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Pulmonary capillary wedge pressure during exercise and long-term mortality in patients with suspected heart failure with preserved ejection fraction

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Aims In patients with suspected heart failure with preserved ejection fraction (HFpEF), invasive exercise testing may be considered when measurements at rest are inconclusive. However, the prognostic impact of invasive exercise testing is uncertain, so far.

Methods and results We retrospectively analysed mortality in 355 patients [mean age 61.2 ± 11.3 years, 235 (66.2%) women] with unexplained dyspnoea and suspected HFpEF. During an invasive haemodynamic stress test pulmonary capillary wedge pressure (PCWP) at rest and the PCWP response to exercise, expressed as the ratio of PCWP at peak exercise to workload normalized to body weight [PCWL (mmHg/W/kg)], were recorded. Both PCWP at rest and PCWL were significant and independent predictors of long-term mortality. Adding PCWL to PCWP at rest improved reclassification of patients into survivors or non-survivors with a net reclassification improvement (NRI) of 0.56 (95% CI: 0.29–0.83; $P < 0.001$). Ten-year mortality was 6.6% in subjects with low PCWP at rest (≤12 mmHg) and low PCWL (≤25.5 mmHg/W/kg); 28.2% in patients with low PCWP and high PCWL and 35.2% in those with high PCWP and high PCWL. Compared with patients with low PCWP and low PCWL, the adjusted hazard ratio for mortality was 2.37 (95% CI: 1.09–5.17; $P = 0.029$) for the low-PCWP/high-PCWL group and 4.75 (95% CI: 1.90–11.84; $P < 0.001$) for patients with high PCWP/high PCWL.

Conclusion In patients with suspected HFpEF, invasive exercise testing substantially improves prediction of long-term mortality. An excessive rise of PCWP during exercise despite normal PCWP at rest is associated with increased mortality and may be considered as early HFpEF.

Keywords Heart failure with preserved ejection fraction • Pulmonary capillary wedge pressure • Exercise haemodynamics • Mortality

Introduction

Dyspnoea on exertion presents a diagnostic challenge in patients with preserved left ventricular ejection fraction (EF), no signs of fluid overload, and without significant coronary, pericardial or valvular heart disease. In these patients, heart failure with preserved ejection fraction (HFpEF) is a common cause of symptoms[1]—however, diagnosis and differentiation from non-cardiac causes of dyspnoea is often challenging. Invasive haemodynamic measurements can help to solve this diagnostic puzzle: a mean pulmonary capillary wedge pressure (PCWP) >12 mmHg confirms the diagnosis of HFpEF.[2] In a significant number of patients with suspected HFpEF, however, the diagnosis cannot be established solely based on measurements at rest. In subjects with normal filling pressure at rest, haemodynamic stress testing can be considered, since this might identify HFpEF at mild or early stages, when alterations at rest or

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elevated BNP levels are still absent.[3] A steep increase in PCWP during exercise is a typical haemodynamic response in HFpEF,[4,5] indicating that the dyspnoea on exertion is of cardiac origin. Yet, this subset of patients is currently poorly characterized and data about the prognostic impact of haemodynamics during exercise are lacking.

Thus, the present study investigated the role of exercise testing with PCWP measurements in the diagnostic work-up of patients with unexplained dyspnoea. Specifically, we analysed in a large retrospective cohort of patients with suspected or established HFpEF, whether PCWP at rest and/or an excessive rise of PCWP during exercise improves prediction of long-term mortality.

Methods

Study population

This retrospective study analysed consecutive patients referred to our institution for unexplained dyspnoea (NYHA class II or III) between January 1996 and December 2010. Patients were included in this analysis if a right heart catheterization, an echocardiography, and a coronary angiography had been performed within 12 months. Patients were excluded if they had valvular heart disease (regurgitation or stenosis more than mild), significant coronary artery disease (stenosis in any vessel >50%), or if left ventricular systolic function was impaired, defined as EF ≤50%. Further exclusion criteria were prior cardiac surgery or pacemaker implantation, cardiac shunt, constrictive pericarditis, pulmonary arterial hypertension, and hypertrophic or restrictive cardiomyopathy. For follow-up, patients were contacted by questionnaire or telephone and all available medical records were reviewed by independent physicians. In case of no response, the general practitioner or known relatives were contacted. Follow-up data were available for all 355 patients. The start of follow-up was defined as the date of right heart catheterization. The study was approved by the institutional ethics committee.

