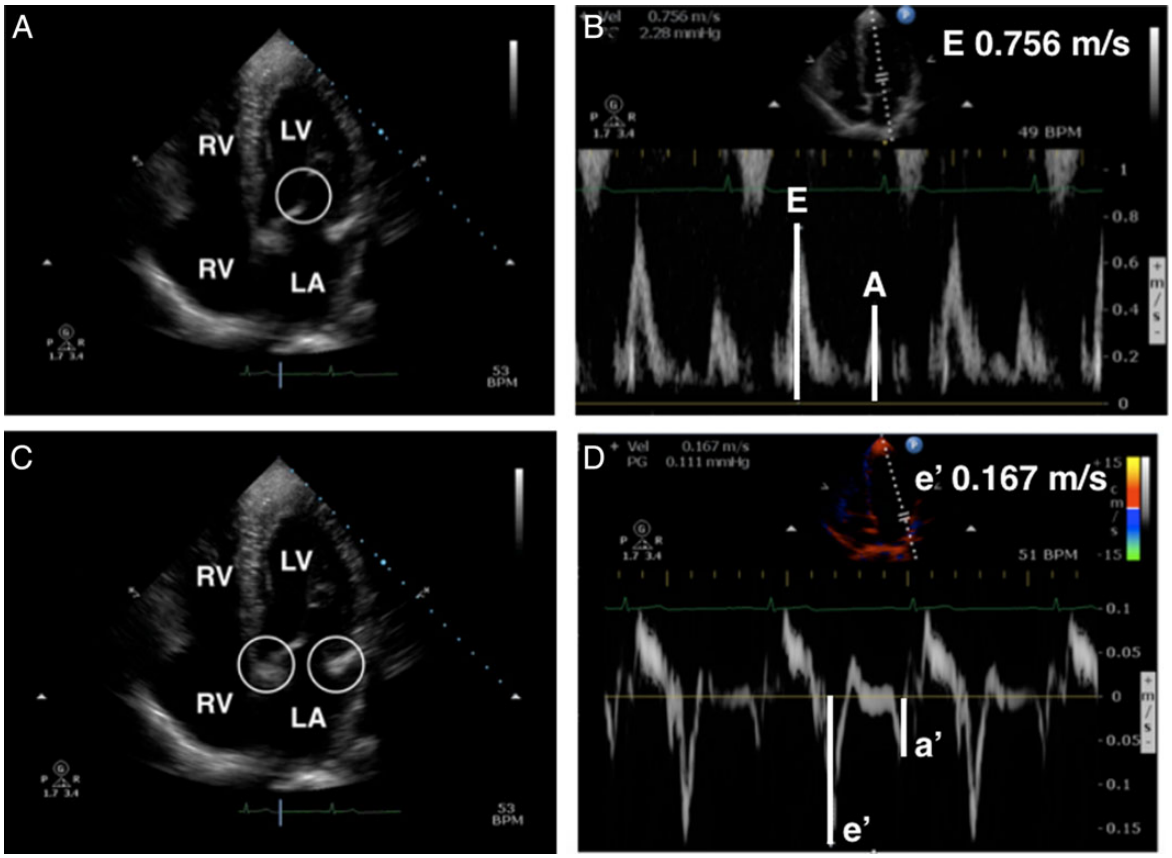


Fig 1 A4C and Doppler images required for measurement of E and e′. (A and B) The circle represents the required position for mitral inflow Doppler sampling (E) at the tip of the MV leaflets. (C and D) The circles represent the required position for TDI sampling (e′) at the medial and/or lateral MV annulus.

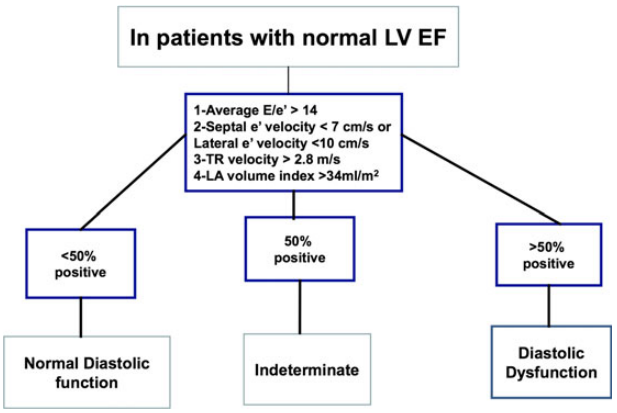


Fig 2 Algorithm for the diagnosis of LV diastolic dysfunction in subjects with normal left ventricular ejection fraction (reproduced with permission from Nagueh *et al* 2016[14]).

