Heart failure with preserved ejection fraction (HFpEF): Implications for the anesthesiologists

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Abstract
Heart failure (HF) is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood. American College of Cardiology Foundation / American Heart Association 2013 guidelines have classified HF into two categories: (i) HF with reduced (≤40%) ejection fraction (HFrEF) or systolic HF, and (ii) HF with preserved (≥50%) ejection fraction (HFpEF) or diastolic HF. Risk factors for HFpEF include age more than 70 years, female gender, hypertension, wide pulse pressure, diabetes mellitus, chronic renal insufficiency, left ventricular hypertrophy, atrial fibrillation, smoking, recent weight gain, and exercise intolerance. Cardiac catheterization and echocardiography are used for the confirmation of diagnosis of HFpEF. Intraoperatively, the hemodynamic goals in patients with HFpEF are avoidance of tachycardia, maintenance of sinus rhythm, and maintenance of higher than usual filling pressure. No specific treatment for HFpEF is established, and therapeutic options include an intravenous diuretic, a beta blocker or calcium channel blocker, a venodilator, and management of co-morbidities.

Keywords: Diastolic dysfunction, diastolic heart failure, heart failure, preserved ejection fraction

Introduction
Heart failure (HF) is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood.[1] It is the most common cause of hospital admission in patients over 65 years of age. American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) 2013 guidelines have classified HF into two categories: (i) HF with reduced (≤40%) ejection fraction (HFrEF) or systolic HF, and (ii) HF with preserved (≥50%) ejection fraction (HFpEF) or diastolic HF, wherein the diagnosis is one of excluding all potential noncardiac causes of HF.[1] HFpEF is further classified into two categories: HFpEF borderline (EF 41–49%), and HFpEF improved (EF >40%). The clinicians should differentiate HFpEF from HFrEF since the etiology, pathophysiology, and management of the two entities may differ considerably. Compared to HFrEF, patients with HFpEF are older, with higher prevalence of hypertension (HT) and atrial fibrillation (AF), and lower prevalence of coronary artery disease (CAD). The prevalence of HFpEF is not only high, but is rising at 1% per year. In the last two decades, the prevalence of HFpEF has risen from 38% to 54% of all HF cases. The 30-day, 1-year, 5-year mortality rates following hospitalization for HF are reported as high as 10.4%, 22%, and 42.3% respectively.[2]
achieve LV filling.\cite{31} Echocardiographically documented diastolic dysfunction has been reported to be associated with high morbidity and mortality in a variety of surgical procedures.\cite{4,7} Diastolic dysfunction has been described as the precursor of diastolic HF. It is important to distinguish diastolic dysfunction from diastolic HF. Diastolic dysfunction is a preclinical state in which abnormal relaxation or increased LV stiffness is compensated for by increasing LA pressure so that LV preload remains adequate (ACC/AHA stage A or B, asymptomatic).\cite{11} The progression to diastolic HF is characterized by signs and symptoms of HF (ACC/AHA stage C or D), and echocardiographic evidence of diastolic dysfunction. The time course of progression from diastolic dysfunction to diastolic HF may be variable, and is usually long in patients with HT and LV hypertrophy. Although, current guidelines (2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery)\cite{8} do not recognize diastolic dysfunction as a perioperative risk factor, recent meta-analysis based on 17 studies (\(N = 3876\)) by Fayad et al., has concluded with moderate certainty that it is an independent risk factor for adverse cardiovascular outcome after noncardiac surgery.\cite{9} Patients with clinical HF or a history of HF are considered at higher risk for developing perioperative complications, and most indices of cardiac risk consider HF as an independent prognostic marker. Active HF carries a higher mortality than CAD, particularly when associated with severe LV dysfunction. Although, there are limited data on perioperative risk stratification related to diastolic dysfunction, a higher rate of major adverse cardiac events, prolonged length of stay, and higher rates of postoperative HF have been reported with diastolic dysfunction.\cite{8}

**Impact of Aging on Diastolic Function**

Several changes in cardiac structure and function occur with aging that contribute to diastolic dysfunction. On the structural level, there is a decrease in myocyte number (due to apoptosis and cell necrosis), an increase in myocyte size (hypertrophy), and an increase in the amount of connective tissue matrix.\cite{10} The myocytes are replaced with fibroblasts, which produce collagen, causing interstitial fibrosis, and stiffening of the heart. The stiffer and less compliant ventricle affects diastolic relaxation as well as systolic contraction. The two main consequences of age-related arterial stiffening are decreased aortic distensibility and increased pulse wave velocity. The loss of distensibility during systole results in a higher systolic pressure, and less stored energy to augment forward flow during diastole manifesting as lower diastolic pressure. The resultant increased pulse pressure is an established risk factor for most cardiovascular (CV) events.

