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Expert Review

Heart Failure With Preserved Ejection Fraction—A Systematic Review and Analysis of Perioperative Outcomes

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THERE ARE MORE THAN 900,000 new cases of heart failure (HF) annually, of which approximately half can be attributed to HF with preserved ejection fraction (HF*p*EF).[1] An estimated 1 in 5 Americans older than 40 will develop HF, and this number is expected to increase even further as the population ages.[2,3] Moreover, it is estimated that the prevalence of HF*p*EF is rising at a rate of around 1% per year compared with HF with reduced ejection fraction (HF*r*EF), making it the most prevalent form of HF in the coming years.[4] A recent study examining more than 11,000 incident cases of HF reported that, between 2005 and 2008, 52% of patients experienced HF*p*EF, whereas only 32% experienced HF*r*EF, with the others having a borderline ejection fraction (EF).[5] Not only is the burden of disease similar to HF*r*EF, the costs to health care also are comparable. A study by Gurwitz et al revealed that even though patients with HF*r*EF have more cardiology encounters and procedures, 5-year costs were similar in both the prevalent ($33,023 with abnormal EF and $32,580 with normal EF; $p = 0.93$) and incident ($49,128 with abnormal EF and $45,604 with normal EF; $p = 0.55$) HF types.[5]

Risk Factors

Men and women have an approximately similar lifetime risk of developing HF. However, in patients >40 years old without antecedent myocardial infarction (MI), the risk is significantly greater in women (1 in 6) compared with men (1 in 9), emphasizing the role of hypertension as an etiological factor for HF in women. This is in line with findings from the Acute Decompensated Heart Failure National Registry, which demonstrated that women less commonly experienced coronary artery disease (CAD), were more likely to experience hypertension, and predominantly presented with HF*p*EF.[6]

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In addition to hypertension and female sex, older age, obesity, and diabetes are recognized risk factors for HF*p*EF.[7–11]

Bhatia et al found that patients with HF*p*EF have lower rates of modifiable risk factors, including smoking, diabetes, and hyperlipidemia. They also have decreased prevalence of peripheral artery disease, angina, prior MI, and prior coronary artery bypass grafting surgery (CABG), but higher rates of atrial fibrillation (AF) and chronic obstructive pulmonary disease.[11] Recent studies have shown the increased prevalence of CAD in patients with HF*p*EF, with numbers reaching almost 70%. In this subgroup of patients with CAD, patients are more likely to be men, with traditional CAD risk factors, but interestingly they do not demonstrate increased rates of ischemic symptoms (ie, angina) compared with patients with HF*p*EF without CAD.[12,13]

Aging is one of the more important risk factors for the development of deranged diastolic function. Aging contributes to reduced ventricular-vascular stiffening, and other metabolic changes lead to oxidative stress and mitochondrial damage.[14,15] A reduced availability of nitric oxide and increased production of endothelial reactive oxygen species also play a part in this process and may lead to micro areas of ischemia and thereby cause interstitial fibrosis and cardiomyocyte stiffness.[16,17]

Definition and Diagnosis

Based on the 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines, HF*p*EF is referred to as the clinical syndrome of HF with an EF $\geq$ 50%. They also recognize the following 2 intermediate categories: HF*p*EF with improved EF ($>$ 40%) and HF*p*EF with borderline EF (40%-49%). Although characteristics of the latter are similar to HF*p*EF, data pertaining to HF*p*EF with improved EF are limited.[2] The presence of abnormal left ventricular (LV) relaxation, filling, diastolic distensibility, and diastolic stiffness as an essential component of the diagnostic criteria initially was proposed by the European Study Group.[7] However, this has been challenged by multiple studies.[18] Zile et al carried out echocardiographic measurements in 63 patients with clinical evidence of HF*p*EF and found that more than 90% of these patients had an elevated LV end-diastolic pressure and 100% of these patients had at least 1 abnormal echocardiographic finding, indicating that such measurements add little to a clinical diagnosis of HF*p*EF.[19] Moreover, definitive diagnosis of ventricular diastolic dysfunction requires cardiac catheterization; as such, subjecting all patients with proposed HF*p*EF to cardiac catheterization may not be justified.[20–22] Furthermore, cardiac catheterization usually is performed once the patient is clinically stable and adequately diuresed, thereby influencing sensitivity of diastolic parameters.[21] Interestingly, LV mass and concentric hypertrophy have been shown to be consistent markers of HF*p*EF.[19,23] Considering some of this evidence, the 2007 European Consensus Statement on HF*p*EF and the 2012 European Society of Cardiology guidelines provide for the demonstration of left atrial (LA) enlargement or LV hypertrophy in addition to the clinical syndrome of HF and preserved EF as "sufficient evidence" for diagnosis of HF*p*EF.[24,25] This is echoed in the latest European Society of Cardiology guidelines from May 2016, which provide a diagnostic framework for HF*p*EF (Table 1[26]) and describe the diastolic abnormalities that can be used to make this diagnosis.

It is unclear whether HF*r*EF and HF*p*EF are part of the same disease spectrum or are distinct clinical syndromes. Diastolic dysfunction is present in both forms. Furthermore, even though patients with HF*p*EF have a normal EF, they demonstrate reduced tissue Doppler velocities, which is consistent with the postulation that both HF*r*EF and HF*p*EF are part of the same syndrome, with progressive systolic decline better defined by tissue Doppler velocities than by LVEF. Unimodal distribution of EF in large HF trials also has been cited as evidence of the single syndrome hypothesis. According to this hypothesis, the major difference between HF*r*EF and HF*p*EF is the degree of LV dilation and remodeling.[27–34]

At the same time, differences in patterns of chamber and myocellular remodeling coupled with differential response to medical therapy have been cited as reasons to consider these as separate disease entities.[4,34–39]

Pathophysiology

Diastolic Dysfunction

HF*p*EF is best defined by the presence of diastolic LV dysfunction comprising prolonged isovolumic relaxation, slow LV filling, raised LA pressure, and increased LV diastolic stiffness.[40–42] This diastolic dysfunction results from a combination of extracellular matrix abnormalities and cardiomyocyte dysfunction. Extracellular matrix stiffness in HF*p*EF is caused by excessive collagen type 1 deposition in conjunction with exaggerated synthesis and decreased breakdown.[36–39,43–45]

Systolic Dysfunction

Even though the EF is preserved in HF*p*EF, various studies have reported systolic dysfunction as evidenced by decreased peak regional myocardial sustained systolic velocities,[28] depressed longitudinal systolic function,[23,29,46] and depressed

Table 1
Diagnostic Criteria for HF*p*EF[26]

1.	Signs and symptoms of HF
2.	LVEF $\geq$ 50%
3.	1. Elevated levels of natriuretic peptides*
	2. At least 1 additional criterion:
	• Relevant structural heart disease (LVH and/or LAE)
	• Evidence of diastolic dysfunction†

Abbreviations: LAE, left atrial enlargement; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy.

*BNP $>$ 35 pg/mL and/or NT-proBNP $>$ 125 pg/mL.

†Refer to American Society of Echocardiography/European Society of Cardiology guidelines for diastolic dysfunction parameters.

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