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Heart Failure With Preserved Ejection Fraction: A Perioperative Review

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HEART FAILURE (HF) with preserved ejection fraction (HFpEF) presents significant challenges for anesthesiologists. Nearly 50% of patients presenting with HF have HFpEF, defined as having clinical HF with a left ventricular ejection fraction (LVEF) >50% and abnormal left ventricular diastolic dysfunction (LVDD).^{1–6} Even though HFpEF is a strong predictor of negative postoperative outcomes, it often is difficult to diagnose and the management strategies are unclear. Although there have been specific articles published with regard to the echocardiography descriptors, diagnosis, and relationship of LVDD with HF, the authors believed it was timely to present a review article for clinicians on the subject of perioperative HFpEF. This article reviews what is known about the pathogenesis, diagnosis, management options, and implications of HFpEF in the perioperative arena.

Definitions: HFpEF, HF With Reduced Ejection Fraction, and LVDD

HF in general is defined as the inability of the heart to function sufficiently to meet the metabolic demands of the body. The diagnosis applies to both phenotypes of HF—HF with reduced ejection fraction (HFrEF) and HFpEF. Both types of HF have similar signs, symptoms, morbidity, and mortality; however, the pathophysiology underlying HFpEF is ill-defined because no single abnormality exists that explains the mechanism of disease. The presence of HF symptoms and the preservation of systolic function often lead to HFpEF, which, until recently, has been referred to as “diastolic HF”. Although the pathologic underpinnings may seem ill-defined, one common attribute in HFpEF is diastolic filling abnormalities of the left ventricle. LVDD is characterized by a stiff left ventricle, with decreased compliance and impaired relaxation, which leads to increased end-diastolic pressure.

Prevalence and Incidence of HFpEF

Due to rapid aging and a longer life expectancy of both sexes, the incidence of HFpEF is growing in the general population. An increasing presence of comorbidities associated with aging is key to understanding the increase in HFpEF prevalence. HFpEF patients generally are older, more hypertensive, obese, diabetic, and likely to have atrial fibrillation compared with patients with HFrEF.^{1,7} A follow-up to the Prevention of Renal and Vascular Endstage

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Disease (PREVEND) study that included 8,592 patients demonstrated the association between age, history of atrial fibrillation, and prevalence of HFpEF.⁸ This community-based cohort trial identified all cases of new-onset HF during 11 years of follow-up and identified risk factors for HFrEF and HFpEF. The age and sex-specific prevalence of HFpEF was 1% in women and 0% in men between ages 25 to 49 years, but increased to 8% to 10% in women and 4% to 6% in men ages 80 years.⁸ This trend toward increased rates of HFpEF with increasing age was supported in other studies, including one that demonstrated that up to 59% of all patients >85 years had HFpEF.^{9,10} Annual mortality ranges from 10% to 30%, with nearly 60% of HFpEF patients dying from cardiovascular causes.⁷ However, noncardiovascular deaths constitute a higher proportion of cause of death in HFpEF compared with HFrEF.⁷

Pathophysiology of HFpEF

HFpEF, like other clinical presentations of HF, is a syndrome comprising various underlying etiologies and comorbid conditions that lead to the presence of both symptoms and signs consistent with the diagnosis.⁹ The cause of HFpEF is multifactorial, but the consistent underlying aspects are similar: a proinflammatory state perpetuated by one or more of several disease states leads to inflammation within the coronary microvasculature and its endothelium. Endothelial dysfunction leads to reductions in available nitric oxide and activity of protein kinase G (PKG). The reduced activity of PKG leads to dysregulation of prohypertrophic pathways and leads to overphosphorylation of titin.^{3,10–13} This causes stiffening of the myocardium and interstitial fibrosis that contribute to the LVDD of the myocardium and results in the presentation of clinical symptoms. The proinflammatory state is attributed to increased central autonomic tone via a central chemoreflex pathway that is responsible for causing diastolic dysfunction and imbalance between the sympathetic and parasympathetic setpoint.¹⁴ Pressure-volume loops show an upward or leftward shift of the LV end-systolic pressure volume relationship, reflecting increased end-systolic myocardial stiffness. Patients with HFpEF typically have normal LV chamber size and greater wall thickness (concentric remodeling), resulting in lower brain natriuretic peptide (BNP) levels.^{1,4} A key determinant of BNP release is diastolic wall stress, thus these levels often are normal in patients with HFpEF. Although LVEF is normal at rest in HFpEF, it does not increase appropriately during stress.¹⁵ This decreased LV contractility may be related to abnormalities in calcium handling, beta-adrenergic signaling, myocardial energetics, or tissue perfusion reserve.¹ Ventricular and vascular stiffening are increased, which lead to an increase in blood pressure. This strains the heart and further impairs diastolic relaxation, thus leading to dramatic increases in filling pressures during stress and exercise.⁴ This also leads to larger-than-expected decreases in systolic blood pressure with decreases in volume. See Table 1 for additional information.