**Etiology and Pathophysiology of HFpEF**

The risk factors for HFpEF include age >70 years, female gender, HT, wide pulse pressure (>60 mmHg), diabetes mellitus, chronic renal insufficiency, LV hypertrophy, AF, smoking, recent weight gain, and exercise intolerance. HFpEF can result either from an impairment of LV compliance (passive mechanism) or from an alteration in LV relaxation (active process)\cite{12} [Table 1]. Structural modifications of the myocardium such as hypertrophy and fibrosis, influence the passive/late phase of diastole, whereas functional factors such as ischemia and sepsis, adversely affect the active/relaxation phase of diastole.\cite{11} In LV diastolic dysfunction, the diastolic portion of the pressure-volume loop (compliance curve) is shifted to the left and upward. Consequently, for a given LV end diastolic volume (LVEDV), LV end diastolic pressure (LVEDP) is increased. The process of transition between contraction and relaxation (systole and diastole) corresponds to the dissociation of actin-myosin cross-bridges that follows the lowering of the intracellular calcium concentration. Detachment of the actin-myosin cross-bridges, activation of the ATPase induced calcium sequestration into the sarcoplasmatic reticulum, sodium/calcium exchanger-induced extrusion of calcium from the cytoplasm, release of calcium from troponin C, and return of the sarcomere to its resting length are all energy-consuming processes. Since myocardial relaxation or lusitropy is an energy consuming process, it is adversely affected by ischemia and other variables, resulting in diastolic dysfunction.\cite{12}

**Diagnosis of Diastolic Dysfunction**

The evaluation of patients with HF is based on clinical triad of history, physical examination, and chest X-ray. The role of biomarkers to predict the onset of future HF, to identify its

**Table 1: Causes of diastolic heart failure**

| Myocardial                     |
|-------------------------------|
| Impaired relaxation           |
| Epicardial or microvascular ischemia |
| Myocyte hypertrophy, Hypertension |
| Cardiomyopathies              |
| Aging                         |
| Hypothyroidism                |
| Increased passive stiffness   |
| Diffuse fibrosis              |
| Post-infarct scarring         |
| Myocyte hypertrophy Infiltrative (eg amyloidosis, hemochromatosis, Fabry’s disease) |
| Endocardial                   |
| Fibroelastosis                |
| Mitral or tricuspid stenosis  |
| Epicardial/Pericardial: Pericardial constriction/Pericardial tamponade |
| Coronary microcirculation     |
| Capillary compression         |
| Venous engorgement            |
| Others: Volume overload/Extrinsic compression by tumor |

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presence, to risk stratify patients, and to guide therapy has been recently investigated. The patients at risk of developing HF, and those with clinical suspicion of having HF must be investigated in detail.

The natriuretic peptides are considered gold standard for the diagnosis of HF. The role of B natriuretic peptide (BNP), N-terminal pro-BNP (NT-proBNP), and troponin is well established for the diagnosis and prognosis of HF. In normal healthy individuals, BNP levels are less than 10 pg/mL. A BNP value of >100 pg/mL has a sensitivity of 90%, and a specificity of 76% for the diagnosis of HF. The patients with HFpEF generally have a little lower value and lower sensitivity for BNP and NT-proBNP, but their overall values are acceptable. Newer biomarkers such as mid-regional pro-atrial natriuretic peptide, mid-regional pro-adrenomedullin, growth differentiation factor-15, and galectin-3 have shown potential in initial studies for their role in prognosis of HF.

Cardiac catheterization and echocardiography are the mainstay methods used for the confirmation of diagnosis of diastolic dysfunction. Catheterization data show an increase in LVEDP (>16 mmHg) with preserved systolic function and normal ventricular volumes.

Echocardiographically, diastolic dysfunction can be assessed by following methods:
(i) Mitral valve inflow pattern with pulse-wave Doppler
(ii) Mitral annular tissue Doppler imaging (TDI)
(iii) Pulmonary venous inflow by pulse-wave Doppler
(iv) Transmitral flow propagation velocity by color flow Doppler and M-mode
(v) Additional parameters: LA volume index, tricuspid regurgitant systolic jet velocity, use of Valsalva maneuver for dynamic assessment of reversal mitral inflow velocity, and isovolumic relaxation time (IVRT).

