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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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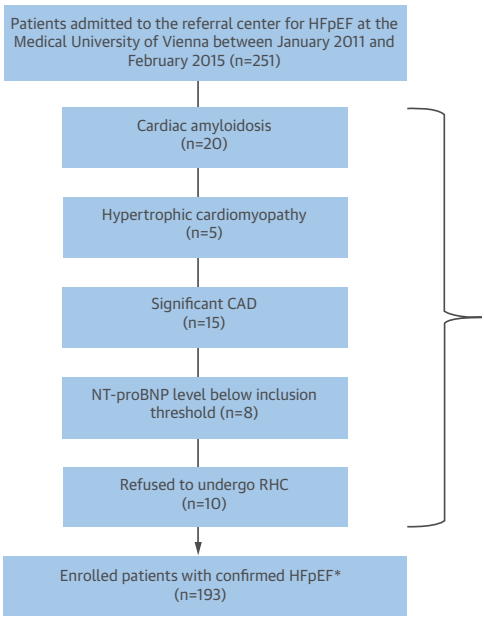
Consecutive patients with HFpEF were included. Baseline evaluation consisted of physical examination, 12-lead electrocardiography, laboratory assessment including serum N-terminal pro-brain natriuretic peptide (NT-proBNP) measurement, transthoracic echocardiography (TTE), lung function test with blood 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.

TABLE 1 Baseline Characteristics

	NYHA Class II (n = 57)	NYHA Classes III and IV (n = 136)	p Value
Clinical parameters			
Age, yrs	68.6 ± 9.4	72.3 ± 8.3	0.008
Female/male	38/19	95/41	0.734
Previous HF hospitalization	12 (21.0)	63 (46.3)	0.001
Time since previous HF hospitalization, days	194.8 ± 90.7	152.1 ± 82.0	0.109
Systolic blood pressure, mm Hg	142.4 ± 19.7	137.3 ± 22.0	0.129
Diastolic blood pressure, mm Hg	79.5 ± 11.2	78.1 ± 13.5	0.475
Heart rate, beats/min	70.8 ± 13.0	72.3 ± 14.9	0.498
Body mass index, kg/m^2	28.6 ± 6.7	31.8 ± 6.7	0.004
6MWD, m	391.7 ± 94.1	279.3 ± 116.4	<0.001
Smoking	20 (35.1)	41 (30.1)	0.494
Atrial fibrillation	28 (49.1)	87 (63.9)	0.054
Diabetes mellitus	16 (28.0)	57 (41.9)	0.076
Hyperlipidemia	29 (50.9)	80 (58.8)	0.342
Hypertension	52 (91.2)	136 (100)	0.002
History of CAD	9 (15.8)	33 (24.3)	0.252
Prior valve surgery	5 (8.8)	17 (12.5)	0.912
COPD	21 (36.8)	41 (30.1)	0.476
Diuretic drugs	32 (56.1)	114 (83.8)	<0.001
Laboratory parameters			
NT-proBNP quartile, pg/ml			0.001
0–600	28 (49.1)	31 (22.8)	
601–1,200	12 (21.1)	24 (17.6)	
1,201–1,800	7 (12.3)	30 (22.1)	
>1,800	10 (17.5)	51 (37.5)	
NT-proBNP, pg/ml	1,261.9 ± 2,021.1	2,194.0 ± 3,111.3	0.038
Hemoglobin, g/dl	13.0 ± 1.7	12.2 ± 1.7	0.006
TSH, μU/ml	2.3 ± 1.7	2.3 ± 1.9	0.800
GFR, ml/min/1.73 m^2	65.4 ± 20.6	57.0 ± 19.4	0.008
HbA_{1c}, %	6.0 ± 0.8	6.3 ± 1.2	0.129
Echocardiographic parameters			
LA diameter, mm	60.6 ± 8.1	63.0 ± 7.7	0.051
LVEDD, mm	43.6 ± 5.1	44.1 ± 5.7	0.543
RA diameter, mm	60.8 ± 8.9	63.5 ± 8.9	0.065
RVEDD, mm	34.5 ± 8.3	37.5 ± 7.6	0.019
IVS, mm	12.7 ± 2.5	13.0 ± 2.4	0.434
LVEF, %	59.1 ± 7.0	58.7 ± 7.1	0.809
E/E′ ratio	13.1 ± 5.8	16.7 ± 6.5	0.023
E/A ratio	1.3 ± 0.9	2.0 ± 1.1	0.035
Impaired RVF	13 (22.8)	48 (35.3)	0.093
TAPSE, mm	19.7 ± 5.4	19.1 ± 5.7	0.559
FAC, %	43.9 ± 11.5	41.4 ± 13.8	0.262
Hemodynamic parameters from catheterization			
Systolic PAP, mm Hg	45.9 ± 15.3	55.7 ± 17.2	0.001
Diastolic PAP, mm Hg	19.0 ± 6.6	23.7 ± 7.3	<0.001
Mean PAP, mm Hg	29.8 ± 9.1	35.7 ± 9.8	<0.001
Mean RAP, mm Hg	11.3 ± 5.5	13.4 ± 5.6	0.031
PAWP, mm Hg	17.6 ± 6.1	20.7 ± 5.7	0.002
SaO_2, %	95.3 ± 2.8	93.6 ± 5.1	0.030
TPG, mm Hg	12.1 ± 5.7	14.9 ± 7.7	0.023
PVR, dynes·s·cm^{-5}	186.9 ± 105.4	242.5 ± 142.3	0.015
DPG, mm Hg	1.4 ± 4.5	2.9 ± 5.9	0.102
PPP, mm Hg	26.9 ± 11.4	32.1 ± 12.8	0.015
CA, ml/mm Hg	3.1 ± 2.0	2.5 ± 0.9	0.010
SV, ml	71.0 ± 19.7	72.4 ± 20.5	0.677
CO thermodilution, l/min	5.4 ± 1.4	5.2 ± 1.3	0.332
CO Fick, l/min	4.5 ± 1.4	4.4 ± 1.1	0.601
Pulmonary parameters			
PaO_2, mm Hg	75.5 ± 11.2	70.9 ± 12.2	0.030
$PaCO_2$, mm Hg	37.9 ± 4.4	37.8 ± 5.2	0.968
DLCO, %	66.1 ± 16.5	62.3 ± 18.3	0.308
Vital capacity, %	90.1 ± 24.5	84.5 ± 25.3	0.203
FEV_1, %	78.7 ± 26.5	73.0 ± 25.0	0.201

