Diagnosis and Treatment of HFpEF

Written by Mary Mosley

Heart failure with preserved ejection fraction (HFpEF) is a distinct clinical entity with diagnostic and treatment challenges. Recommendations to improve diagnosis by incorporating new parameters are being developed by the HFpEF Committee of the Heart Failure Association and were reviewed by Burkert Pieske, MD, Medical University Graz, Graz, Austria. There are no effective treatments for HFpEF currently and trials for new strategies are ongoing.

HFpEF is characterized by normal or only mildly reduced left ventricular ejection fraction (LVEF; ≥50%), a left ventricle (LV) that is not dilated, and the presence of relevant structural disease (LV hypertrophy, left atrial [LA] enlargement) or echocardiographic evidence of diastolic dysfunction, as well as the typical signs and symptoms characteristic of HF, according to the European Society of Cardiology (ESC) 2012 HF Guidelines. A diagnostic gray zone exists for patients with an LVEF between 36% and 49%, because these patients do not have an LVEF less than 35% and thus meet the definition of HF with reduced ejection fraction (HFrEF), said Stefan Blankenberg, MD, University Heart Center, Homburg, Germany.

About 50% of all HF patients have HFpEF [Owan TE et al. *N Engl J Med* 2006]. The Gutenberg Health Study (GHS) with 15,000 participants (50% women; 26.17% overall with functional cardiac disorders) showed that the prevalence of HFpEF was 4.03% of participants with symptomatic and 15.4% with asymptomatic systolic disorders [Deuchi FG et al. *Eur Heart J* 2013]. After a median 11.5-year follow-up in the middle-aged, community-based PREVEND cohort study, 374 of 8592 participants developed HF, of which 34% was HFpEF [Brouwers FP et al. *Eur Heart J* 2013].

The clinical presentation of HFpEF is similar to HFrEF, stated Jan-Christian Reil, MD, University of Saarland, Homburg, Germany. The described risk factors for HFpEF are female gender, age, arterial hypertension, diabetes mellitus (DM), chronic renal failure, sleep apnea syndrome, and obesity. The GHS showed that age, hypertension, body mass index (BMI), and DM were the strongest predictors of HFpEF (Table 1). PREVEND showed that atrial fibrillation (AF) and cystatin C concentration were risk factors for HFpEF in older women.

Mortality rates in patients with HFpEF ranged from 10% to 30%, and were higher in epidemiologic studies compared to clinical trials with selected patients, said Dr. Reil. The MAGGIC meta-analysis of 31 studies with 41,972 patients showed that mortality was lower in patients with HFpEF (adjusted HR, 0.68; 95% CI, 0.64 to 0.710) than in those with HFrEF [Meta-analysis Global Group in Chronic Heart Failure. *Eur Heart J* 2012]. Among patients with HFpEF, those who also have coronary artery disease have a significantly worse prognosis [Hwang SJ et al. *J Am Coll Cardiol* 2014]. However, the mortality rate for patients with HFpEF appears to be driven by the HF per se, not the comorbidities or other risk factors; this finding is based on a review of trials such as the Digitalis Investigation Group (DIG) and the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) [Campbell RT et al. *J Am Coll Cardiol* 2012].

Heterogeneity within the group of HFpEF patients complicates diagnosis. The current ESC diagnostic scheme relies on factors at rest, but for many patients increased filling pressures are only provoked with exercise, said Dr. Reil, and phenotype diversity in HFpEF is not fully addressed: There are controversial correlations between E and E' and invasively measured filling pressures, with both good and poor correlations existing in the literature. The key diagnostic parameter is elevated LV filling pressure at rest or with exercise, indicating a common hemodynamic end point for different pathological mechanisms, said Dr. Reil.

Diagnosis of HFpEF may be refined with biomarkers. Brain natriuretic peptide (BNP) does not sufficiently distinguish HFpEF from HFrEF, stated Prof. Blankenburg, but MR- proAdrenomedullin has been clearly associated with diastolic dysfunction and HFpEF in the GHS [Neumann JT et al. Atherosclerosis 2013]. Prof. Reil stated that BNP correlated well with LV end diastolic pressure (LVEDP) and wall stress and thus is an established marker for the diagnosis of HFpEF [Iwanaga Y et al. *J Am Coll Cardiol* 2006]. Galactin-3 is a marker of fibrosis [Zile M et al.