Preclinical HFpEF: LVDD With a Preserved EF

LVDD, a requirement for the clinical diagnosis of HFpEF, has been associated with poor outcomes in both cardiac and noncardiac surgery.^{16–23} The presence of both preoperative LVDD on transthoracic echocardiography (TTE) and the identification of LVDD intraoperatively are predictors of worse perioperative outcomes.²³ There were several studies

whose cohort included normal EF and significant LVDD—at least grade II; however, more typically grade-III diastolic dysfunction—which has been referred to as “preclinical HFpEF”. It is important to note, however, that these patients were not classified as having HF; thus, the majority of literature on clinical studies in the perioperative arena is on the preclinical findings of HFpEF. A summary of these studies are provided in Table 2. Although inhaled anesthetic gases and other anesthetic agents that reduce afterload have a beneficial effect on diastolic function, the impact of anesthetics, surgical manipulation, and hemodynamic instability on changes in perioperative LVDD and how this relates to HFpEF need further clarification and study.

Association with Mortality and Major Adverse Cardiac Events

Kaw et al performed a meta-analysis on 12 prospective and retrospective clinical studies examining preoperative LVDD and mortality and major adverse cardiac events (MACE) in cardiac surgery perioperatively.²¹ A subgroup analysis was performed on patients with LVDD, comparing patients with normal LVEF, defined as >40%, and patients with reduced LVEF (<40%). Mortality was shown to increase with preoperative grade-III LVDD.²¹ Dalén et al studied 41,906 patients undergoing coronary artery bypass grafting (CABG) and found that all-cause mortality was statistically higher long term for patients with HF independent of EF.²⁷ Increasing grade of LVDD also was predictive of a greater incidence of adverse events, including stroke, renal failure, prolonged ventilation, deep sternal wound infection, or redo surgery.^{17,19} Intraoperatively, LVDD has been shown to predict increased difficulty in weaning from cardiopulmonary bypass.^{24,30} Both studies observed an association between moderate and severe LVDD, with difficulty in separating from cardiopulmonary bypass and hemodynamic instability requiring more inotropic and mechanical support. However, LVEF was not used in the stratification of these investigations, thus larger studies are necessary to verify whether preclinical HFpEF increases perioperative hemodynamic instability and, specifically, MACE. Investigators in many of the studies defined MACE differently, including myocardial ischemia, arrhythmias, cardiovascular death, clinical pulmonary edema, and HF; they also included various LVDD measurement techniques and definition of parameters.^{19,26,29,31}

Preoperative Risk Evaluation and HFpEF

Currently, neither the Society of Thoracic Surgeons risk score nor the European System for Cardiac Operative Risk Evaluation (EuroSCORE) uses preclinical signs of HFpEF to risk-assess patients preoperatively. Patients who report symptoms consistent with congestive HF within 2 weeks before a procedure are risk stratified as part of the Society of Thoracic Surgeons risk score, but LVDD is not part of that assessment. Afilalo et al²³ and Sastry et al¹⁶ found that preoperative LVDD was predictive of post-CABG outcomes, including in-hospital mortality and major morbidity. This poses the question of whether screening patients with preclinical signs of HFpEF improves risk stratification of surgical patients.

Perioperative LVDD has a significant association with postoperative congestive HF and pulmonary edema, both of which may be clinical signs of HFpEF. Cho et al evaluated perioperative LVDD in 692 patients undergoing low-to-moderate risk noncardiac surgery,

including 166 with pulmonary edema postoperatively. Of those with edema, preoperative TTE showing an E/e' ratio >15 increased the risk of postoperative pulmonary edema and MACE.²⁹ Increases in pulmonary edema and longer intensive care unit and hospital stays also have been associated with an E/e' ratio >12 .²⁸ Matyal et al found a significantly longer hospitalization in patients with perioperative LVDD, including longer hospitalization within the HFpEF patient subgroup.¹⁷

Diagnosis of HFpEF

The clinical diagnosis of HF requires the presence of symptoms consistent with those listed in Table 3.³² Differentiation of noncardiac from cardiac causes can be difficult, especially when the clinical symptoms are vague and nondescript, as HF patients commonly report to their anesthesiologist. Shortness of breath, exercise intolerance, and fatigue can have multiple causes, but these symptoms along with findings consistent with signs of HFpEF lead to the diagnosis. These symptoms occur because of physiologic alterations in cardiac function, specifically diastolic filling and the diastolic pressures required for ventricular filling.

