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Right ventricular-vascular coupling in heart failure with preserved ejection fraction and pre- versus post-capillary pulmonary hypertension.

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ABSTRACT

Aims: Many patients with heart failure with preserved ejection fraction (HFpEF) develop post-capillary pulmonary hypertension (PH) due to increased left-sided filling pressures. However, a subset of patients develops combined post- and pre-capillary PH. We studied the value of echocardiographic right-sided characterization for the discrimination between pre- versus post-capillary PH in HFpEF, using invasive haemodynamics as gold standard.

Methods and results: 102 consecutive HFpEF patients with simultaneous right heart catheterization and echocardiography were identified. Patients were divided into: 'no PH', 'isolated post-capillary PH' and 'post- and pre-capillary PH'. Systolic pulmonary arterial pressure (SPAP), tricuspid valve annular plane systolic excursion (TAPSE), right ventricular-vascular coupling (TAPSE/SPAP) and VO_2-max were assessed. Primary endpoint was all-cause mortality. A total of 97 patients were included: 22% no PH, 47% isolated post-capillary PH and 31% post- and pre-capillary PH. Patients with post- and pre-capillary PH had more often diabetes mellitus (47 vs. 24%, p=0.04), had more heart failure hospitalizations (57 vs. 26%, p=0.007) and lower VO_2-max (10 vs. 13 ml/min/kg, p=0.008), compared to those with isolated post-capillary PH. Patients with post- and pre-capillary PH also had more reduced TAPSE (17 vs. 21 mm, p=0.001) and TAPSE/SPAP (0.3 vs. 0.5, p<0.001). TAPSE/SPAP ratio <0.36 had a good accuracy to identify patients with additional pre-capillary PH (C-statistic 0.86, sensitivity 86% and specificity 79%). TAPSE/SPAP ratio was associated with increased mortality (HR 2.51 [95% CI 1.25-5.01], p=0.009).

Conclusion: Abnormal right ventricular-vascular coupling identifies patients with HFpEF and additional pre-capillary PH, and predicts poor outcome in HFpEF.

Keywords: HFpEF – Pre- and post-capillary pulmonary hypertension – Right ventricular function

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is associated with poor outcomes.(1) Although the mechanisms behind HFpEF remain incompletely understood, reduced relaxation and compliance of the left ventricle (LV) play a dominant role.(2) In a recent meta-analysis, we have confirmed that pulmonary hypertension (PH) is common in HFpEF, and that PH-HFpEF is strongly related to RV failure and death.(3,4)

The majority of patients with PH-HFpEF have isolated post-capillary PH due to increased left-sided filling pressures and resulting pulmonary venous congestion.(5) However, a subset of HFpEF patients develops combined post- and pre-capillary PH, characterized by an increased pulmonary artery wedge pressure (PAWP) of ≥15 mmHg in combination with an elevated diastolic pressure gradient (DPG) and/or increased pulmonary vascular resistance (PVR).(6) Genetic predisposition, endothelial dysfunction and neurohormonal activation may all explain the development of pre-capillary PH in HFpEF.(6) Characterization of patients with additional pre-capillary PH is important, since this group possibly represents a distinct subtype within the HFpEF phenotypic spectrum, that might respond to pulmonary vasodilator therapy.(7)

In the present study, we aimed to investigate the clinical characteristics of combined post- and pre-capillary PH, and its association with RV failure and death, in patients with HFpEF. We then sought to identify non-invasive determinants for the discrimination of pre- versus post-capillary PH. For this purpose, we investigated HFpEF patients who underwent simultaneous right heart catheterization and echocardiography.

METHODS

Study design

This observational cohort study was performed in consecutive outpatients who had a clinical diagnosis of HFpEF, based on heart failure symptoms (New York Heart Association [NYHA] functional class ≥ II) and LV ejection fraction ≥45%, who had suspected PH based on echocardiographic findings, and who were therefore referred for routine left and right-sided heart catheterization between October 2011 and September 2014 at our clinic. Patients that did not had echocardiography simultaneously with right heart catheterization or patients with organic valvular heart disease were excluded. Additional inclusion criteria for the present study were LV diastolic dysfunction (E/e' ≥13 or mean e' septal and lateral wall <9 cm/s) and/or left atrial (LA) dilatation (LA volume index ≥34 ml/m^2 or LA parasternal diameter ≥45 mm) and/or N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) ≥125 ng/l.(8) The study conforms to the Declaration of Helsinki and the Medical Research Involving Human Subjects Act. The institutional review board and local ethic committee approved this study. All assessments that were used in the present study were performed in the context of regular care and the need for individual informed consent was waived.

