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Functional Status, Pulmonary Artery Pressure, and Clinical Outcomes in Heart Failure With Preserved Ejection Fraction

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ABSTRACT

BACKGROUND Patients with heart failure with preserved ejection fraction have functional impairment resulting in reduced quality of life. Specific pathological mechanisms underlying symptoms have not yet been defined.

OBJECTIVES The aim of this study was to identify hemodynamic and other patient-related variables that are associated with New York Heart Association (NYHA) functional class and to analyze functional class in perspective with other clinical, laboratory, imaging, and hemodynamic parameters with respect to its influence on outcomes.

METHODS Between January 2011 and February 2015, 193 patients with confirmed heart failure with preserved ejection fraction were enrolled.

RESULTS Those in more advanced NYHA functional classes (III and IV; n = 136) were older ($p = 0.008$), had higher body mass indexes ($p = 0.004$), and had higher levels of N-terminal pro-brain natriuretic peptide ($p = 0.001$) compared with less symptomatic patients (NYHA class II; n = 57). Furthermore, parameters reflecting left ventricular diastolic dysfunction were more pronounced in advanced NYHA classes (early mitral inflow velocity/early diastolic mitral annular velocity; $p = 0.023$) as well as parameters reflecting right ventricular afterload (diastolic pulmonary artery pressure; $p < 0.001$). By multivariate regression analysis, age ($p = 0.007$), body mass index ($p = 0.002$), N-terminal pro-brain natriuretic peptide ($p < 0.001$), early mitral inflow velocity/mitral peak velocity of late filling ($p = 0.031$), and diastolic pulmonary artery pressure ($p < 0.001$) were independently associated with advanced NYHA class. After 21.9 months of follow-up, 64 patients (33.2%) reached the combined endpoint, defined as hospitalization for heart failure and/or cardiac death. By multivariate Cox analysis, NYHA functional class was independently associated with outcome (hazard ratio: 2.133; $p = 0.040$), as well as N-terminal pro-brain natriuretic peptide (hazard ratio: 1.655; $p < 0.001$) and impaired right ventricular function (hazard ratio: 2.360; $p = 0.001$).

CONCLUSIONS Symptoms of breathlessness in patients with heart failure with preserved ejection fraction are multifactorial and largely related to body mass index, left ventricular diastolic function, and the pulmonary vasculature. Clinically meaningful therapeutic interventions should target body weight, left ventricular stiffness, and concomitant pulmonary vascular disease. (J Am Coll Cardiol 2016;68:189–99) © 2016 by the American College of Cardiology Foundation.

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Nearly one-half of patients presenting with heart failure (HF) display normal or near normal left ventricular (LV) systolic function (1). This condition has been defined as HF with preserved ejection fraction (HFpEF) and is associated with substantial mortality and morbidity (2,3). HFpEF is characterized by impaired LV diastolic function due to abnormal relaxation and increased chamber stiffness (4), caused by alterations in collagen metabolism with subsequent myocardial fibrosis as well as by changes in cardiomyocyte titin homeostasis, resulting in elevated LV diastolic filling pressures (5–7). In their daily lives, affected patients have exercise intolerance, resulting in reduced quality of life (8). It is

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CAD = coronary artery disease

CI = confidence interval

dPAP = diastolic pulmonary artery pressure

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HR = hazard ratio

LV = left ventricular

NT-proBNP = N-terminal pro-brain natriuretic peptide

NYHA = New York Heart Association

PAWP = pulmonary artery wedge pressure

PVR = pulmonary vascular resistance

RHC = right heart catheterization

RV = right ventricular

RVD = right ventricular dysfunction

RVF = right ventricular function

TTE = transthoracic echocardiography

broadly accepted that hemodynamic parameters, determined mainly by LV function, during systole and/or diastole, are associated with the severity of exercise impairment in patients with HF (9,10). Our group and others have recently drawn attention to the right ventricle and its prognosis-limiting role in HFpEF (11–14). Parameters of right ventricular function (RVF) as well as those reflecting right ventricular (RV) afterload have not been examined in the context of physical activity so far.