Mitral inflow patterns can be categorized into one of four distinct categories.[3] The normal pattern consists of two peaks (E and A) in the Doppler diastolic filling profile that occur in response to the pressure gradient between the LA and LV. “E” wave occurs early in diastole following opening of mitral valve when LV pressure falls below LA pressure, and “A” wave occurs late in diastole when atrial contraction increases LA pressure above LV pressure. Normally, the E/A ratio in young subjects is greater than one, and a ratio of 0.75 may be considered normal above 75 years of age. The normal deceleration time (DT) of E wave is 160–240 msec. A shortened DT reliably predicts poor LV compliance and an advanced stage of diastolic dysfunction.[13] The first pattern of altered LV filling is termed “delayed relaxation”.

In this pattern, there is reduced peak rate and amount of early filling (due to decreased LA-LV pressure gradient), and atrial filling is enhanced, resulting in a reversed E/A ratio (<1). This pattern can be seen in older persons and patients with LV hypertrophy and CAD. The “pseudo-normalization” pattern, with E/A ratio greater than one, results from an increase in LA pressure that compensates for the slow LV relaxation and restores early diastolic LV pressure gradient to the baseline level. LA volume increases with progressive worsening of diastolic function. It can be differentiated from normal pattern by reducing the preload using nitroglycerin or with a Valsalva maneuver, potentially uncovering an E<A pattern. Another way to circumvent the preload dependency of transmitral Doppler is the use of myocardial (or annular) velocities by TDI. In the “restrictive” pattern, early filling is increased abnormally, and as a result of diminished atrial filling (reduced atrial contractility), the E/A ratio is often greater than two.

In clinical situations of changing preload, heart rate and rhythm disturbances, TDI is more sensitive tool in the assessment of diastolic function, compared to Doppler diastolic filling pattern and pulmonary venous waveform pattern. In this modality, myocardial velocity is measured as e’ and a’, and is preload independent. The diastolic dysfunction is verified if e’ is < 10 cm/s (<50 years of age) or <8 cm/s (>50 years), or e’/a’ ratio is < 1 after Valsalva. Valsalva maneuver distinguishes normal from pseudonormal filling patterns. A decrease of E/A ratio of >50% or an increase in A-wave velocity during the maneuver, not caused by E and A fusion, are highly specific for increased LV filling pressures.

Another echocardiographic method to diagnose diastolic dysfunction, is the ratio of transmitral E wave velocity to mitral annular velocity, i.e., E/e’ ratio.[3] The criteria recommended in a recent update by the American Society of Echocardiography for diagnosing diastolic dysfunction are LA volume index >34 mL/m², tricuspid jet velocity >2.8 m/s, E/e’ > 14, septal e’ velocity <7 cm/s, and lateral e’ velocity <10 cm/s.[14] LV diastolic function is normal if more than half of the available variables do not meet the cut-off values for identifying abnormal function. LV diastolic dysfunction is present if more than half of the available parameters meet these cut off values. The study is inconclusive if half of the parameters do not meet the cut off values.[14]

**Perioperative Implications**

The perioperative management of patients with HFpEF can be challenging due to CV changes that occur with the disease
process and old age. A history of HF, independent of CAD, is associated with increased morbidity and mortality after noncardiac surgery.\[15\] A thorough preoperative assessment is required in order to risk stratify these patients. This includes assessment of the functional capacity as individuals with <4 metabolic equivalents functional capacity are at an increased risk for perioperative complications. The laboratory tests should include routine blood test to exclude anemia, electrolyte disturbance, and tests for renal/hepatic/thyroid functions. Chest X-ray may reveal cardiomegaly, pleural effusion, prominent upper lobe veins, and alveolar edema. Noninvasive and invasive preoperative cardiac testing should not necessarily be performed unless results will affect patient management. Patients with severe or symptomatic cardiovascular disease and/or active cardiac conditions should undergo evaluation by a cardiologist and treatment before noncardiac surgery. Specific beta-blockers used in HF management such as bisoprolol, carvedilol, or metoprolol, should be continued, including on the day of surgery. Angiotensin converting enzyme inhibitors or angiotensin receptor blockers are continued if patient is not hypotensive; however, there is risk of hypotension particularly during induction of anesthesia.