Right catheterization protocol

All patients underwent right heart catheterization performed by a single cardiologist (E.S.H.) and simultaneous echocardiography by a single experienced ultrasound technician (Y.M.H.). Hemodynamic measurements were performed with patient in fasting state and in supine position. The system was zeroed and referenced at patients' heart level as previously described.(9) A 7F thermodilution balloon-tipped catheter was inserted through the femoral vein. The catheter was advanced into the right atrium and RV, and subsequently positioned in the pulmonary artery and wedge position. Right atrial pressure (RAP), pulmonary artery pressures (PAP) and PAWP were recorded at end-expiration. Cardiac output was obtained using the Fick equation. Pulmonary vascular resistance, cardiac index, stroke volume, pulse

pressure and DPG were calculated using standard formulas. Pulmonary arterial compliance was determined as stroke volume / pulse pressure and expressed as ml/mmHg.

Patients were divided into subgroup: '*no PH*' (i.e. mean PAP <25 mmHg), *isolated post-capillary PH* (i.e. mean PAP ≥25 mmHg, PAWP ≥15 mmHg, DPG <7 mmHg and PVR ≤3.0 Wood Unit [WU]), *combined post- and pre-capillary PH* (i.e. mean PAP ≥25 mmHg and PAWP ≥15 mmHg with DPG ≥7 mmHg and/or PVR >3.0 WU) and *pre-capillary PH* (i.e. mean PAP ≥25 mmHg and PAWP <15 mmHg).(10) The latter two groups were combined as one group with additional pre-capillary PH.

Echocardiographic protocol

Echocardiographic images were acquired using a Vivid S6 system (General Electric, Horton, Norway) with a 2.5- to 3.5-mHz probe. Analyses were performed independently by two blinded investigators (T.M.G. and Y.M.H.) using GE EchoPAC version BT12. RV systolic function was assessed using multiple parameters. Tricuspid annular plane systolic excursion (TAPSE) was obtained in M-mode.(11) In addition, the systolic annular tissue velocity of the lateral tricuspid annulus (RV S') was measured.(11) Furthermore, RV free wall longitudinal strain was measured as previously reported, with good inter- and intra-observer variability.(12) Finally, RV fractional area change (FAC) was measured using the end-systolic and end-diastolic area of the RV in the apical four chamber view.(11) Each parameter for RV systolic function was measured in duplicate and averaged.

Systolic PAP (SPAP) was estimated on echocardiography using the peak velocity of the tricuspid regurgitation (TR) jet derived from continuous-wave Doppler. The peak velocity was converted to a pressure gradient using the modified Bernoulli equation and was subsequently added to an estimation of RAP obtained from the diameter and collapsibility of the inferior vena cava (IVC).(11) For an IVC with diameter <2.1 cm that collapses ≥50% with

a sniff, the RAP value of 3 mmHg was used, an IVC with diameter ≥2.1 cm that collapses <50% suggests RAP of 15 mmHg. If IVC diameter and collapse did not fit this scenario, an intermediate value of 8 mmHg was used.(11) Right ventricular-vascular coupling was approximated by calculating the ratio of TAPSE to echocardiographic derived SPAP (i.e. TAPSE/SPAP).(13) TAPSE/SPAP ratio was validated against TAPSE/SPAP with SPAP derived from right heart catheterization. The TAPSE/SPAP ratio was also compared with the TAPSE/TR velocity ratio.

Exercise capacity test

Patients underwent a cardiopulmonary exercise test on a treadmill according to the Weber auto protocol. Patients were encouraged to provide a maximum exertion. Stop criteria that were considered included: patient reached plateau phase for one minute, patient cannot walk further or is unable to maintain walking speed, decrease in breathing reserve and O_2 heart rate. Reaching the expected VO_2 max value was not considered a stop criterion. Peak VO_2 was expressed in ml/min/kg and as percentage of predicted.

Outcome

The primary outcome measure was defined as all-cause mortality, ascertained from the electronic medical records.

Statistical analyses

Differences between groups were tested using Independent Samples T-tests for normally distributed continuous variables, Mann-Whitney U tests for skewed distributed continuous variables and Chi-squared tests for categorical variables. Accuracy for identifying pre-capillary PH was calculated using C-statistic and by plotting receiver operating characteristic

(ROC) curves. Multivariable survival analyses were performed using Cox regression models. The maximum number of events per adjustment variable in the logistic regression analysis was set at 10, based on previous recommendations.(14) Multicollinearity was tested using linear regression. In addition, survival was illustrated in Kaplan-Meier curves and tested using log-rank tests. Blant-Altman analysis was performed to analyse agreement between TAPSE/SPAP ratio derived from Doppler echocardiography and TAPSE/SPAP obtained from right heart catheterization. Statistical significance was considered achieved with p-value <0.05. All statistical analyses were performed using SPSS (Version 22, 2013).