Values are mean ± SD or n (%).

A = mitral peak velocity of late filling; CA = pulmonary arterial compliance; CAD = coronary artery disease; CO = cardiac output; COPD = chronic obstructive pulmonary disease; DLCO = diffusion capacity of the lung for carbon monoxide; DPG = diastolic pressure gradient; E = early mitral inflow velocity; E′ = early diastolic mitral annular velocity; FAC = fractional area change; FEV_1 = forced expiratory volume in 1 s; GFR = glomerular filtration rate; HbA_{1c} = glycated hemoglobin; HF = heart failure; IVS = interventricular septum; LA = left atrial; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; $PaCO_2$ = partial pressure of carbon dioxide; PaO_2 = partial pressure of oxygen; PAP = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PPP = pulmonary pulse pressure; PVR = pulmonary vascular resistance; RA = right atrial; RAP = right atrial pressure; RVEDD = right ventricular end-diastolic diameter; RVF = right ventricular function; SaO_2 = arterial saturation of oxygen; 6MWD = 6-min walking distance; SV = stroke volume; TAPSE = tricuspid annular plane systolic excursion; TPG = transpulmonary gradient; TSH = thyroid-stimulating hormone.

Continued in the next column

>220 pg/ml (18), and evidence of LV diastolic dysfunction by TTE (18,19).

For confirmation of diagnosis, RHC was performed. HFpEF was confirmed if pulmonary artery wedge pressure (PAWP) exceeded 12 mm Hg. Functional classification was determined according to criteria committee of the NYHA (20).

TTE. Board-certified physicians performed TTE (Vivid 5 and Vivid 7, GE Healthcare, Wauwatosa, Wisconsin). All measurements were assessed according to the guidelines of the American Society of Echocardiography (21). LV ejection fraction was assessed using the biplane Simpson method. Pulsed-wave Doppler was performed to obtain the early (E) and late (A) ventricular filling velocities. E′ (early diastolic mitral annular velocity) was assessed at the septal and lateral side of the mitral annulus with tissue Doppler imaging. RVF was assessed by integrating visual assessment of contractility of the RV outflow tract, RV apex, and interventricular septum from different views. In support, RVF was quantified by cardiac magnetic resonance imaging studies in a subset of patients (n = 97), which is the established gold

standard. There was good agreement between the 2 methods (intraclass correlation coefficient = 0.91).

CARDIAC CATHETERIZATION. For hemodynamic confirmation of HFpEF, a 7-F Swan-Ganz catheter (Baxter Healthcare, Munich, Germany) was inserted using a femoral approach. CathCorLX (Siemens AG, Erlangen, Germany) was used to measure pressures, which were recorded as average of 8 measurements over 8 recorded heart cycles. Cardiac output was assessed by thermodilution and by the Fick method. Pulmonary pulse pressure was calculated as the difference between systolic pulmonary artery pressure and diastolic pulmonary artery pressure (dPAP) and pulmonary arterial compliance as the ratio of stroke volume to pulmonary pulse pressure. The diastolic pressure gradient was calculated as the difference between dPAP and PAWP. The transpulmonary pressure gradient was calculated by subtracting PAWP from mean PAP. Pulmonary vascular resistance (PVR) was calculated by dividing transpulmonary pressure gradient by cardiac output.

OTHER TESTS. Capillary blood from the earlobe was measured using an ABL 510 blood gas analyzer (Radiometer Medical ApS, Bronshoj, Denmark). Serum NT-proBNP was measured using an immunologic test (Elecsys Systems, Roche Diagnostics, Mannheim, Germany).