Cardiac catheterization and exercise protocol

Patients were examined in a supine position on their regular medication by standard techniques using a Swan-Ganz catheter inserted via a brachial vein. PCWP was measured at end expiration at rest and averaged over ≥3 breathing cycles during exercise. The Fick method was used for obtaining cardiac output (CO) by calculating arteriovenous oxygen difference from mixed venous and arterialized capillary oxygen saturation taken from a hyperaemized earlobe. Oxygen uptake at rest was calculated by a previously published formula and nomogram values, stratified for age, level of workload and sex, were taken from the literature for calculations during exercise.[6]

After measurement at rest, patients performed a cycle ergometry (Lode B.V. Medical technology, Type 917900, Groningen, Netherlands). Adapted to individual physical capacity, exercise was started at 25 or 50 W and increased until exhaustion in increments of 25 or 50 W, respectively. Every exercise level was continued for 5 min, pulmonary artery (PA) pressure was recorded continuously and PCWP and CO at Minute 3 on each level. Blood pressure (BP) was obtained non-invasively with an oscillometric digital sphygmomanometer before cycling and at Minute 5 of each level of exercise. At the end of the maximum exercise level, directly before cessation of the stress test, the catheter was withdrawn from PA and right atrial (RA) pressure was determined.

Table 1 Clinical and echocardiographic characteristics with univariable hazard ratios for all-cause mortality

	All patients (n = 355)	Survivors (n = 297)	Non-survivors (n = 58)	*P*-value	Hazard ratio (95% CI)	*P*-value
Age (years)	61.2 ± 11.3	59.6 ± 11.1	69.5 ± 7.9	<0.001	1.14 (1.10–1.18)	<0.001
Body mass index (kg/m^2)	27.8 ± 4.5	27.7 ± 4.5	28.5 ± 4.6	0.189	1.05 (0.99–1.11)	0.100
Male sex	120 (33.8%)	99 (33.3%)	21 (36.2%)	0.672	1.20 (0.70–2.04)	0.514
Diabetes mellitus	38 (10.7%)	24 (8.1%)	14 (24.1%)	<0.001	2.83 (1.55–5.17)	0.001
Arterial hypertension	240 (67.6%)	193 (65%)	47 (81%)	0.017	2.28 (1.18–4.40)	0.014
Atrial fibrillation[a]	27 (7.6%)	19 (6.4%)	8 (13.8%)	0.052	2.73 (1.29–5.80)	0.009
Left bundle branch block	13 (3.7)	9 (3.0%)	4 (6.9%)	0.152	2.04 (0.74–5.64)	0.168
eGFR (mL/min/1.73 m^2)[b]	85.3 ± 21	86.9 ± 21.3	77.1 ± 24.4	0.002	0.97 (0.96–0.99)	<0.001
Ejection fraction (%)[c]	68 ± 7	68 ± 7	68 ± 8	0.845	1.01 (0.97–1.04)	0.707
Haemoglobin (g/dL)	14.0 ± 1.3	14.0 ± 1.3	14.0 ± 1.6	0.763	0.91 (0.73–1.12)	0.370
Sodium (mmol/L)	141 ± 3	141 ± 3	141 ± 4	0.934	0.97 (0.90–1.05)	0.434
LVEDD (mm)	48 ± 5	48 ± 5	48 ± 6	0.478	0.99 (0.94–1.04)	0.678
LVEDDI (mm/m^2)	26.0 ± 2.9	26.0 ± 2.8	25.9 ± 3.4	0.841	1.00 (0.98–1.01)	0.737
LVEDV (mL)	110 ± 26	110 ± 26	108 ± 30	0.590	1.00 (0.99–1.01)	0.804
LVEDVI (mL/m^2)	59 ± 13	59 ± 12	58 ± 15	0.754	1.00 (0.98–1.02)	0.737
Left ventricular mass (g)	179 ± 52	175 ± 50	199 ± 56	0.001	1.08 (1.03–1.13)	0.001
LVMI (g/m^2)	96 ± 25	93 ± 24	108 ± 30	0.001	1.02 (1.01–1.039	<0.001

Hazard ratio for left ventricular mass is per 10 g increase; all other hazard ratios for continuous variables are per unit increase.
eGFR, estimated glomerular filtration rate; LVEDD, left ventricular end-diastolic diameter; LVEDDI, left ventricular end-diastolic diameter index; LVEDV, left ventricular end-diastolic volume; LVEDVI, left ventricular end-diastolic volume index; LVMI, left ventricular mass index
[a]Paroxysmal or persistent.
[b]Modification of Diet in Renal Disease (MDRD) formula.
[c]Teichholz method.