RESULTS

A total of 102 HFpEF patients with suspected PH on a previous echocardiography who were referred for right heart catheterization were identified. Four patients who did not had a simultaneous echocardiography. Thus in total, 97 patients were included in the present analysis. Seventy-six patients (78.4%) had PH, defined as mean PAP ≥25 mmHg (**Table 1**). Of these, 46 (47.4%) had isolated post-capillary PH, 24 patients (24.7%) had combined post- and pre-capillary PH, and six patients (6.2%) had isolated pre-capillary PH according to the diagnostic definition. Fourteen patients (14%) did not undergo a conclusive exercise capacity test. In 79 (81.4%) patient, tricuspid regurgitation jet was sufficient to estimate SPAP. Patients with PH-HFpEF were more symptomatic (i.e. higher NYHA functional class, more diuretic use and reduced exercise capacity), compared to patients without PH (**Table 1**). Permanent atrial fibrillation was also more prevalent in PH-HFpEF (43 versus 5%, p=0.004).

Characteristics of pre- versus post-capillary PH in HFpEF

As seen in **Table 1**, PAWP was comparable between patients with isolated post-capillary PH and additional pre-capillary PH. However, patients with additional pre-capillary PH had more

often diabetes mellitus, and there was a trend that these patients more often had chronic obstructive pulmonary disease (COPD). HFpEF patients with pre-capillary PH had the highest NT-proBNP levels, were more often previously hospitalized for heart failure, and had the lowest exercise capacity. RV function and TAPSE/SPAP ratio was lower in patients with a pre-capillary component of PH, compared to isolated post-capillary PH.

Individual data of the six patients with isolated pre-capillary PH are depicted in **Supplementary Table 1**. Four of these patients had COPD, three had diabetes mellitus and PVR ranged from 5.3 to 9.3 WU.

Outcome of pre- versus post-capillary PH in HFpEF

During a median follow-up of 816 (547 – 1047) days, 20 patients (20.6%) died. The results of the Cox regression model for the prediction of death are depicted in **Table 2**. In univariable analyses, diabetes mellitus, COPD, RV function, TAPSE/TR velocity and TAPSE/SPAP ratio, PAP, PVR and the presence of additional pre-capillary PH were all associated with mortality. The presence of PH *per se* was not associated with increased mortality. RV function according to TAPSE, RV S' and FAC remained associated with mortality after adjustment of age and sex. Also reduced TAPSE/SPAP ratio remained associated with death after adjustment for age and sex (**Table 2**), and after adjustment for diabetes mellitus and COPD (**Supplementary Table 2**). There was multicollinearity between TAPSE/SPAP ratio and other established echocardiographic measurements of RV function and with invasive pulmonary pressures (**Supplementary Table 2**).

Identification of pre- versus post-capillary PH in HFpEF

The results of the C-statistics to discriminate between isolated post-capillary PH and additional pre-capillary PH are depicted in **Table 3**. The non-invasively derived

TAPSE/SPAP ratio had a C-statistic of 0.86. The ROC-analysis for TAPSE/SPAP ratio demonstrates a good accuracy for the prediction of any pre-capillary PH in HFpEF, with a sensitivity of 87% and specificity of 79% for TAPSE/SPAP 0.36 (**Figure 1**). **Figure 2** illustrates the survival curve when patients were divided according to TAPSE/SPAP ratio <0.36 (Log-rank p=0.006). In **Table 3** in the **Supplementary Material**, baseline characteristics are presented when patients were divided according to TAPSE/SPAP <0.36. Patients with low TAPSE/SPAP ratio had a higher prevalence of atrial fibrillation, more previous HF hospitalizations, higher PAP and PVR, lower pulmonary arterial compliance, more LV diastolic dysfunction, lower peak VO_2-max and higher NT-proBNP.

In a sub analysis, after exclusion of the six patients with isolated pre-capillary PH, echocardiographic TAPSE/SPAP ratio remained predictive of mortality, after adjustment for age and sex: HR 2.25 per standard deviation decrease (95% CI 1.09-4.67), p=0.029 and Log-rank p=0.036 for TAPSE/SPAP <0.36.

The non-invasive TAPSE/SPAP ratio correlated strongly with the invasively derived TAPSE/SPAP ratio (r=0.71, p<0.001), (**Supplementary Figure)**. Blant-Altman analysis for the comparison between TAPSE/SPAP derived from right heart catheterization and from echocardiography is also illustrated in the **Supplementary Figure**.

DISCUSSION

In our study of HFpEF patients undergoing simultaneous right heart catheterization and echocardiography, we found that patients with a pre-capillary component of PH had significantly lower exercise capacity and were more at risk for RV failure, HF hospitalizations and death, compared to HFpEF patients without pre-capillary PH. Abnormal right ventricular-vascular coupling (i.e. reduced TAPSE/SPAP ratio) identified these HFpEF patients with a pre-capillary component of PH, and predicted poor outcomes.