STATISTICAL ANALYSIS. Statistical analysis was performed using IBM SPSS Statistics version 21.0 (IBM, Armonk, New York). Two-sided p values <0.05 were considered to indicate statistical significance. Data are expressed as mean ± SD or as frequencies and percentages. Continuous variables were compared using the Student *t* test or Wilcoxon rank sum test, as appropriate. To assess differences between dichotomous variables, the chi-square test was applied. The influence of several parameters on NYHA functional class was investigated first by univariate logistic regression. To identify the most relevant predictors for each category, a separate multiple regression model was selected from the scope of variables that reached statistical significance in univariate analysis in the respective category by a stepwise procedure. The significance limit for a predictor to enter the model was 0.05. Results were expressed as odds ratio with 95% confidence interval (CI).

Univariate and multivariate Cox regression models were calculated to examine factors associated with adverse outcomes. Predictors in the multiple Cox model were selected from the set of variables that reached statistical significance in univariate analysis, by a forward selection procedure with the significance limit to enter the model set to 0.05. Results were expressed as hazard ratios (HRs) with 95% CIs. Likewise, an analysis to determine predictors of outcomes was performed in a subset of patients who had undergone cardiac magnetic resonance. Survival curves were estimated using the Kaplan-Meier method; the log-rank test was used to compare survival differences.

RESULTS

BASELINE CHARACTERISTICS. Between January 2011 and February 2015, 251 patients from outpatient clinics were referred for suspicion of HFpEF. Of those, 58 did not enter the registry, because of alternative diagnoses: 20 patients had cardiac amyloidosis and 5 had hypertrophic cardiomyopathy. Another 23 patients did not meet the inclusion criteria (i.e., presence of significant CAD [n = 15] or NT-proBNP lower than the inclusion cutoff value [n = 8]). Ten patients refused to undergo RHC. Ultimately, 193 patients with confirmed HFpEF were enrolled (Figure 1).

Patients presenting with NYHA functional class III or IV (n = 136) were significantly older (p = 0.008) and more frequently reported previous hospitalizations (p = 0.001) compared with those presenting with NYHA class II (n = 57). Furthermore, patients with higher NYHA classes had higher body mass indexes (BMIs) (p = 0.004), more often had arterial hypertension (p = 0.002), and were more frequently taking diuretic agents (p < 0.001).

With respect to laboratory parameters, patients in NYHA class III or IV had higher NT-proBNP serum levels (p = 0.001), lower hemoglobin levels (p = 0.006), and lower glomerular filtration rates (p = 0.008). On average, parameters reflecting LV diastolic dysfunction were more severely altered in patients in advanced NYHA classes (E/E′ ratio, p = 0.023), which was accompanied by larger RV end-diastolic diameters (p = 0.019). Parameters reflecting RV afterload were higher in patients in NYHA class III or IV (dPAP, p < 0.001; PVR, p = 0.015). Furthermore, capillary partial pressure of oxygen was lower in these patients (p = 0.030) (Table 1).

DETERMINANTS OF NYHA FUNCTIONAL CLASS. Logistic regression models to delineate variables associated with NYHA functional class are shown in Table 2. With respect to each parameter cluster, the following variables independently associated with functional class were identified: 1) clinical: advanced age (p = 0.007), higher BMI (p = 0.002), previous HF hospitalizations (p = 0.005); 2) laboratory: higher NT-proBNP serum levels (p < 0.001); 3) TTE: higher E/A ratio (p = 0.031); and 4) invasive hemodynamic

parameters: higher dPAP ($p < 0.001$). No relationship was encountered between NYHA functional class and parameters reflecting pulmonary function.

NYHA FUNCTIONAL CLASS AND OUTCOME. After a mean follow-up period of 21.9 ± 13.1 months, 64 patients (33.2%) reached the combined endpoint. Sixteen patients died for cardiac reasons and 3 for other reasons (1 of stroke, 1 of pancreatic cancer, and 1 of complications due to catheterization, which was not registry related and was not performed at our referral center) (22).

In the Kaplan-Meier analysis, patients with higher NYHA classes showed shorter event-free survival compared with those in NYHA class II or III (log-rank $p < 0.001$) (**Figure 2**), even when a combined endpoint including all-cause mortality was chosen (log-rank $p = 0.001$). More than 60% of patients in NYHA class IV experienced events within the first 12 months.

After adjustment for other clinical parameters, NYHA functional class was an independent predictor of outcome ($p = 0.008$). Further parameters associated with a worse prognosis were as follows: 1) clinical: atrial fibrillation ($p = 0.014$) and diabetes mellitus ($p = 0.005$); 2) laboratory: higher NT-proBNP serum levels ($p < 0.001$) and lower hemoglobin levels ($p = 0.002$); 3) TTE: larger RV end-diastolic diameter ($p = 0.007$), impaired RVF by visual assessment ($p < 0.001$), and tricuspid annular plane systolic excursion <16 mm ($p = 0.013$); 4) invasive hemodynamic parameters: higher systolic pulmonary artery pressure ($p < 0.001$); and 5) pulmonary function: lower capillary partial pressure of oxygen ($p = 0.005$) and lower vital capacity ($p = 0.007$) (**Table 3**).

In a separate analysis (**Table 4**) pooling independent predictors of outcome across clusters, only NYHA functional class ($p = 0.040$), NT-proBNP ($p < 0.001$), and impaired RVF by visual assessment ($p = 0.001$) remained significantly associated with outcomes. An analysis confined to the subset of patients who had undergone cardiac magnetic resonance confirmed the finding that NYHA functional class (HR: 2.566; 95% CI: 1.063 to 6.194; $p = 0.036$), NT-proBNP (HR: 1.486; 95% CI: 1.104 to 2.001; $p = 0.009$), and impaired RVF (HR: 2.773; 95% CI: 1.432 to 5.371; $p = 0.002$) were independent predictors of outcome.