However, some pharmacological interventions are supported by smaller studies. Calcium channel blockers can improve exercise capacity and morbidity and spironolactone has been shown to reduce mortality but only in those with elevated serum natriuretic peptides.[15]

Recent clinical HFpEF guidelines have concentrated on pharmacological management of associated comorbidities, including systemic hypertension, fluid overload, AF, and tachycardia.[16]

In HRrEF, heart rate control is clearly important. Patients with EF<35% are currently established on maximal β-blockade and increasingly also the non-β-mediated, sino-atrial node-slowing drug ivabradine if their heart rate remains over 75 after maximal medical therapy, as advocated by NICE TA 267.

## Perioperative care

Preoperative cardiology consultation and optimization is recommended in the presence of uncontrolled heart failure, IHD, hypertension, or AF.

The extent and invasiveness of intraoperative cardiac monitoring should be decided on a case-by-case basis according to the severity of DD and surgical procedure. The therapeutic window for fluid management is notoriously small in DD patients and intraoperative fluid management should focus on minimizing LV filling pressure while avoiding inadequate preload and its associated low-output state. Goal-directed fluid restriction using cardiac output monitoring may be useful, but further studies are needed to evaluate this approach in patients with known DD.

Owing to the potential problems with extubation in patients with DD, a more gradual approach may be beneficial and, in severe cases, postoperative critical care admission should be considered.

## Acute heart failure

In acute heart failure (AHF), heart rate lowering should be done with caution, balanced against the risk of bradycardia and cardiogenic shock, as patients with DD are less able to increase their stroke volume and are more reliant on heart rate for modulation of their cardiac output. Rate control is the clinical priority in all patients with AF, but in those with severe DD, acute AF, and shock, return of sinus rhythm should be a key consideration.

Ventricular inotropy (contractility) and lusitropy (relaxability) are physiologically coupled. Both are affected by catecholamine-induced calcium transit out of and back into the sarcoplasmic reticulum. Also, any increase in inotropy will cause a reciprocal increase in lusitropy via increased elastic recoil. Inotropic drugs tend to improve lusitropy via these mechanisms, but this is not guaranteed.

The β-agonist dobutamine $\leq 5\ \mu g\ kg^{-1}\ min^{-1}$ has demonstrable lusitropic effect in normal hearts, but in heart failure patients, this is blunted and above this dose, lusitropy is non-existent.[17] Tachycardia and arrhythmias are common side-effects.

The β-independent phosphodiesterase inhibitor milrinone[18] and, more recently, the calcium-sensitizer levosimendan[19] have both demonstrated short-term improvement of diastolic parameters in patients with decompensated heart failure, but definite improvements in mortality have been harder to establish. These drugs may benefit DD patients in combination with established β-blockade.

Few studies have evaluated outcomes in treatments for AHF, a recent exception being the RELAX-AHF randomized, placebo-controlled trial, which evaluated a 48 h infusion of serelaxin, the recombinant form of human relaxin-2. Treatment was well tolerated and significantly improved dyspnoea, early AHF worsening, length of hospital stay, and 180 day cardiovascular and all-cause mortality equally in both HFpEF and HFrEF patients.[20] Where so many others have failed, serelaxin may succeed to become a DD treatment option of the future.

## Summary

DD is a common and frequently overlooked clinical entity in surgical and critical care patients. It has been associated with increased perioperative risk over a broad range of surgical specialities, so early recognition, and management of this condition are important if complications are to be avoided. New treatments are emerging for both chronic and AHF and the expansion of echocardiography with TDI into perioperative medicine and critical care has made recognition of DD much easier.