Statistical analysis

Our primary outcome measure was all-cause mortality during the follow-up. PCWP at rest and the PCWP response to exercise were analysed as continuous and as dichotomized variables. To describe the PCWP response to exercise, the ratio of PCWP at peak exercise to workload normalized to body weight was calculated [PCWL (mmHg/W/kg)]. This variable is less dependent on patient cooperation than PCWP at peak exercise, because in patients who stop exercise prematurely peak PCWP may be misleadingly low, while PCWL can still detect abnormal haemodynamics. Moreover, PCWL has been shown to be a characteristic haemodynamic criterion for HFpEF in a previous study.[5] In 19 patients, pulmonary capillary wedge position could not be reached at peak exercise. For these missing PCWP values, imputation based on diastolic pulmonary artery pressure (PAPd) was used.

Categorical variables are reported as percentages, and normally distributed continuous variables as mean and standard deviation. For categorical variables, differences between groups were tested with the χ^2 test or Fisher's exact test where appropriate. For comparison of continuous variables, Student's *t*-test was employed. In the two-sided test, a $P-$value <0.05 was regarded as significant. Survival curves were generated by Kaplan Meier analyses and compared by the log-rank test. Cox proportional hazards models were used to calculate hazard ratios (HRs) with associated 95% confidence intervals (CI). Owing to limited number of events, we took a parsimonious approach to the multivariable Cox regression models. Apart from our primary pre-specified variables, PCWP at rest and PCWL, these models included clinical and echocardiographic predictors of mortality listed in *Table 1* that were significant ($P < 0.05$) by univariable analysis as well as gender, body mass index, history of atrial fibrillation, and left bundle branch block, as additional factors with known impact on prognosis. To assess *c*-statistics of variables for mortality, receiver-operating characteristic (ROC) curves were constructed. Optimal cut-off points were identified by the Youden index. ROC curves were compared using the method described by DeLong *et al.*[7] To evaluate the improvement in classification by addition of certain variables, NRI and integrated discrimination improvement (IDI) were calculated using the algorithms developed by Frank Harrell (based on Pencina's method).[8] Statistical analyses were run in R, Version 3.0.2 (R Development Core Team, Vienna, Austria).

Results

Clinical, echocardiographic, and haemodynamic characteristics

Between January 1996 and December 2010, 1351 consecutive patients with preserved EF who underwent echocardiography, coronary angiography, and right heart catheterization for unexplained dyspnoea