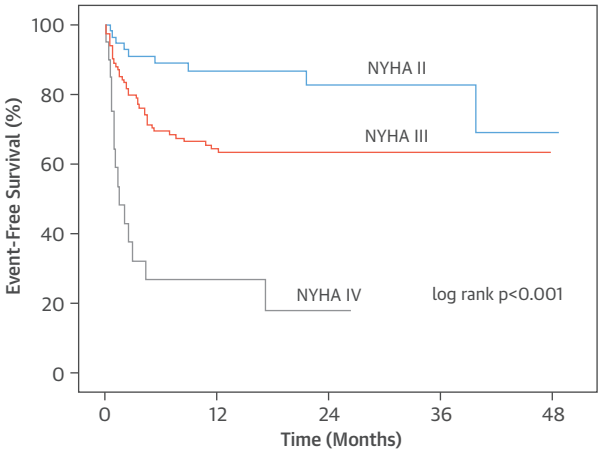
Advanced NYHA functional class (HR: 2.287; 95% CI: 1.114 to 4.698; $p = 0.024$), higher serum NT-proBNP levels (HR: 1.518; 95% CI: 1.206 to 1.911; $p < 0.001$), and reduced RVF (HR: 2.295; 95% CI: 1.403 to 3.753; $p = 0.001$) remained predictive of adverse outcome if a combined endpoint including all-cause mortality was chosen.

TABLE 2 Clinical, Laboratory, Echocardiographic, Hemodynamic, and Pulmonary Parameters Associated With New York Heart Association Class in Patients With Heart Failure With Preserved Ejection Fraction

	Univariate		Multivariate	
	Odds Ratio (95% CI)	**p Value**	**Odds Ratio (95% CI)**	**p Value**
Clinical parameters				
Age	1.048 (1.012–1.087)	0.010	1.057 (1.015–1.100)	0.007
Body mass index	1.080 (1.024–1.139)	0.004	1.096 (1.035–1.161)	0.002
Previous HF hospitalization	3.327 (1.617–6.846)	0.001	2.905 (1.373–6.149)	0.005
Atrial fibrillation	1.877 (1.002–3.516)	0.049		
Sex	0.863 (0.446–1.672)	0.663		
Systolic blood pressure	0.989 (0.974–1.003)	0.130		
Diastolic blood pressure	0.991 (0.968–1.015)	0.473		
Heart rate	1.008 (0.986–1.031)	0.497		
Smoking	0.772 (0.398–1.494)	0.442		
Diabetes mellitus	1.849 (0.945–3.616)	0.072		
Hyperlipidemia	1.379 (0.741–2.568)	0.311		
History of CAD	1.709 (0.758–3.852)	0.196		
COPD	0.763 (0.379–1.536)	0.448		
Laboratory parameters				
NT-proBNP quartile	1.686 (1.278–2.224)	<0.001	1.676 (1.257–2.233)	<0.001
Hemoglobin	0.779 (0.649–0.936)	0.008		
TSH	1.178 (0.914–1.517)	0.206		
GFR	0.979 (0.963–0.995)	0.010		
HbA_{1c}	1.277 (0.925–1.763)	0.138		
Echocardiographic parameters				
LA diameter	1.043 (0.999–1.088)	0.054		
LVEDD	1.018 (0.961–1.078)	0.541		
RA diameter	1.036 (0.998–1.075)	0.067		
RVEDD	1.052 (1.007–1.098)	0.022		
IVS	1.054 (0.924–1.204)	0.432		
LVEF	0.992 (0.927–1.061)	0.806		
E/E′ ratio	1.117 (1.012–1.232)	0.028		
E/A ratio	1.982 (1.019–3.856)	0.044	2.691 (1.094–6.621)	0.031
Impaired RVF	1.906 (0.936–3.881)	0.075		
TAPSE <16 mm	1.312 (0.545–3.159)	0.544		
FAC <35%	1.379 (0.615–3.093)	0.435		
Hemodynamic parameters from catheterization				
Systolic PAP	1.043 (1.017–1.070)	0.001		
Diastolic PAP	1.117 (1.052–1.186)	<0.001	1.123 (1.054–1.195)	<0.001
Mean PAP	1.078 (1.032–1.125)	0.001		
Mean RAP	1.075 (1.006–1.148)	0.034		
PAWP	1.101 (1.034–1.173)	0.003		
SaO_2	0.899 (0.814–0.993)	0.036		
PPP	1.039 (1.007–1.072)	0.018		
CA	0.729 (0.557–0.955)	0.022		
PVR	1.004 (1.001–1.008)	0.017		
TPG	1.066 (1.008–1.128)	0.025		
LVEDP	1.060 (0.994–1.131)	0.075		
DPG	1.056 (0.989–1.128)	0.104		
SV	1.004 (0.987–1.021)	0.674		
Pulmonary parameters				
PaO_2	0.969 (0.941–0.997)	0.033		
$PaCO_2$	0.999 (0.931–1.071)	0.968		
DLCO	0.988 (0.965–1.011)	0.306		
Vital capacity	0.991 (0.978–1.005)	0.203		
FEV_1	0.991 (0.978–1.005)	0.202		

p values were derived from simple or multiple logistic regression analysis.
CI = confidence interval; LVEDP = left ventricular end-diastolic pressure; other abbreviations as in **Table 1**.