Intraoperatively, the hemodynamic goals in patients with HFpEF are avoidance of tachycardia (to increase duration of diastole), maintenance of sinus rhythm (atrial kick is lost with AF), and maintenance of higher than usual filling pressure (to fill poorly compliant LV) in the absence of decompensated HF. In decompensated HF, the goal would be to prevent pulmonary congestion. Hence, careful titration of fluids is necessary. Tachycardia precipitated by events such as intubation, surgical stimulus, hypovolemia, hypercapnia, postoperative pain, etc., should be avoided/treated aggressively. The patients with diastolic dysfunction are predisposed to greater hemodynamic instability and greater sensitivity to volume status.\[16\] The possible mechanisms include, the higher resting sympathetic tone and an altered beta receptor sensitivity. Loss of the sympathetic tone with the induction of general or neuraxial anesthesia often results in hypotension. These patients often have depleted intravascular volume because of more frequent use of diuretics, and age-related changes in renal function. As they are severely dependent on preload to fill the LV, the reduction in preload induced by anesthesia may result in profound hypotension. Thirdly, the direct effects of IV and volatile anesthetics can impair cardiac inotropy and lusitropy, and produce both arterial and venous vasodilatation.

For elderly patients with known diastolic dysfunction, placing an intra-arterial cannula for invasive blood pressure (BP) measurement and frequent blood sampling is based on the same considerations as applied in the younger patients, and depends on the experience and local practice. There are no recommendations on the routine use of invasive monitors such as central venous catheter, pulmonary artery catheter, or transesophageal echocardiography (TEE) for intraoperative monitoring. Perioperative TEE is indicated to determine the cause of unexplained or life-threatening hemodynamic instability when equipment and expertise are available.\[8\]

Induction of anesthesia should be accomplished in a smooth and controlled manner. An alteration in filling pressure in patients with diastolic dysfunction can result from positive pressure ventilation, reduced venous return, and impaired atrial contractility.\[17\] The induction dose of most agents is decreased by 30–50%, and induction may be prolonged due to a slow circulation time. There is limited clinical data on the effect of anesthetic agents on diastolic function. A comparison among isoflurane, desflurane, and sevoflurane found no significant effect on diastolic function in healthy volunteers as well as in those with diastolic dysfunction.\[18\] Among intravenous anesthetic agents, barbiturates, and ketamine exert similar effects on diastolic function by inhibiting sarcolemmal transport of calcium ions, and ketamine, in addition can reduce chamber compliance. Etomidate, propofol, morphine, midazolam, and remifentanil do not appear to have any effect on diastolic performance.\[19\] It is also important to prevent hypoxemia and hypercarbia, as these patients are prone to pulmonary HT. It is reasonable to maintain the BP within 10–20% of the baseline value. Diastolic BP must be maintained, as low diastolic BP can lead to myocardial ischemia. An attempt should be made to keep the pulse pressure less than the diastolic BP. The potential beneficial effects of a regional technique (afterload reduction, postoperative analgesia, reduced stress response to surgery) must be balanced on an individual basis against the risk of hypotension. Hemodynamic management of acute decompensated HF includes use of vasodilators/inodilators (milrinone and levosimendan) to decrease LVEDP and myocardial oxygen consumption.

In the early postoperative period, hypoxemia and/or AF are among the most commonly encountered complications. Perioperative AF has been shown to precipitate HF in patients with diastolic dysfunction. The catheter ablation of AF improves diastolic function.\[20\] In addition, when vascular sympathetic tone is restored upon emergence from general anesthesia or resolution of neuraxial blockade, the noncompliant heart may not be able to tolerate the increased shift in central blood volume thus resulting in decompensated HF. Low dose nitroglycerin (e.g. 0.5 mcg/kg/min), may prevent this from occurring due to its beneficial effects on pulmonary vasculature.
Nonetheless, the assessment of the postoperative patient with suspected HF should include an electrocardiogram (for ischemia, AF) and echocardiography (for volume status, diastolic, and systolic ventricular function).

No specific treatment for HFPpEF is established, and therapeutic options include an intravenous diuretic, a beta-blocker or calcium-channel blocker, a venodilator such as nitroglycerin, and management of co-morbidities. General guidelines for patients with HFPpEF include regular moderate activity, aerobic exercises, smoking cessation, weight reduction, fluid restriction (up to 1.5–2 L/day), and sodium restriction.

Conclusion

As the number of elderly patients continues to grow, the anesthesiologist will more frequently encounter patients with diastolic dysfunction. Cardiovascular changes that occur in these patients, place them at a high risk of perioperative morbidity and mortality. The anesthesiologist should understand the age-related cardiovascular changes, the pathophysiology of the disease, and the appropriate perioperative management.

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Conflicts of interest

There are no conflicts of interest.

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