It is increasingly evident that both PH and RV dysfunction are of major importance in HFpEF, given their high prevalence and strong association with adverse prognosis.(3) The development of additional pre-capillary PH in HFpEF is of particular concern given its strong prognostic impact.(7) Identification of pre-capillary PH in HFpEF also potentially opens the door to the pulmonary vasculature as a potential treatment target in patients with PH-HFpEF, but currently no drugs that are approved for the treatment of pulmonary arterial hypertension (group 1 PH) have been proven safe and beneficial in patients with PH-HFpEF.(7) Hence, in the latest European Society of Cardiology Guidelines for the Diagnosis and Treatment of PH, the use of such therapies has a class III recommendation for patients with PH due to left heart disease (group 2 PH).(10) There are currently several on-going trials with other specific drugs to treat PH-HFpEF, including riociguat (NCT02744339), vericiguat (NCT01951638) and nitrite (NCT02742129).

Characteristics of pre- versus post-capillary PH in HFpEF

The present patient cohort was rigorously screened for HFpEF according to the current recommendations. We observed that 31% of the HFpEF patients referred for catheterization had a pre-capillary component of PH, of which six patients had isolated pre-capillary PH, with a PAWP less than 15 mmHg. One might argue whether the latter are true HFpEF patients. Although patients are divided into different PH groups by definition of hemodynamic measurements, LV filling pressures in HFpEF might be <15 mmHg at resting conditions, since filling pressures are highly variable over time and are also influenced by volume status and physical activity.(15) In those patients, LV filling pressures may typically rise with exercise.(16) Thus, HFpEF patients with optimal diuretic dose may demonstrate temporally lower or only borderline elevated LV filling pressures at rest, while mean PAP remains high in the setting of secondary vasculopathy. In the absence of invasive

haemodynamics during exercise, we cannot exclude that some of these patients might still be misclassified as HFpEF. However, based on the current diagnostic work-up for HFpEF – in which echocardiography still is the first line bedside tool – our patients clearly had HFpEF according to the current definition. In the present study, none of the patients were on pulmonary vasodilator therapy at the time of hemodynamic assessment.

We did observe a trend that COPD was more prevalent in patients with (additional) pre-capillary PH. COPD is a common finding in HFpEF, with a previously reported prevalence rate of 24% in multiple HFpEF studies.(3) We have to keep in mind that the diagnostic evaluation between COPD and HFpEF is challenging, since both patient groups may share signs and symptoms (e.g. dyspnea on exertion), the presence of a "preserved" LVEF, and the strong association with PH.(10) Therefore, one should be aware of an overlap between both diseases and the present study demonstrates the need for hemodynamic testing in these patients, to better discriminate between group 2 and 3 PH.

Patients with a pre-capillary component of PH-HFpEF were characterized by severely depressed exercise capacity. The reduced exercise capacity in patients with pre-capillary PH could therefore be relate to reduced pulmonary vascular function, higher pulmonary pressures and resulting impaired RV function, which was clearly demonstrated in the combined post- and pre-capillary PH group. Recently, the prognostic value of tricuspid regurgitation recorded during exercise was demonstrated in HFpEF, which was independent of LV diastolic dysfunction.(17) Interestingly, Borlaug *et al.* also noticed that patients with HFpEF displayed impaired RV reserve with exercise, even in the early stages of the disease, suggesting the importance of biventricular dysfunction in HFpEF.(16)

Another characteristic of patients with additional pre-capillary PH was the presence of diabetes mellitus. This finding is consistent with a prior invasive study of HFpEF with pre-capillary PH, in which the presence of comorbidities distinguished these patients from those

with idiopathic pulmonary arterial hypertension.(18) This suggests that the development of pre-capillary PH in HFpEF is not solely the result of chronic backward transmission of left-sided filling pressures, but that other mechanisms might play a role. Indeed the multi-hit hypothesis, wherein endothelial dysfunction and systemic inflammation driven by a combination of comorbidities (such as diabetes and COPD), has been postulated to contribute to pulmonary vascular remodelling in HFpEF.(19)

Identification of pre- versus post-capillary PH in HFpEF

The present study described the important value of pre-capillary PH in HFpEF. The definition of pre-capillary PH hinges on invasively derived measurements. However, it is rather impractical to routinely perform right heart catheterizations in all HFpEF patients.

RV afterload is predominantly determined by increased PVR and elevated PAP.(20) However, since RV function is highly sensitive to alterations in afterload,(21) it has recently been suggested that characterization of RV function in HFpEF may be best framed in relation to prevailing RV load.(22) The relationship of RV function to afterload (i.e. right ventricular-vascular coupling) and cardiovascular outcome has been established for both PAH and heart failure.(13,23) In the present study, we demonstrated that the non-invasive TAPSE/SPAP ratio <0.36 has a strong prognostic value and is also useful in discriminating HFpEF patients with additional pre-capillary PH from HFpEF patients without pre-capillary PH. While TAPSE/SPAP does not directly measure pulmonary vascular resistance, our results show that the presence of abnormal right ventricular-vascular coupling (reflected by the TAPSE/SPAP ratio) increased the probability that the patient may have a pre-capillary component of PH, although further verification is required. TAPSE/SPAP ratio may also be used as an endpoint in trials targeting PH-HFpEF.