FIGURE 2 Kaplan-Meier Analysis According to New York Heart Association Functional Class



	Months				
	0	12	24	36	48
NYHA class II					
Number at risk	57	57	54	53	29
Event-free survival (%)	100	96	98	100	79
Failure (%)	0	4	2	0	21
NYHA class III					
Number at risk	116	113	107	99	62
Event-free survival (%)	97	96	93	99	59
Failure (%)	3	4	7	1	41
NYHA class IV					
Number at risk	20	19	15	11	7
Event-free survival (%)	95	79	79	82	29
Failure (%)	5	21	21	18	71

NYHA = New York Heart Association.

DISCUSSION

Multimorbidity is a hallmark of patients with HFpEF. Attentive studies of well-characterized clinical cohorts have demonstrated that comorbid conditions, including chronic lung diseases, atrial fibrillation, chronic kidney disease, and obesity, are concomitant with the cardiac pathology (15,16). Although dyspnea and exercise intolerance are cardinal symptoms of HF, they may also be caused by concomitant conditions. This is the first analysis to determine clinical and hemodynamic determinants of NYHA functional class as well as its prognostic relevance in patients with HFpEF (**Central Illustration**).

The association between advanced NYHA functional class and poor prognosis has previously been reported (23). O'Connor et al. (24) followed 2,498 consecutive patients with HF and found that class IV symptoms were an independent predictor of long-term mortality, although the cutoff value for preserved LV ejection fraction was >40%, compared with >50% in our analysis. Ahmed et al. (25) observed 988 patients with HFpEF in a retrospective manner with a mean follow-up duration of 38.5 months and found higher NYHA classes to be associated with poorer outcomes. In contrast with the aforementioned trials, we performed invasive hemodynamic assessment for a definitive diagnosis of HFpEF, angiographically excluded relevant CAD (which is a frequent comorbid condition in HFpEF), and were able to confirm the prognostic relevance of NYHA functional class on HF hospitalization and cardiac death. Factors underlying physical impairment, including clinical characteristics as well as specific hemodynamic alterations, are not well understood.

Taken together, exercise intolerance in patients with HFpEF is related to elevated LV filling pressures at rest or during exercise (26–28). Several investigators, including our group, have recently called attention to the prognostic importance of RVF and RV afterload in patients with HFpEF (11–14). Mohammed et al. (13) prospectively followed 562 patients with HFpEF and found that patients with RV dysfunction (RVD) had more pronounced diastolic dysfunction, lower cardiac output, and higher systolic pulmonary artery pressure. In addition, the presence of RVD was associated with higher all-cause and cardiovascular mortality rates as well as with higher HF hospitalization rates (13). The prognosis-limiting role of RV contractile impairment and RV afterload was also confirmed by Melenovsky et al. (12). In addition to the aforementioned studies, our group complemented RV assessment by invasive hemodynamic measurements in 142 patients with HFpEF and emphasized the relevance of RVD and pulmonary vascular disease on outcomes (11). Furthermore, our group recently showed that RVD, assessed by magnetic resonance imaging, was independently associated with cardiac events (14). However, whether RVD and pulmonary vascular disease have an impact on exercise impairment has not been investigated.

Interestingly, the diastolic pressure gradient, which has been recently introduced as the most reliable parameter for the assessment of pulmonary vascular disease (29) and has been related with outcomes in this specific patient population (30), was not associated with functional impairment in our cohort. Nevertheless, the diastolic pressure gradient sums up with PAWP to dPAP, which was the only parameter linked to symptom severity. Although only subtle, other parameters reflective of pulmonary vascular disease were different between NYHA classes. PVR was higher ($p = 0.015$) and pulmonary arterial compliance was lower ($p = 0.010$) in patients in NYHA classes III and IV, and both parameters were associated with functional class in the univariate regression