Furthermore, although exercise intolerance and dyspnea are cardinal symptoms of HF, they may also be caused by a series of comorbid conditions known to be associated with HFpEF (e.g., chronic obstructive pulmonary disease, chronic kidney disease, obesity) (15,16). Taken together, the exact pathological mechanisms underlying exercise intolerance and breathlessness in this patient population are not fully understood.

We sought to identify hemodynamic and other patient-related variables that are associated with New York Heart Association (NYHA) functional class and to analyze functional class in perspective with other clinical, laboratory, imaging, and hemodynamic parameters with respect to its influence on outcomes.

METHODS

SUBJECTS AND STUDY DESIGN. The Division of Cardiology of the Medical University of Vienna, a tertiary referral center for HFpEF, performed this prospective, observational cohort analysis. Approval from the local ethics committee was obtained before initiating the study (EK #796/2010). Written informed consent was collected from all patients prior to enrollment and any study-related procedure.

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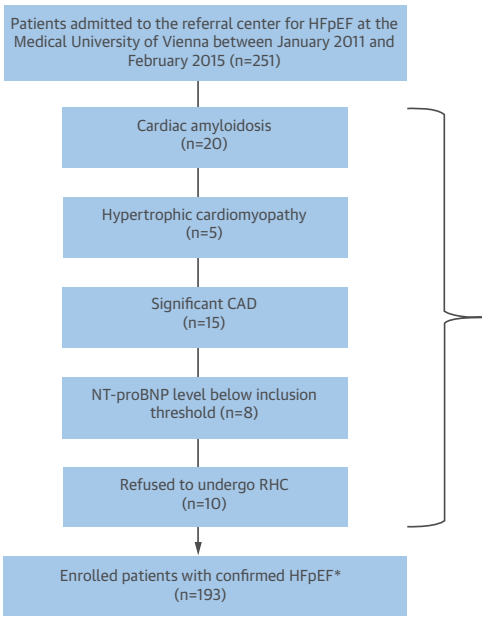
Consecutive patients with HFpEF were included. Baseline evaluation consisted of physical examination, 12-lead electrocardiography, laboratory assessment including serum N-terminal pro-brain natriuretic peptide (NT-proBNP) measurement, transthoracic echocardiography (TTE), lung function test with blood gas analysis, and right heart catheterization (RHC) followed by coronary angiography. F.D. and A.A.K. performed clinical baseline examination and NYHA class allocation using the following criteria: self-reported walking distance, limitation or symptoms in daily activities, and limitation or symptoms in climbing stairs (17). TTE was performed by S.A., and RHC was performed by J.M. and D.B. Physicians performing TTE and RHC were blinded to NYHA class allocation and vice versa.

Patient follow-up was performed by outpatient visits or telephone calls in cases of physical immobility. The primary study endpoint was hospitalization for HF and/or cardiac death. Patients with significant valvular or congenital heart disease, as well those with prior valve surgery with more than mild residual stenosis or regurgitation, were excluded. Patients with histories of myocardial infarction, significant coronary artery disease (CAD) (at least 1 lesion with stenosis grade ≥50%), or regional wall motion abnormalities of the left ventricle were excluded. History of CAD including prior stent implantation or prior coronary artery bypass graft was not considered an exclusion criterion.

DIAGNOSTIC DEFINITIONS. HFpEF was diagnosed according to the current consensus statement of the European Society of Cardiology (18) and the guidelines of the American College of Cardiology Foundation and American Heart Association (19). The following criteria had to be fulfilled: signs or symptoms of HF (18,19), evidence of preserved or normal LV ejection fraction >50% (18), serum NT-proBNP

FIGURE 1 Patient Flowchart



*All patients had invasively measured pulmonary artery wedge pressures >12 mm Hg. BNP = brain natriuretic peptide; CAD = coronary artery disease; HFpEF = heart failure with preserved ejection fraction; RHC = right heart catheterization.