We observed that patients with low TAPSE/SPAP ratio displayed some distinct characteristics, such as higher prevalence of atrial fibrillation, more severe LV diastolic dysfunction and higher NT-proBNP, compared with patients with higher TAPSE/SPAP ratio. This finding is perhaps an indication of more advance staged heart failure in those patients with low right ventricular-vascular coupling. In a recent sub analysis from the RELAX trial, Hussain *et al.* demonstrated similar findings. In their study, HFpEF patients with RV dysfunction and impaired right ventricular-vascular coupling also seemed to have more advanced heart failure.(22)

Limitations

Some limitations merit emphasis. First, patients with HFpEF and suspected PH on previous echocardiography were clinically referred for right heart catheterization and this might have introduced a selection bias. Second, the haemodynamic assessment was only performed at resting condition. Especially when the diagnosis of HFpEF is uncertain, as was the case for the six patients with PAWP <15 mmHg, availability of LV filling pressures obtained during exercise would have abled use to better discriminate between group 2 PH and other PH groups. In addition, the sample size was small and the study was also not powered to investigate multivariate associations with outcome using >2 adjustment variables. Furthermore, despite the high correlation with the invasively derived TAPSE/SPAP ratio, the non-invasive assessment of TAPSE/SPAP, measured with Doppler echocardiography, could only be assessed in those patients with sufficient tricuspid regurgitation, which may have introduced another selection bias.

Conclusion

Patients with HFpEF and an important pre-capillary component of PH are at increased risk for RV failure and death, compared to patients with HFpEF without additional pre-capillary PH. Impaired right ventricular-vascular coupling (reflected by reduced TAPSE/SPAP ratio) suggests more advanced heart failure and identifies these vulnerable HFpEF patients with additional pre-capillary PH.

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Table 1: Baseline characteristics of the total study population and subgroups

	No PH (n=21)	**PH (n=76)**	**p-value** PH versus no PH	**PH (n=76)**		
				Isolated post-capillary PH (n=46)	**Additional pre-capillary PH (n=30)**	**p-value** Post- versus pre-capillary PH
Demographics						
Age (years)	70.8±8.1	74.5±8.8	0.09	74.7±7.3	74.2±10.8	0.83
Male sex	7 (33%)	23 (30%)	0.79	11 (24%)	12 (40%)	0.14
Body mass index (kg/m^2)	27.5±4.7	28.7±6.0	0.39	28.1±5.8	29.6±6.3	0.29
Comorbidities						
Hypertension	14 (67%)	50 (66%)	0.94	31 (67%)	19 (63%)	0.72
Coronary artery disease	7 (33%)	26 (34%)	0.94	14 (30%)	12 (40%)	0.39
Atrial fibrillation			**0.004**			0.17
Paroxysmal	5 (24%)	10 (13%)		7 (15%)	3 (10%)	
Permanent	1 (5%)	33 (43%)		16 (35%)	17 (57%)	
Diabetes mellitus	6 (29%)	25 (33%)	0.71	11 (24%)	14 (47%)	**0.04**

COPD	3 (14%)	13 (17%)	0.76	5 (11%)	8 (27%)	0.07
Heart failure characteristics						
NYHA functional class			**<0.001**			0.17
II	17 (81%)	22 (29%)		16 (35%)	6 (20%)	
III	4 (19%)	54 (71%)		30 (65%)	24 (80%)	
Diuretics use	13 (62%)	62 (82%)	**0.04**	37 (80%)	25 (83%)	0.52
Previous HF hospitalization	4 (19%)	29 (38%)	0.10	12 (26%)	17 (57%)	**0.007**
Haemodynamics						
Heart rate (bpm)	67±14	72±12	0.07	72±11	73±14	0.65
Systolic blood pressure (mmHg)	149±23	150±25	0.93	155±21	141±28	**0.02**
Diastolic blood pressure (mmHg)	66±16	70±12	0.16	71±13	69±11	0.41
Cardiac output (l/min)	6.6±2.0	5.4±1.2	**0.01**	5.8±1.2	4.7±1.1	**<0.001**
Cardiac index (l/min/m^2)	3.6±1.0	2.8±0.7	**<0.001**	3.1±0.6	2.5±0.6	**<0.001**
Mean PAWP (mmHg)	10±3	19±5	**<0.001**	20±4	18±6	0.09
Systolic PAP (mmHg)	31±6	55±14	**<0.001**	49±9	64±16	**<0.001**