TABLE 3 Predictors of Outcome

	Event (n = 64)	No Event (n = 129)	Univariate		Multivariate	
			Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Clinical parameters						
Age, yrs	72.6 ± 8.3	70.5 ± 8.9	1.023 (0.993–1.054)	0.136		
Female/male	39/25	94/35	1.654 (1.000–2.735)	0.050		
Body mass index, kg/m^2	31.9 ± 7.8	30.3 ± 6.3	1.030 (0.995–1.066)	0.090		
NYHA classes III and IV	55 (85.9)	81 (62.7)	3.109 (1.536–6.293)	0.002	2.623 (1.291–5.331)	0.008
6MWD, m	227.1 ± 143.9	328.0 ± 132.8	0.506 (0.304–0.841)	0.009		
Systolic blood pressure, mm Hg	136.6 ± 23.0	139.9 ± 20.5	0.995 (0.982–1.007)	0.393		
Diastolic blood pressure, mm Hg	77.3 ± 14.2	79.1 ± 12.2	0.993 (0.973–1.013)	0.509		
Heart rate, beats/min	70.5 ± 15.4	72.5 ± 13.8	0.992 (0.975–1.010)	0.401		
Smoking	22 (34.3)	39 (30.2)	1.201 (0.715–2.016)	0.489		
Atrial fibrillation	47 (73.4)	68 (52.7)	2.149 (1.233–3.744)	0.007	2.003 (1.148–3.494)	0.014
Diabetes mellitus	35 (54.7)	38 (29.4)	2.253 (1.373–3.695)	0.001	2.030 (1.233–3.341)	0.005
Hyperlipidemia	34 (53.1)	75 (58.1)	0.848 (0.519–1.385)	0.510		
Hypertension	63 (98.4)	125 (96.9)	2.143 (0.297–15.460)	0.450		
History of CAD	16 (25.0)	26 (20.2)	1.258 (0.715–2.216)	0.426		
COPD	23 (35.9)	39 (30.2)	1.484 (0.846–2.603)	0.169		
Laboratory parameters						
NT-proBNP quartile (pg/ml)			1.722 (1.378–2.151)	<0.001	1.628 (1.295–2.047)	<0.001
0–600	11 (17.2)	48 (37.2)				
601–1,200	6 (9.4)	32 (24.8)				
1,201–1,800	13 (20.3)	25 (19.4)				
>1,800	34 (53.1)	24 (18.6)				
Hemoglobin, g/dl	11.7 ± 1.7	12.9 ± 1.7	0.730 (0.628–0.847)	<0.001	0.793 (0.685–0.918)	0.002
GFR, ml/min/1.73 m^2	50.6 ± 17.6	63.9 ± 19.8	0.972 (0.960–0.984)	<0.001		
HbA_{1c}, %	6.5 ± 1.1	6.1 ± 1.1	1.281 (1.020–1.609)	0.033		
Echocardiographic parameters						
LA diameter, mm	63.5 ± 7.8	61.6 ± 7.8	1.028 (0.997–1.060)	0.076		
LVEDD, mm	43.6 ± 5.8	44.1 ± 5.4	0.983 (0.940–1.029)	0.461		
RA diameter, mm	64.9 ± 9.2	61.5 ± 8.6	1.031 (1.004–1.059)	0.022		
RVEDD, mm	39.6 ± 7.7	35.0 ± 7.6	1.061 (1.029–1.094)	<0.001	1.052 (1.014–1.092)	0.007
LVEF, %	60.1 ± 7.9	58.0 ± 6.4	1.025 (0.977–1.076)	0.312		
E/E′ ratio	14.3 ± 5.1	15.8 ± 6.8	0.971 (0.892–1.056)	0.491		
E/A ratio	1.9 ± 1.1	1.6 ± 1.1	1.254 (0.609–2.586)	0.593		
Significant TR	43 (67.2)	62 (48.1)	1.777 (1.045–3.023)	0.034		
Impaired RVF	33 (51.6)	28 (21.7)	2.681 (1.640–4.381)	<0.001	6.291 (2.795–14.163)	<0.001
TAPSE <16 mm	22 (53.6)	21 (24.4)	2.621 (1.416–4.852)	0.002	0.347 (0.150–0.801)	0.013
FAC <35%	22 (40.0)	24 (26.9)	1.906 (1.111–3.272)	0.019		
Hemodynamic parameters from catheterization						
Systolic PAP, mm Hg	61.0 ± 16.6	49.3 ± 16.3	1.029 (1.016–1.042)	<0.001	1.029 (1.016–1.043)	<0.001
Diastolic PAP, mm Hg	25.2 ± 6.3	21.0 ± 7.5	1.071 (1.038–1.105)	<0.001		
Mean PAP, mm Hg	38.1 ± 8.8	32.1 ± 9.9	1.050 (1.027–1.075)	<0.001		
Mean RAP, mm Hg	14.8 ± 6.2	11.9 ± 5.1	1.081 (1.035–1.130)	<0.001		
PAWP, mm Hg	21.8 ± 5.8	18.9 ± 5.9	1.069 (1.025–1.114)	0.002		
SaO_2, %	93.0 ± 4.7	94.6 ± 4.6	0.948 (0.907–0.990)	0.016		
SV, ml	77.0 ± 21.5	69.7 ± 19.2	1.014 (1.002–1.026)	0.024		
DPG, mm Hg	3.4 ± 6.4	2.0 ± 5.2	1.061 (1.009–1.115)	0.020		
TPG, mm Hg	16.3 ± 7.8	13.1 ± 6.8	1.059 (1.025–1.095)	0.001		
PVR, dynes·s·cm^{-5}	265.9 ± 155.5	208.4 ± 120.5	1.003 (1.002–1.005)	<0.001		
CA, ml/mm Hg	2.5 ± 1.1	2.8 ± 1.5	0.804 (0.612–1.057)	0.118		
Pulmonary parameters						
PaO_2, mm Hg	68.3 ± 12.4	74.3 ± 11.4	0.960 (0.936–0.983)	0.001	0.945 (0.908–0.983)	0.005
$PaCO_2$, mm Hg	38.7 ± 5.2	37.4 ± 4.8	1.050 (0.996–1.107)	0.068		
DLCO, %	56.0 ± 17.1	66.6 ± 17.2	0.966 (0.945–0.987)	0.001		
Vital capacity, %	75.5 ± 25.0	91.3 ± 23.6	0.973 (0.960–0.986)	<0.001	0.975 (0.957–0.993)	0.007
FEV_1, %	65.4 ± 23.8	79.1 ± 25.2	0.977 (0.965–0.990)	<0.001		

Values are mean ± SD or n (%). p values were derived from simple and multiple Cox regression analysis.