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Table 1. Predictors of Heart Failure With Preserved Ejection Fraction

	Asymptomatic Diastolic Dysfunction		Asymptomatic Systolic Dysfunction		Heart Failure with preserved EF		Heart Failure with reduced EF	
	Adj. OR (95% CI)	p Value	Adj. OR (95% CI)	p Value	Adj. OR (95% CI)	p Value	Adj. OR (95% CI)	p Value
Gender, female vs male	1.16 (0.97-1.38)	0.11	**0.54 (0.41-0.71)**	**<0.0001**	**1.98 (1.42-2.75)**	**<0.0001**	**0.45 (0.25-0.79)**	**0.0059**
Age, Years	**1.11 (1.10-1.12)**	**<0.0001**	1.01 (1.00-1.03)	0.043	**1.14 (1.11-1.16)**	**<0.0001**	**1.08 (1.04-1.11)**	**<0.0001**
BMI, kg/m²	**1.05 (1.03-1.07)**	**<0.0001**	1.01 (0.98-1.04)	0.66	**1.12 (1.09-1.16)**	**<0.0001**	**1.14 (1.08-1.19)**	**<0.0001**
Diabetes, yes vs no	*1.45 (1.07-1.94)*	*0.015*	*1.81 (1.15-2.85)*	*0.011*	***2.59 (1.69-3.95)***	***<0.0001***	*1.22 (0.56-2.67)*	*0.61*
Dyslipidemia, yes vs no	**1.33 (1.10-1.60)**	**0.0026**	0.97 (0.73-1.29)	0.84	1.12 (0.80-1.58)	0.51	1.44 (0.85-2.43)	0.17
Family history of MI, yes vs no	0.98 (0.78-1.22)	0.84	1.12 (0.82-1.54)	0.47	1.05 (0.70-1.58)	0.80	1.72 (0.98-3.05)	0.061
Hypertension yes vs no	**2.29 (1.88-2.79)**	**<0.0001**	1.33 (1.00-1.76)	0.048	**2.30 (1.54-3.45)**	**<0.0001**	1.35 (0.75-2.45)	0.32
Smoking Status, yes vs no	1.03 (0.80-1.32)	0.83	1.21 (0.89-1.65)	0.22	1.26 (0.77-2.06)	0.36	1.86 (0.99-3.49)	0.055

BMI=body mass index; EF=ejection fraction; MI=myocardial infarction.

J Cardiovasc Trans Res 2013]. BNP and Galactin-3 may indicate changes in LVEDP relationships, said Prof. Reil.

Treatment is different for HFpEF compared with HFrEF, with only the latter having evidence-based treatments and a clear treatment strategy, said Prof. Blankenberg. The treatment of HFpEF remains empiric, stated Scott D. Solomon, MD, Brigham and Women's Hospital, Boston, Massachusetts, USA, with no drugs proven effective in RCTs. Treatment comprises relieving congestion with diuretics, treating ischemia, controlling blood pressure, and controlling and maintaining the rate of sinus rhythm in AF.

There was no significant clinical benefit of the addition of spironolactone, candesartan, or irbesartan in patients with HFpEF.

New treatment approaches are being investigated, including drugs that work through the myocardial cyclic guanosine monophosphate (cGMP) pathway; earlier studies with sildenafil, which targets the PDE5 pathway, however, did not demonstrate clinical benefit [Redfield MM et al. *JAMA* 2013].

The Phase 2 SOCRATES-PRESERVED [NCT01951638] trial aims to study the effect of a novel soluble guanylate cyclase stimulator (vericiguat) on the primary end point of NT-proBNP and LA volume at 12 weeks.

The PARAGON-HF study [NCT01920711] in HFpEF will evaluate the neprilysin inhibitor, LCZ696, with a primary end point of CV death and total HF hospitalization. LCZ696, an angiotensin-receptor/neprilysin inhibitor (ARNI) can replicate effects of the angiotensin-receptor blocker (ARB) valsartan as well enhance the levels of endogenous natriuretic-peptide vasodilators. The PARAMOUNT study with LCZ696 showed a significant (p=0.005) reduction in the primary end point of NT-proBNP at 12 weeks as compared with valsartan [Solomon SD et al. *Lancet* 2012], and PARADIGM-HF [NCT01035255] was terminated early because of overwhelming efficacy, stated Dr. Solomon.

The 2014 HFpEF recommendations promote (1) the preclinical detection of end-organ damage for risk stratification and prevention, (2) the establishment of an easily applicable Stage A initial diagnostic workup, which considers comorbidities that can also be performed by internists and cardiologists outside of hospital, (3) the establishment of a Stage B diagnostic pathway with a scoring system for uncertain cases, and (4) descriptions on how to assess etiology and major pathophysiology for individualized management (Stage C). The recommendations will include new Echo imaging parameters that have emerged as diagnostic and novel biomarkers.