Diastolic PAP (mmHg)	11±3	20±6	**<0.001**	18±4	24±6	**<0.001**
Mean PAP (mmHg)	18±3	35±8	**<0.001**	31±5	41±9	**<0.001**
Mean RAP (mmHg)	4±3	10±5	**<0.001**	8±4	11±5	**0.005**
PVR (WU)	1.3±0.4	3.1±2.1	**<0.001**	1.9±0.6	4.9±2.3	**<0.001**
PAC (ml/mmHg)	5.4±1.9	2.4±1.0	**<0.001**	2.8±0.8	1.9±1.0	**<0.001**
Echocardiography						
LV ejection fraction (%)	57±5	57±5	0.72	57±5	56±5	0.29
LV mass index (kg/m^2)	101±27	94±31	0.38	91±35	99±25	0.28
E/e’	11.8 [8.3-14.1]	12.7 [10.1-16.5]	0.12	12.1 [9.9-15.5]	14.4 [10.1-21.4]	0.20
Mean e’ septal/lateral wall	7.8 [6.2-8.7]	7.5 [6.2-8.9]	0.90	7.6 [6.5-9.6]	7.0 [4.9-8.5]	0.12
LAVi (ml/m^2)	42±18	48±16	0.18	49±18	47±14	0.67
TAPSE (mm)	22.9±6.1	19.6±4.8	**0.01**	21.2±4.5	17.1±4.3	**0.001**
RV S’ (cm/s)	9.6±2.4	9.1±2.8	0.56	9.9±2.7	7.7±2.4	**0.001**
FWLS (%)	-21.5±6.2	-19.9±5.7	0.32	-21.8±5.7	-17.5±4.9	**0.004**
FAC (%)	51±12	45±13	0.13	50±11	39±12	**<0.001**
TR velocity (m/s) (n=79)	2.7±0.4	3.2±0.5	**0.003**	3.0±0.4	3.5±0.6	**0.001**

TAPSE/TR velocity ratio (n=74)	2.6±0.7	1.8±0.3	**0.01**	1.8±0.3	1.3±0.3	**<0.001**
TAPSE/SPAP ratio* (n=74)	0.4±0.2	0.4±0.2	**0.01**	0.5±0.2	0.3±0.1	**<0.001**
Exercise capacity (n=83)						
Peak VO_2-max (ml/min/kg)	14.8±3.5	11.6±3.6	**0.001**	12.5±3.8	10.1±2.8	**0.008**
Peak VO_2-max of predicted (%)	70±17	60±18	**0.04**	65±18	51±15	**0.003**
Laboratory test						
NT-proBNP (ng/l)	486 [216-1233]	1087 [497-2021]	**0.01**	840 [425-1816]	1548 [701-2340]	**0.04**

Data is reported as mean ± standard deviation, median [interquartile range] and n (%). COPD chronic obstructive pulmonary disease; FAC fractional area change; FWLS free wall longitudinal strain; HF heart failure; LAVi left atrial volume index; NT-proBNP N-terminal prohormone of brain natriuretic peptide; NYHA New York Heart Association; PAC pulmonary arterial compliance; PAP pulmonary arterial pressure; PAWP pulmonary artery wedge pressure; PH pulmonary hypertension; PVR pulmonary vascular resistance; RAP right atrial pressure; RV S' systolic annular tissue velocity of the lateral tricuspid annulus; SPAP systolic pulmonary artery pressure; TAPSE tricuspid valve annular plane systolic excursion; TR tricuspid regurgitation; VO_2-max maximal oxygen consumption. *Echocardiographic derived TAPSE/SPAP.

Table 2: Cox regression model for the prediction of death in HFpEF

	Unadjusted HR	p-value	Adjusted HR*	p-value
Age	1.02 (0.97-1.08)	0.41		
Male sex	0.83 (0.30-2.31)	0.73		
Body mass index	0.98 (0.91-1.06)	0.98		
Coronary artery disease	2.23 (0.91-5.48)	0.08		
Atrial fibrillation	1.51 (0.62-3.65)	0.36		
Diabetes mellitus	3.58 (1.46-8.77)	**0.005**	3.66 (1.48-9.06)	**0.005**
COPD	3.71 (1.49-9.24)	**0.005**	3.64 (1.43-9.26)	**0.007**
TAPSE‡	1.78 (1.05-3.01)	**0.03**	1.81 (1.06-3.08)	**0.03**
RV S'‡	2.45 (1.34-4.48)	**0.001**	2.65 (1.43-4.92)	**0.002**
FWLS†	1.55 (0.96-2.50)	0.07		
FAC‡	2.13 (1.33-3.40)	**0.001**	2.20 (1.35 (3.60)	**0.002**
TR velocity	1.42 (0.95-2.12)	0.09		
TAPSE/TR velocity ratio‡	2.16 (1.17-3.97)	**0.01**	2.19 (1.17-4.09)	**0.01**
TAPSE/SPAP ratio*‡	2.42 (1.24-4.70)	**0.003**	2.51 (1.25-5.01)	**0.009**
Mean PAWP†	0.81 (0.51-1.30)	0.38		
Systolic PAP†	1.44 (1.05-1.98)	**0.03**	1.78 (1.16-2.73)	**0.008**
Mean PAP†	1.46 (1.03-2.08)	**0.03**	1.85 (1.15-2.99)	**0.01**
Cardiac index	1.36 (0.85-2.16)	0.20		
PVR†	1.52 (1.14-2.03)	**0.004**	1.72 (1.24-2.38)	**0.001**
PAC‡	1.81 (0.99-3.30)	0.05		
PH versus no-PH	1.49 (0.43-5.10)	0.53		
Pre- versus post-capillary PH	3.91 (1.37-11.11)	**0.01**	4.35 (1.51-12.54)	**0.006**