TR = tricuspid regurgitation; other abbreviations as in Tables 1 and 2.

TABLE 4 Cox Regression of Multivariate Significant Predictors of Outcome From the Parameter Clusters

	Multivariate From Parameter Clusters		Pooled Multivariate	
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
NYHA classes III and IV	2.623 (1.291–5.331)	0.008	2.133 (1.035–4.393)	0.040
Atrial fibrillation	2.003 (1.148–3.494)	0.014		
Diabetes mellitus	2.030 (1.233–3.341)	0.005		
NT-proBNP quartile	1.628 (1.295–2.047)	<0.001	1.655 (1.313–2.087)	<0.001
Hemoglobin	0.793 (0.685–0.918)	0.002		
RVEDD	1.052 (1.014–1.092)	0.007		
Impaired RVF	6.291 (2.795–14.193)	<0.001	2.360 (1.428–3.901)	0.001
TAPSE	0.347 (0.150–0.801)	0.013		
Systolic PAP	1.029 (1.016–1.043)	<0.001		
PaO_2	0.945 (0.908–0.983)	0.005		
Vital capacity	0.975 (0.957–0.993)	0.007		

Abbreviations as in Tables 1 and 2.

analysis (PVR, $p = 0.017$; pulmonary arterial compliance, $p = 0.022$). Exercise impairment is therefore caused by a combination of both pulmonary vascular disease and elevated LV filling pressures. In parallel, PVR was associated with outcomes in the univariate model (Table 3), but did not reach statistical significance in the multivariate model. Systolic pulmonary artery pressure, a parameter reflective of both right-sided and left-sided heart hemodynamics, was found to be the only independent hemodynamic predictor of outcomes in the multivariate model (HR: 1.029; $p < 0.001$). The fact that hemodynamic parameters reflecting both left heart pathology as well as changes in the pulmonary circulation are more relevant to symptoms and outcomes than PVR alone is in line with the current understanding that HFpEF harbors a variety of phenotypes, only 1 of which is the pulmonary hypertension phenotype (31).

A major contribution of LV filling pressures to experienced symptoms is further supported by the findings on echocardiography, where E/A ratio was higher in patients in NYHA class III or IV ($p = 0.035$) and was independently associated with functional class ($p = 0.031$).

Obesity is common among patients with HFpEF, and Lip et al. (32) recently found higher BMI to be associated with the development of HFpEF. Haass et al. (33) confirmed a high prevalence of BMI >26 kg/m^2 in a majority of affected patients but found the highest event rates in patients with BMIs >35 kg/m^2 as well as those with BMIs <23 kg/m^2. Although there is a U-shaped relationship between BMI and outcomes, it is independently associated with the development and severity of symptoms ($p = 0.002$). Recently, Kitzman et al. (34) demonstrated that in obese patients with HFpEF, dietary weight loss, with or without exercise training, significantly improved peak oxygen consumption as well as NYHA functional class (34). Furthermore, Haykowsky et al. (35) recently showed that besides subcutaneous fat deposits, patients with HFpEF have increased thigh intramuscular fat, which is an independent predictor of reduced aerobic capacity. Higher intramuscular fat may compete with active muscle tissue for nutritive blood flow during exercise, and oxygen delivery to active muscle cells is reduced. Furthermore, increased intramuscular fat is associated with reduced mitochondrial mass and impaired oxidative metabolism (36). These findings are in line with the hypothesis proposed by Paulus and Tschöpe (37) that comorbidities, such as obesity, induce a proinflammatory state resulting in myocardial structural and functional alterations. Mohammed et al. (38) found more pronounced cardiac hypertrophy as well as reduced capillary density in patients with HFpEF at autopsy, which is well in accordance with reduced capillary density in the skeletal muscle described by Kitzman et al. (39).

In accordance with this, Haykowsky et al. (40,41) showed that peripheral, noncardiac factors are important contributors to exercise intolerance in patients with HFpEF. In addition to altered skeletal muscle composition, abnormal skeletal muscle mitochondrial function (42), as well as abnormal arterial stiffness (43), may contribute to reduced functional capacity.