Diagnostic Criteria for HFpEF

Diagnostic criteria for HFpEF are important because the literature has varied in the description of HFpEF and in the inclusion criteria of studies published in the last decade. Guidelines by both the American College of Cardiologists and American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) provide direction with specific diagnostic criteria. The ACC/AHA use the following diagnostic criteria: (1) the presence of HF symptoms in the setting of a preserved EF, (2) LVEF $\geq 50\%$, and (3) abnormal LV diastolic function.³³ This is referred to by the ACC/AHA as “diastolic HF”, requiring the identification of LVDD and the exclusion of other noncardiac causes of the patient’s reported symptoms. In the perioperative period the identification of symptoms consistent with HF is crucial to making the appropriate diagnosis because symptomatic LVDD is associated with increased cardiac events and associated mortality. Specifically examining HFpEF and CABG, the HFpEF and HFrEF groups reached similar mortality rates at 5-year follow-up, with a 33% all-cause mortality compared with 15% in the normal LV systolic and diastolic group.³¹ It is recommended that a comprehensive Doppler evaluation be completed during echocardiography, especially in the setting of known or suspected HF.¹⁵ Frequently reported symptoms of HF include dyspnea, exercise intolerance, and fluid retention.^{6,34} These clinical findings are summarized in Table 3.

The ACC/AHA guidelines are nonspecific and emphasize clinical history but lack of other identifiable causes of HF to make the diagnosis. However, the ESC guidelines for HF include more defined diagnostic criteria for HFpEF. The ESC definition stresses the importance of appropriate history gathering when diagnosing HFpEF. The diagnosis, if present, should be made preoperatively because HF is a risk factor for poor outcomes after noncardiac surgery.³⁵ Population studies have demonstrated a significant prevalence of LVDD among the general population; therefore, the findings of diastolic filling

abnormalities alone should not portend a diagnosis of HFpEF.³⁶ It is yet to be determined whether LVDD is presymptomatic HF in the setting of preserved systolic function.³⁵

The ESC guidelines focus on the following main points: (1) symptoms of HF, (2) LVEF 50%, (3) LV end-diastolic volume $<97 \text{ mL/m}^2$, and (4) the presence of LVDD.³⁵ The diagnosis of LVDD can be difficult, and there are various suggested diagnostic methods, including Doppler mitral inflow velocities and mitral inflow velocity ratios between the early (E-wave) and atrial (A-wave) diastolic filling periods. The ratio of the E-wave to the tissue Doppler velocities of the mitral annulus (e') can be used to suggest elevated diastolic filling pressures.³⁵ In addition, the presence of enlarged left atrial volume index and elevations in BNP or N-terminal pro-BNP (NTproBNP) can indicate LVDD and elevated LV filling pressures. To this point, the ESC's recommendations do not specifically indicate the preferred method of determining LVDD but recommend that the evaluation performed should focus on evidence of structural and Doppler findings that confirm the presence of LVDD is consistent with the diagnosis of HFpEF. A summary of both the ACC/AHA and the ESC definitions and diagnostic criteria are presented in Table 4.

Perioperative Evaluation of Diastolic Function

Guidelines by the American Society of Echocardiography and investigations conducted during the perioperative setting can guide the anesthesiologist on how best to diagnose the presence of LVDD.^{37,38} Specific to diastolic function and its evaluation, the literature is predominantly based on TTE findings.^{38,39} The underlying cause of impairment in diastolic relaxation can be linked to abnormal calcium handling.⁴⁰ Although the anesthetized patient has been shown to have preserved myocardial performance measures through maintenance of ventriculoarterial coupling when exposed to both volatile and intravenous anesthetic agents,^{41,42} abnormal vascular tone from external or native sympathetic-driven activation can lead to elevations in left ventricular end-diastolic pressure and left atrial pressure.⁴³ To further complicate the difficulty associated with the performance of intraoperative evaluation of LVDD, there are data to suggest that abnormal calcium homeostasis in the anesthetized state may affect the diastolic filling of the left ventricle.⁴⁴ The major measurements of diastolic function are (1) mitral inflow velocities and ratios, (2) tissue Doppler velocities and the ratio of E-wave velocities to e' velocities, and (3) the pattern of venous flow into the left atrium from the pulmonary veins.^{38,39,45} A revised perioperative echocardiographic approach to quantification of diastolic function was published by Mahmood et al in 2012.⁴⁶ The significance of this work was to dichotomize the perioperative state into reduced compliance/ high filling pressures (LVDD) and normal compliance using the lateral tissue Doppler velocity in which tissue Doppler imaging was either $\geq 10 \text{ cm/sec}$ or $<10 \text{ cm/sec}$.⁴⁷ One limitation of this approach was that it required the performance of TTE to accurately measure the indexed size of the left atrium.

In regard to these prior studies, the authors suggest that the performance of lateral tissue Doppler measurements, dividing the perioperative state into $\geq 10 \text{ cm/sec}$ and $<10 \text{ cm/sec}$ and determining E/ e' ratios and E/A ratios, is helpful in the classification and diagnosis of LVDD.³⁹ Clearly, the direct application of the TTE-derived guidelines does not allow for accurate classification of many perioperative patients.³⁹ Using these studies to guide clinical

practice and the criteria summarized in Table 5, the authors classify patients into the following groups: normal, impaired relaxation with normal-range LV end-diastolic filling pressures, and LVDD with elevated diastolic filling pressures.⁴⁷

The diagnostic criteria, as seen on echocardiography, can be demonstrated through routine two-dimensional analysis and measurements and using a comprehensive Doppler evaluation approach to measuring tissue and blood Doppler-derived flow. In an example of HFpEF, Figure 1 demonstrates normal systolic function in the form of preserved systolic function. Figure 2 demonstrates the common Doppler findings pertaining to tissue Doppler velocities, mitral inflow velocities, and pulmonary venous flow consistent with LVDD and elevated left ventricular end-diastolic pressure, requisite findings of HFpEF. These images, in conjunction with patient history consistent with HF symptoms, demonstrate the 4 diagnostic criteria as established by the ESC.