## Declaration of interest

None declared.

## MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

## References


1. Liu Y, Haddad T, Dwivedi G. Heart failure with preserved ejection fraction: current understanding and emerging concepts. *Curr Opin Cardiol* 2013; **28**: 187–96
2. Zile MR, Gottdiener JS, Hetzel SJ *et al*. Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. *Circulation* 2011; **124**: 2491–501
3. Bernard F, Denault A, Babin D *et al*. Diastolic dysfunction is predictive of difficult weaning from cardiopulmonary bypass. *Anesth Analg* 2001; **92**: 291–8
4. Lee EH, Yun SC, Chin JH *et al*. Prognostic implications of preoperative E/e' ratio in patients with off-pump coronary artery surgery. *Anesthesiology* 2012; **116**: 362–71
5. Salem R, Denault AY, Couture P *et al*. Left ventricular end-diastolic pressure is a predictor of mortality in cardiac surgery independently of left ventricular ejection fraction. *Br J Anaesth* 2006; **97**: 292–7
6. Matyal R, Hess PE, Subramaniam B *et al*. Perioperative diastolic dysfunction during vascular surgery and its association with postoperative outcome. *J Vasc Surg* 2009; **50**: 70–6
7. Cho DH, Park SM, Kim MN, Kim SA, Lim H, Shim WJ. Presence of preoperative diastolic dysfunction predicts postoperative pulmonary edema and cardiovascular complications in patients undergoing noncardiac surgery. *Echocardiography* 2014; **31**: 42–9
8. Flu WJ, van Kuijk JP, Hoeks SE *et al*. Prognostic implications of asymptomatic left ventricular dysfunction in patients undergoing vascular surgery. *Anesthesiology* 2010; **112**: 1316–24
9. Papanikolaou J, Makris D, Saranteas T *et al*. New insights into weaning from mechanical ventilation: left ventricular diastolic dysfunction is a key player. *Intensive Care Med* 2011; **37**: 1976–85
10. Moschietto S, Doyen D, Grech L, Dellamonica J, Hyvernat H, Bernardin G. Transthoracic echocardiography with Doppler tissue imaging predicts weaning failure from mechanical ventilation: evolution of the left ventricle relaxation rate during a spontaneous breathing trial is the key factor in weaning outcome. *Crit Care* 2012; **16**: R81
11. Sanfilippo F, Corredor C, Fletcher N *et al*. Diastolic dysfunction and mortality in septic patients: a systematic review and meta-analysis. *Intensive Care Med* 2015; **41**: 1004–13
12. McMurray JJ, Adamopoulos S, Anker SD *et al*. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012; **14**: 803–69
13. Nagueh SF, Appleton CP, Gillebert TC *et al*. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr* 2009; **10**: 165–93
14. Nagueh SF, Smiseth OA, Appleton CP *et al*. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An update from the American Society of Echocardiography and the European Association of cardiovascular imaging. *J Am Soc Echocardiogr* 2016; **29**: 277–314
15. Pitt B, Pfeffer MA, Assmann SF *et al*. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014; **370**: 1383–92
16. Writing Committee M, Yancy CW, Jessup M *et al*. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013; **128**: e240–327
17. Parker JD, Landzberg JS, Bittl JA, Mirsky I, Colucci WS. Effects of beta-adrenergic stimulation with dobutamine on isovolumic relaxation in the normal and failing human left ventricle. *Circulation* 1991; **84**: 1040–8
18. Monrad ES, McKay RG, Baim DS *et al*. Improvement in indexes of diastolic performance in patients with congestive heart failure treated with milrinone. *Circulation* 1984; **70**: 1030–7
19. Parissis JT, Panou F, Farmakis D *et al*. Effects of levosimendan on markers of left ventricular diastolic function and neurohormonal activation in patients with advanced heart failure. *Am J Cardiol* 2005; **96**: 423–6
20. Filippatos G, Teerlink JR, Farmakis D *et al*. Serelaxin in acute heart failure patients with preserved left ventricular ejection fraction: results from the RELAX-AHF trial. *European Heart Journal* 2014; **35**: 1041–50