Same abbreviations as in Table 1. *Echocardiographic derived TAPSE/SPAP. †Per standard deviation increase; ǂper standard deviation decrease. The multivariable analysis was adjusted for age and sex.

Table 3: C-statistic of the identification of pre-capillary PH in HFpEF

Variable	C-statistic
Mean PAP	0.91
PAC	0.86
Systolic PAP	0.86
TAPSE/SPAP ratio*	0.86
Cardiac index	0.79
FAC	0.77
TAPSE	0.76
Peak VO_2-max % of predicted	0.76
RV S'	0.73
Mean RAP	0.73
FWLS	0.70
TAPSE/TR velocity ratio	0.69
NT-proBNP	0.68
TR velocity	0.66
Diabetes mellitus	0.61
Age	0.57
Male sex	0.57
COPD	0.57

Same abbreviations as in Table 1. *Echocardiographic derived TAPSE/SPAP.

FIGURE LEGENDS

Figure 1: Receiver operating characteristic curve for identification of pre-capillary pulmonary hypertension. TAPSE/SPAP ratio 0.36 had a sensitivity of 86% and specificity of 79% for identifying HFpEF patients with additional pre-capillary pulmonary hypertension.

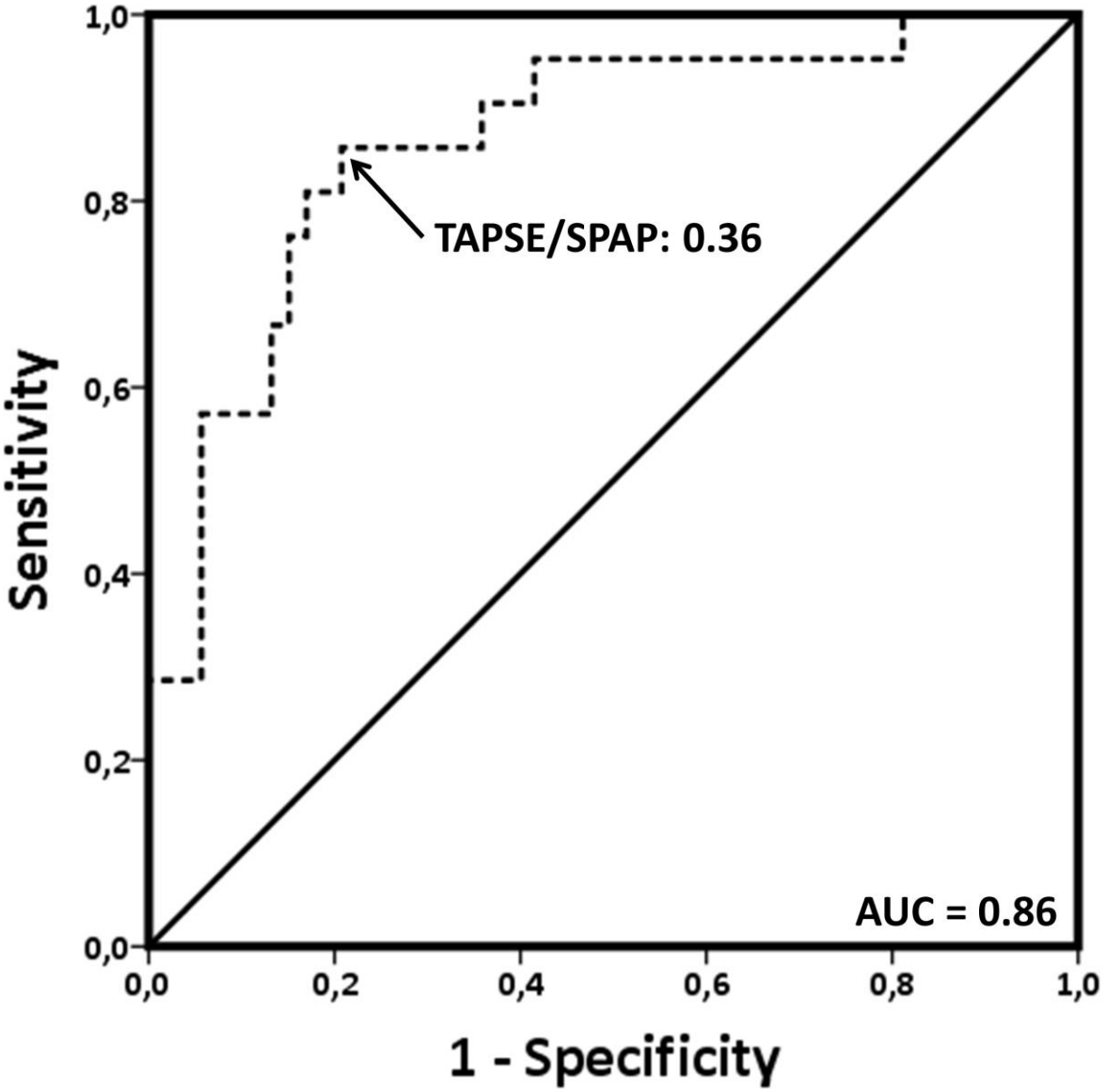
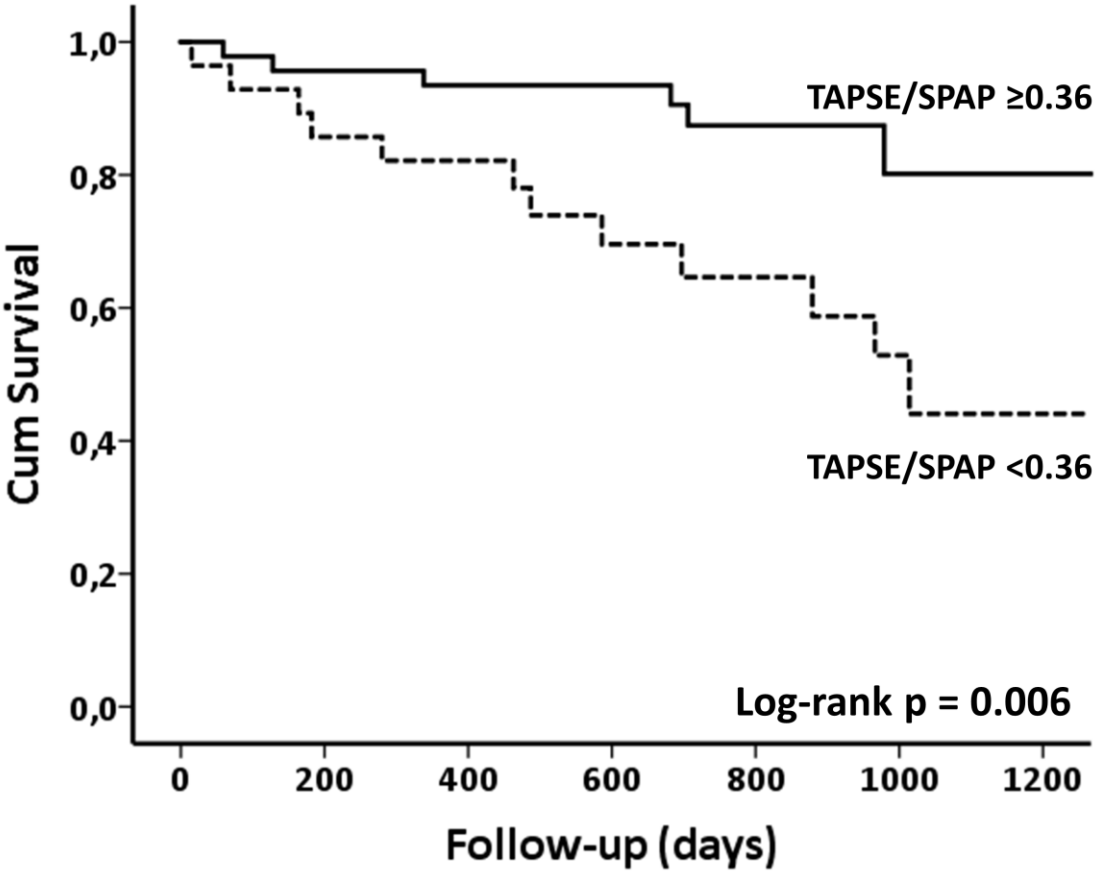


Figure 2: Kaplan-Meier survival curve for the prediction of death.



TAPSE/SPAP ≥0.36	46	43	42	42	40	39	40
TAPSE/SPAP <0.36	28	23	22	19	18	16	16