Testing in the Perioperative Setting

In addition to echocardiographic assessments, which can be performed in the preoperative or intraoperative period, other assessments are suggested to be beneficial in the assessment of HF. These assessments include laboratory analysis of biomarkers specific to elevated intracardiac filling pressures, echocardiography stress testing, cardiac magnetic resonance imaging, and right-and left-heart catheterization.^{35,48} During the perioperative period, some of these studies such as magnetic resonance imaging or heart catheterization have limited utility due to time constraints. With appropriate lead time on the identification of HF symptoms, routine TTE for anatomic and functional analysis is considered a class-I indication in the ACC/AHA and ESC guidelines.^{34,35} If the TTE study reveals normal systolic and diastolic function but the clinical suspicion is high, the performance of a diastolic stress test may elucidate the presence of HFpEF in patients who report exercise intolerance but do not have abnormal LVDD on resting echocardiography.^{49–51} Recommendations for diastolic stress testing should occur when resting evaluation of LV diastolic function is indeterminate. Exercise is preferred over dobutamine stress testing and is considered positive for stress-induced diastolic dysfunction if all of the 3 following measurements are present: average $E/e' > 14$, peak tricuspid regurgitation velocity (TR) > 2.8 m/sec, and septal $e' < 7$ cm/sec.⁵¹ Increases of $E/e' > 14$ have a 90% sensitivity and 71% sensitivity for HFpEF and suggest that exercise diastolic stress testing may rule out HFpEF.⁵² When requesting the performance of this study specifically for diastolic evaluation, it is critical to appropriately request the specific information from the stress test because diastolic stress evaluation is not routine at all centers.

Biomarker testing is another potentially helpful diagnostic test during the perioperative period.⁴⁹ Although there are new potential markers being discovered (IGFBP7, copeptin, MR-proADM, ST2, and galectin-3), the suspicion of HF and elevated filling pressures can be further supported through BNP or NTproBNP testing.⁵³ Elevated biomarkers can be useful in both the diagnosis and after medical interventions for improved diastolic filling. Measurement of BNP or NTproBNP in the setting of clinical uncertainty or after treatment to assess changes is considered a class-I indication in the ACC/AHA guidelines and a class-IIa indication in the ESC guidelines.^{34,35} In the preoperative evaluation, assessment of HF

with BNP may prove useful in risk stratification for these patients because HF itself is an independent risk for perioperative cardiovascular morbidity and mortality. The ESC guidelines indicate that BNP ≥ 200 pg/mL or NTproBNP ≥ 220 pg/mL is consistent with HF.⁵ Even though using BNP and NTproBNP can be helpful, there are instances in which the BNP result can be inaccurate. In the setting of atrial fibrillation, the level of BNP can be elevated in the absence of significant LVDD and elevated diastolic filling pressures.^{54,55} Other signs of elevated diastolic filling pressures should be used to confirm HFpEF, which can be difficult to determine in the presence of atrial fibrillation as well. Because atrial fibrillation will result in the loss of an A-wave on transmitral Doppler inflow, other methods such as E/e' and pulmonary venous flow patterns should be used to assess diastolic function.

Obesity is a commonly associated comorbid condition with HFpEF, and it is speculated that increased body mass itself is an additional contributing factor to the symptoms experienced when obesity and HFpEF coexist.^{6,56} A confounder in the evaluation of an obese patient with suspected HFpEF is that obesity is associated with lower-than-expected BNP levels for the degree of diastolic pressure elevation and HF symptoms.^{15,57,58} BNP results that do not reach the cutoff for HFpEF in very obese patients, or in some patients without baseline values, should not rule out the presence of diastolic HF if clinical suspicions are high.

Perioperative Evaluation Strategy

The diagnosis of HF first requires the suspicion of HF to elicit historic symptoms consistent with the diagnosis. In the perioperative period the preanesthesia evaluation already is well positioned to be used to discover these symptoms because dyspnea, exercise tolerance, respiratory symptoms, and chest pain commonly are assessed.⁵⁹ When patients report poor exercise tolerance, dyspnea with exertion, or increasing fluid retention, the performance of a resting TTE is an important first step to determine LV systolic and diastolic function. When these studies are ambiguous, additional testing, such as BNP or diastolic stress testing, can be helpful. Diastolic stress testing is recommended when resting evaluation of LV diastolic function is indeterminate.