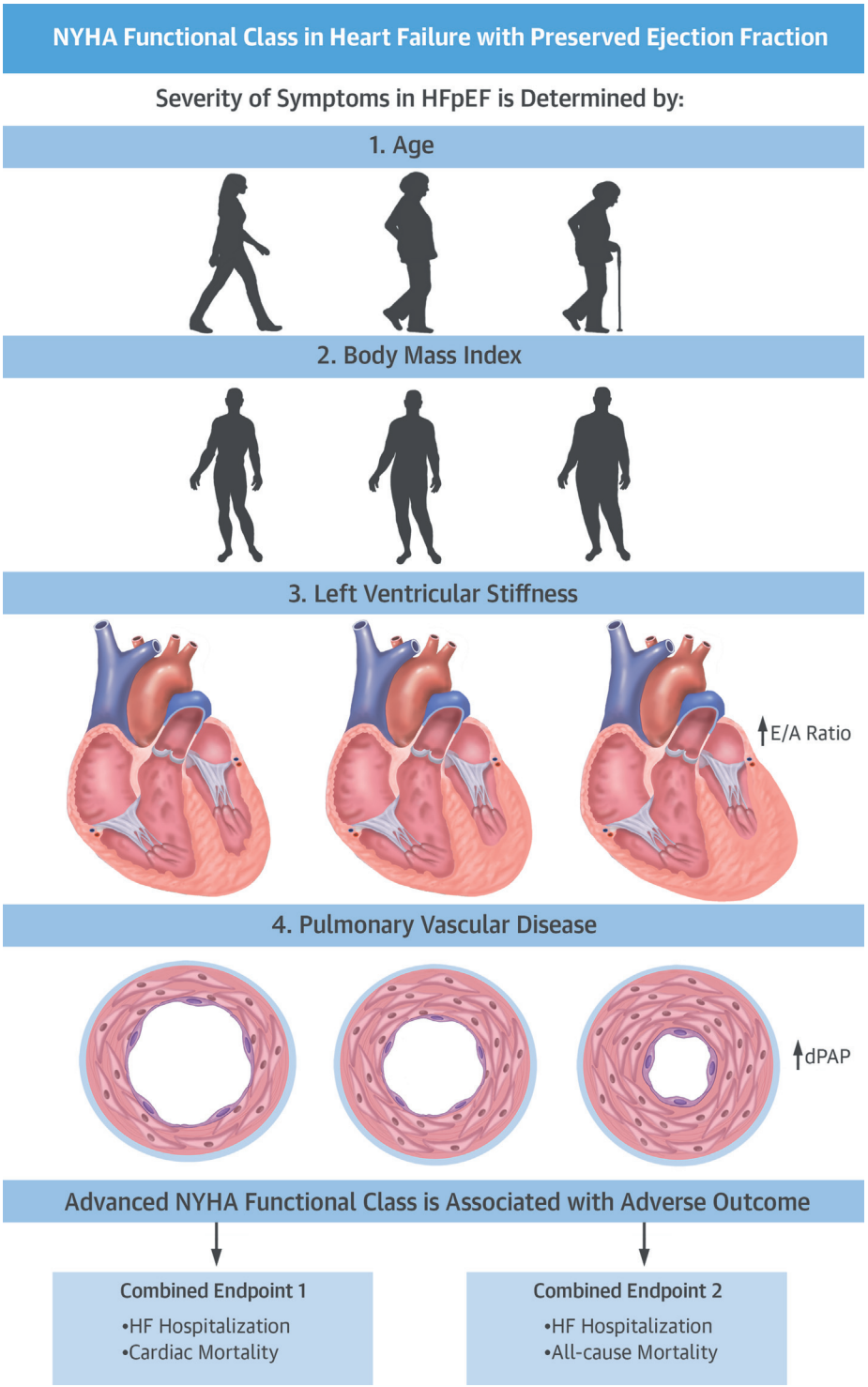
STUDY LIMITATIONS. Although NYHA functional class is used worldwide in patients with HF, there is notable interobserver variability, especially between classes II and III (17). In addition, cardiac assessments were not performed during cardiopulmonary exercise, and noncardiac components (e.g., skeletal muscle) potentially associated with reduced exercise tolerance were not investigated.

However, given differential outcomes and distinct clinical characteristics between NYHA classes, baseline allocation to respective functional classes seems valid. Because this study was performed at a single center, a center-specific bias cannot be excluded. However, there are some major advantages in limiting data collection to a single center: 1) inclusion of a homogenous patient population; 2) adherence to a constant clinical routine; 3) consistent quality of echocardiographic and right heart catheter workup; and 4) constant follow-up of the patient cohort.

CONCLUSIONS

The present study shows the prognostic importance of NYHA functional class on outcomes in patients

CENTRAL ILLUSTRATION **New York Heart Association Functional Class in Heart Failure With Preserved Ejection Fraction**



Dalos, D. et al. J Am Coll Cardiol. 2016;68(2):189-99.

Advanced New York Heart Association (NYHA) functional class is associated with adverse outcomes in this patient population. dPAP = diastolic pulmonary artery pressure; HF = heart failure; HFpEF = heart failure with preserved ejection fraction.

with HFpEF. Furthermore, it clearly delineates that in addition to advanced age and higher BMI, distinct hemodynamic parameters reflecting both LV filling impairment and pulmonary vascular disease underlie the cardinal symptom of HFpEF. Thus, future treatment efforts should target both the left ventricle and the pulmonary vasculature to alleviate symptoms and improve outcomes.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: In patients with HFpEF, dyspnea is related to impaired LV filling, pulmonary vascular disease, age, and BMI, and NYHA functional class predicts clinical outcomes.

TRANSLATIONAL OUTLOOK: Prospective studies that target body weight, LV diastolic dysfunction, and the pulmonary vasculature are needed to improve both prognosis and quality of life in patients with HFpEF.

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KEY WORDS functional capacity, heart failure, outcome