When performed with the patient under general anesthesia, Doppler echocardiography filling parameters should emphasize the lateral mitral annular tissue Doppler velocity because that is the most load-independent measure in the diastolic evaluation, and even though tissue Doppler is not completely load-independent, it is recognized as the least affected parameter with changes in preload.³⁸ The presence of abnormal diastolic filling patterns assists the authors in perioperative management by augmenting the allowable fluid administration and supports the early use of inotropic support for alterations in hemodynamics as opposed to additional fluid administration to avoid the consequences of pulmonary edema and vascular overload. In the event the patient is found to have elevated diastolic filling pressures, the first-line intervention for hypotension often is inotropic support and not fluid administration to prevent further increases in left atrial pressure, which may result in pulmonary edema.

Management Options in HFpEF

As previously stated, identifying patients who have or are at risk for HFpEF is the first step in perioperative management.⁶⁰ It is important to optimize comorbid conditions before surgery, including aggressive control of chronically uncontrolled hypertension and avoidance of significant hyperglycemia. Sinus rhythm should be restored if possible, and the atrial fibrillation rate should be controlled. Continuous positive airway pressure devices should be worn for patients with obstructive sleep apnea.⁶¹ Intraoperative echocardiography is the most effective tool to monitor increasing grades of LVDD.⁶¹ Furthermore, it has been demonstrated that the grade of severity of LVDD can change throughout the course of general anesthesia, and decisions regarding fluid and medication management should not be made solely based on the preoperative assessment.⁴⁸ Fluid administration in a patient with LVDD may be necessary to improve LV filling, but excessive fluid administration may result in increased end-diastolic pressure that may exacerbate pulmonary venous congestion, leading to pulmonary edema.⁶¹

Large trials using angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers have yielded disappointing results and have shown neutral outcomes.⁶² A review of the prospective clinical studies of renin-angiotensin (RAS) inhibitors (CHARM-Preserved, I-Preserve, PEP-CHF) have shown no clear benefit with regard to mortality or hospitalization for HF.⁶³ Both beta-blocker and spironolactone trials have yielded inconclusive results.⁶² The Treatment of Preserved Cardiac Function HF with an Aldosterone Antagonist trial was a randomized, double-blind trial that examined 3,445 patients with HFpEF assigned to spironolactone or placebo over a 3-year period. No difference in death from cardiovascular causes, cardiac arrest, or hospitalization for HF was found between the 2 groups.⁶⁴ A recent meta-analysis examined the effect of beta-blocker therapy on mortality and hospitalization for HF in HFpEF patients. Fifteen observational studies and 2 randomized controlled trials (RCTs) were included. In the observational studies, beta-blocker therapy was associated with lower mortality but not HF hospitalization, whereas beta-blocker therapy was not associated with a decrease in mortality or morbidity in the RCTs, indicating the need for additional trials.⁶⁵ Experimental data have suggested that phosphodiesterase-5 inhibitors may enhance cardiovascular function by dilation of the pulmonary vascular bed, enhancement of right ventricular contractility, reduction of ventricular interdependence, and prevention of cardiomyocyte remodeling and, therefore, might be of promise in HFpEF. However, a randomized, double-blind, placebo-controlled clinical trial of 216 patients with stable HFpEF did not result in significant improvement in exercise capacity or clinical status after 24 weeks of sildenafil administration.⁶⁶

Currently, no treatment has been proven to reduce morbidity and mortality in patients with HFpEF.⁶⁷ Comorbid conditions should be treated optimally. Most medications typically avoided in HFrEF also should be avoided in HFpEF, with the exception of verapamil and diltiazem.⁶⁸ Exercise training improves quality of life and symptoms.⁶⁸ Significantly fewer exercise therapy trials exist for the HFpEF population than for patients with HFrEF, but a meta-analysis indicated that moderate-intensity exercise programs elicited improvements in LVDD and health-related quality of life.⁶⁹ Options for management are included in Table 6.

Future Directions: The New HFpEF Paradigm

Arterial hypertension long has been believed to cause chronically elevated afterload, leading to ventricular remodeling and resulting in HFpEF. Recent work by Paulus et al proposed a new paradigm for the sequence of events that leads to myocardial remodeling and dysfunction.¹⁰ Their paradigm focused on the comorbidities obesity, diabetes mellitus, chronic obstructive pulmonary disease, and hypertension, all of which are capable of causing the systemic proinflammatory state.⁷⁰ This chronic inflammation is believed to cause the coronary microvascular endothelial cells to produce reactive oxygen species. Reactive oxygen species limit the bioavailability of nitric oxide, which decreases PKG.¹⁰ Low PKG levels have been associated with increased cardiomyocyte tension and hypertrophy.⁷⁰ This leads to concentric LV remodeling and increased collagen deposition, LVDD, and HFpEF.¹⁰ This new paradigm proposed possible therapeutic strategies that should aim at treating endothelial dysfunction by reducing inflammation, nitric oxide donors, phosphodiesterase-5 inhibitors, and the antioxidative properties of statins.¹⁰

Although there is a paucity of current data for the management of HFpEF, there are several promising therapies under investigation. A meta-analysis of 11 studies and almost 18,000 patients with HFpEF showed a trend of reduction in mortality rates in statin users; additional RCTs are needed.⁶² The most promising drug therapy is the angiotensin-receptor neprilysin inhibitor LCZ696. PARAMOUNT was a phase-II, multicenter trial comparing the change in NT-proBNP in HFpEF patients treated with LCZ696 compared with treatment with valsartan and resulted in a further reduction of NT-proBNP in the LCZ696 group.⁷¹ This now is being tested in the phase III trial PARAGON-HF (Efficacy and Safety of LCZ696 compared to Valsartan on Morbidity and Mortality in HF Patients with Preserved Ejection Fraction study).⁷⁰ Elevated heart rate was found to be an independent predictor of adverse clinical outcomes; each standard deviation (12.4 bpm) increase in heart rate was associated with a 13% increased risk of cardiovascular death or hospitalization for HF.⁷² As such, rate control has been analyzed using treatments such as vagal and carotid artery stimulation in the I-Preserve Trial (irbesartan patients with HF and preserved systolic function).⁷⁰ Finally, promise has been shown using wireless pulmonary artery pressure monitoring to guide management and reduce decompensation in HFpEF patients. In the prospective, single-blinded, randomized CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA (CHAMPION) Class III HF Patients trial, 119 patients were assigned randomly to either standard treatment or treatment guided by the implanted pressure sensor. After an average of 18 months of follow-up, the hemodynamically guided treatment group was 50% less likely to be hospitalized for HF.⁷³ These studies may have implications for perioperative physicians who often are asked to guide perioperative loading conditions in patients with HFpEF.

Conclusion

Identifying perioperative patients with HFpEF can be challenging for anesthesiologists because the diagnosis can be discrete. Guidance of fluid administration and medication management in this HF population are difficult due to changes in loading conditions that occur during the perioperative period. Proper perioperative risk stratification, optimization of

comorbidities, and the ability to diagnose and manage worsening perioperative LVDD are all important factors to consider. Although substantial outcome data exist on the direct correlation of HFpEF to poor outcomes, significant gaps exist on perioperative treatment and the role anesthesiologists can play to improve outcomes in HFpEF patients. Future studies on preoperative optimization, intraoperative monitoring and management, and treatment of acute decompensation are warranted.

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Fig 1.

The biplane method of measuring LVEF. (A) The midesophageal 4-chamber (ME 4C) view at 0 degrees during diastole (*ME 4Cd*) in which the endocardial boarder is traced. (B) The border is traced with the ME 4C view during systole (*ME 4Cs*). (C) The second view for the biplane method is the midesophageal 2-chamber (ME 2C) view at 90 degrees. The ME 2C view during diastole (*ME 2Cd*) in which the endocardium is traced. (D) The ME 2C view during systole (*ME 2Cs*) with the endocardium traced. The end diastolic volume of the left ventricle can be seen (A) with a volume of 100 mL, which with a body surface area of 1.6 is 63 mL/m². The biplane EF (B) measured 50%.

Fig 2.

The Doppler evaluation of diastolic filling. (A) The tissue Doppler velocities of the lateral mitral annulus are seen measuring 7 cm/sec, which is below the threshold of normal (10 cm/sec), indicating diastolic dysfunction. (B) To further verify the presence of diastolic dysfunction and the presence of elevated diastolic filling pressures, pulse-wave Doppler measurements of mitral inflow are demonstrated. Here the E-wave velocity is seen to be 125 cm/sec and larger than the A wave. This gives an E/e' ratio of 18 (>13), and the E:A ratio is >1 . In addition, the E-wave velocity is $>100 \text{ cm/sec}$. Even though not sensitive for increased filling pressures, it is specific. (C) The pulmonary venous flow measured using pulse-wave Doppler is seen. In this example, despite evidence of significantly elevated diastolic filling pressures, the pulmonary venous flow appears codominant, demonstrating how pulmonary venous flow can be nonspecific in the setting of diastolic dysfunction.

Table 1Characteristics of HFpEF^{1,3,4,5,7,15}

HFpEF		HFrEF
Echocardiographic findings		
Diastolic dysfunction	Very prevalent finding—impaired left heart filling	Common but not diagnostic
Tissue Doppler	Reduced myocardial tissue Doppler velocities	Reduced tissue Doppler velocities
Left ventricle dimensions	Normal LV chamber size	Dilated LV chamber size
Left ventricle wall thickness ⁵	Increased wall thickness (concentric remodeling) ⁵	Lower LV mass:volume ratio ⁵
EF	Normal (>50%)	Reduced (<30%)
Physiologic findings		
Pressure-volume loops ⁵	Pressure-volume loops show an upward or leftward shift of the LV end-systolic pressure volume relationship, reflecting increased myocardial stiffness ⁵	Decreased myocardial contractility (rightward and downward) ⁵
Vascular changes	Ventriculoarterial stiffening	Less ventriculoarterial stiffening
Loading conditions ¹⁵	Greater blood pressure variability from changes in loading conditions—both preload and afterload ¹⁵	Afterload reduction actually increases stroke volume
Wall tension and BNP release ⁴	Increased wall thickness and lower and BNP ⁴	High BNP levels
Structural alterations ³	Cardiomyocyte hypertrophy and myocardial interstitial fibrosis ³	Eccentric remodeling
Clinical differences and comorbidities		
Age	Older median age	Younger median age
Sex	More likely to be female	No sex predilection
Hypertension	Very high prevalence of systolic hypertension	Not associated with hypertension
Medical comorbidities ¹	Higher frequency of obesity, diabetes mellitus, metabolic syndrome, renal dysfunction, anemia, and atrial fibrillation ¹	Less prevalent ¹
5-year mortality ⁷	20%–40% ⁷	30%–50% ⁷

Abbreviations: BNP, brain natriuretic peptide; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular.

Summary of Current Studies Regarding Perioperative HFpEF in Both Cardiac and Noncardiac Surgery

Author (Year)	Study Population	Number of Patients/Study Design	Findings
Cardiac			
Bernard et al (2001) ²⁴	CABG, combined valve, and redo surgeries	66 patients (8 HFpEF patients)/prospective	Increased inotropic support in patients with normal LVEF and grade II and III LVDD
Salem et al (2006) ¹⁸	CABG, valve, and other cardiac surgery	3,024 total patients (1,279 HFpEF patients of 2,445 CABG patients and 311 HFpEF patients of 895 non-CABG patients)/prospective	LVEDP was an independent risk factor of mortality independent of LVEF
Sastry et al (2010) ¹⁶	Off-pump CABG	925 patients (54 HFpEF patients)/retrospective	Increased in-hospital mortality and length of ICU stay
Groban et al (2010) ²⁵	CABG; CABG and valve	205 patients/retrospective E/e' was used to analyze clinical outcomes, and a second separate analysis was performed using LVEF on clinical outcomes	E/e' 8 independently related to increased ICU length of stay and need for inotropic support
Marui et al (2015) ²⁶	CABG	1,877 patients (152 HFpEF patients)/prospective	Cumulative incidence of all-cause death at 5 years was increased; the risk of cardiac death and sudden death was greater than that in the normal group (normal LVEF and no history of heart failure); readmission for heart failure was significant
Dalén et al (2016) ²⁷	CABG	41,906 patients (1,216 HFpEF patients)/retrospective	Patients were divided into 4 groups: no HF and normal EF; no HF and reduced EF; HFpEF; and HFREF; normal LVEF defined as 40%; all-cause mortality was evaluated for a mean follow-up of 6 years; statistically strong significant association between HF and mortality that was independent of EF
Kaw et al (2016) ²¹	Mostly CABG, off-pump CABG; 1 study on vascular patients	12 studies/meta-analysis (retrospective and prospective studies included)	Mortality increased with preoperative diagnosis of diastolic dysfunction (DD) regardless of systolic function and varied with severity of DD, reaching statistical significance with grade III LVDD (restrictive); patients were more likely to experience MACE and prolonged ventilation; grades I and II LVDD had higher prevalence but were not statistically significant; grade III was statistically significant
Noncardiac			
Matyal et al (2009) ¹⁷	Vascular	313 total patients (134 HFpEF patients)/prospective	DD was associated with adverse events (most common was postoperative congestive HF) and longer length of stay; systolic function was not associated
Flu et al (2010) ⁷⁴	Open or endovascular elective vascular procedures	1,005 patients (209 HFpEF patients)/prospective	Associated with 30-day cardiovascular events and long-term cardiovascular mortality
Cabrera Schulmeyer et al (2012) ²⁸	Abdominal (41%) Orthopedic (33%) Urologic (8%) Other noncardiac procedures	82 patients (prospective) DD assessed using E/e' ; patients divided into the following 3 groups: E/e' <8, 8< E/e' <15, and E/e' >15; risk-stratified using LVEF	Higher incidence of cardiovascular complications, including pulmonary edema, arrhythmia, and death despite LVEF
Cho et al (2013) ²⁹	Low-to-intermediate risk noncardiac surgery	692 patients (633 patients had LVEF >50%, 132 patients had E/e' >15; separately evaluated patients with LVEF >50% and E/e' >15)/prospective	Increased postoperative pulmonary edema and MACE (MACE defined as 30-day mortality, MI, complete AV block, Afib, Vfib, tachycardia)

Author (Year)	Study Population	Number of Patients/Study Design	Findings
Fayad et al (2016) ²²	Multiple noncardiac	Meta-analysis of 13 studies (3,800 patients)/prospective and retrospective	Moderate certainty that patients with PDD will experience increased postoperative morbidity and mortality within 30 days of noncardiac surgery than patients without PDD

Abbreviations: Afib, atrial fibrillation; AV, atrioventricular; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; HFpEF, heart failure with preserved ejection fraction; ICU, intensive care unit; LVDD, left ventricular diastolic dysfunction; LVEF, left ventricular ejection fraction; LVEDP, left ventricular end-diastolic pressure; MACE, major adverse cardiac event; MI, myocardial infarction; PDD, peroperative diastolic dysfunction; Vfib, ventricular fibrillation.

Table 3

Common Clinical Symptoms Reported by Patients With HF and Standard Descriptive Nomenclature for HF Severity

Symptoms of HF	
Fatigue	
Shortness of breath	
Dyspnea	
Dyspnea on exertion	
Ankle swelling	
Breathlessness	
Nocturnal dyspnea	
Orthopnea	
Dizziness	
ACC/AHA stages of HF	
Stage A	At high risk for HF but without structural heart disease or symptoms of HF
Stage B	Structural heart disease but without signs or symptoms of HF
Stage C	Structural heart disease with prior or current symptoms of HF
Stage D	Refractory HF requiring specialized interventions
NYHA functional classifications	
Class 1	No limitations of physical activity; ordinary physical activity does not cause symptoms of HF
Class 2	Slight limitation of physical activity; comfortable at rest but ordinary physical activity results in symptoms of HF
Class 3	Marked limitations in physical activity; comfortable at rest but less-than-ordinary physical activity causes symptoms of HF
Class 4	Unable to carry on any physical activity without symptoms of HF or symptoms of HF at rest

NOTE: Adapted from Oktay and Shah.³²

Abbreviations: ACC/AHA, American College of Cardiologists and American Heart Association; HF, heart failure; NYHA, New York Heart Association.

Table 4

Definitions and Criteria for the Diagnosis of HF With Preserved EF by the American College of Cardiologists and American Heart Association and the ESC³⁴

ACC/AHA (2013) definition of HFpEF	
<ul style="list-style-type: none"> • Presence of symptoms consistent with HF • LVEF $\geq$ 50% • Abnormal LVDD diastolic function 	
ESC (2016) definition of HFpEF	
<ul style="list-style-type: none"> • Presence of symptoms consistent with HF • LVEF $\geq$ 50% • LV end-diastolic volume <97 mL/m² • Presence of LVDD <ul style="list-style-type: none"> – Mean e' TDI <9 cm/sec – E/e' ≥ 13 – Left atrial volume index >34 mL/m² – LV mass index ≥ 115 g/m² for males or ≥ 95 g/m² for females – BNP ≥ 35 pg/mL or NT-proBNP ≥ 125 pg/mL (not routine; suggestive of diastolic dysfunction) 	

Abbreviation: ACC/AHA, American College of Cardiologists and American Heart Association; ESC, European Society of Cardiology; HFpEF, heart failure with preserved ejection fraction; LVDD, left ventricular diastolic dysfunction; LVEF, left ventricular ejection fraction; TDI, tissue Doppler imaging.

Table 5

Criteria Used for Intraoperative Classification of Diastolic Function

	Lat TDI e'	E/A	E/e'	Pulmonary Veins
Normal function	10 cm/sec	>1	8	S>D
Impaired relaxation	<10 cm/sec	<1	9–12	S>D
Elevated filling pressures (pseudonormal) (Restrictive filling)	<10 cm/sec	>1	13 S	<D systolic blunting

Abbreviations: D, diastolic; S, systolic; TDI, tissue Doppler imaging.

Table 6Perioperative Management Goals for HFpEF patients^{47,60,61,63,64,67,70–72}

Clinical Goals for the Perioperative Management of HFPEF	
<i>What is known</i> ^{47,61}	
Management strategies	<ul style="list-style-type: none"> • LVDD is an independent risk factor for perioperative cardiovascular events • Intraoperative echocardiography is the best tool to assess diastolic dysfunction • Echocardiographically-guided hemodynamic management may be a safe alternative to standard management • Elevated heart rate in HFpEF patients is associated with increased risk of cardiovascular death and HF hospitalization
Comorbid conditions Optimization ^{60,61}	<ul style="list-style-type: none"> • Aggressive control of chronically uncontrolled hypertension • Tight glycemic control for diabetes mellitus • Maintain normal sinus rhythm • Rate control patients with chronic atrial fibrillation (verapamil, diltiazem, or beta-blocker) • CPAP devices for patients with OSA • Avoid fluid retention
Treatments to avoid ^{63,67}	<ul style="list-style-type: none"> • Thiazolidinediones (glitazones) • NSAIDs and COX-2 inhibitors (may cause sodium and water retention) • ARB in combination with ACE inhibitor and mineralocorticoid antagonist
<i>What is not known</i> ^{62–64,67,70–72}	
Treatments	<ul style="list-style-type: none"> • The benefit of multiple traditional therapies of HF treatment: ACE-I/ARBs, statins, beta-blocker • The role of angiotensin-receptor neprilysin inhibitors

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; COX-2, cyclooxygenase 2; CPAP, continuous positive airway pressure; HFpEF, heart failure with preserved ejection fraction; LVDD, left ventricular diastolic dysfunction; NSAIDs, nonsteroidal anti-inflammatory drugs; OSA, obstructive sleep apnea.