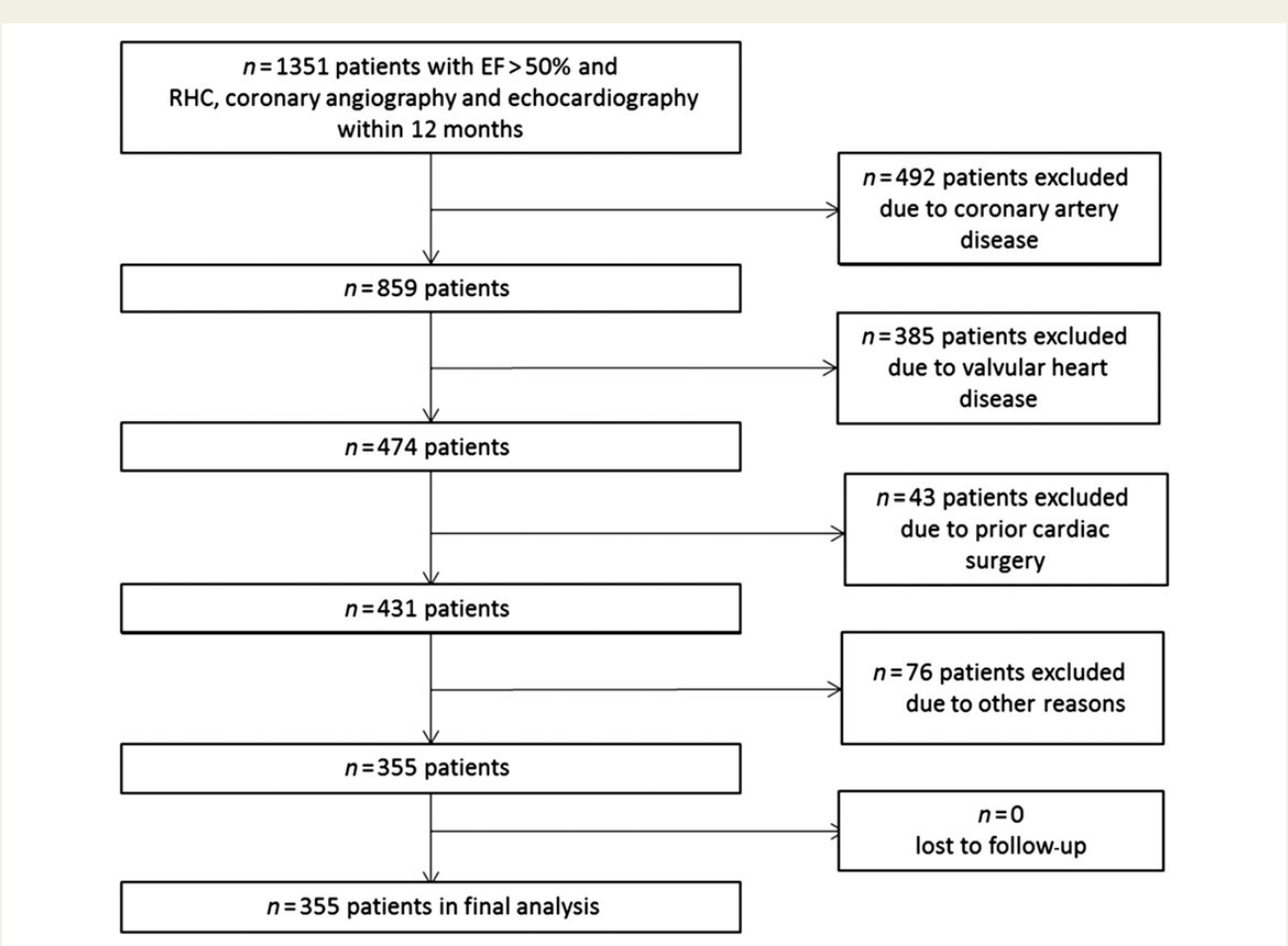


Figure 1 Flow chart of patient selection.

were identified. The median interval between right heart catheterization and echocardiography as well as between right heart catheterization and coronary angiography was 4 days (inter-quartile range 1–18 and 1–13 days, respectively). According to our pre-specified selection criteria, 996 patients were excluded from this analysis (*Figure 1*). Baseline clinical and demographic data of the remaining 355 patients are presented in *Table 1*.

Follow-up data beyond the index hospitalization were available for all patients. The median follow-up was 9.3 years (inter-quartile range 5.0–13.9 years). During the follow-up, 58 patients died. In the overall

Table 2 Resting and exercise haemodynamics with univariable hazard ratios for all-cause mortality

	All patients (n = 355)	Survivors (n = 297)	Non-survivors (n = 58)	P-value	Hazard ratio (95% CI)	P-value
Heart rate (b.p.m.)						
At rest	69.7 ± 12.3	69.2 ± 11.8	72.6 ± 14.2	0.055	1.02 (1.00–1.049)	0.058
Peak exercise	114.9 ± 22.1	116.2 ± 22.5	108.5 ± 19.2	0.015	0.98 (0.97–0.99)	0.001
Systolic BP (mmHg)						
At rest	148 ± 21.2	145.9 ± 20.6	158.9 ± 20.9	<0.001	1.02 (1.01–1.03)	0.001
Peak exercise	187.5 ± 29.2	186.7 ± 29.7	191.4 ± 26.1	0.282	1.00 (0.99–1.01)	0.897
Diastolic BP (mmHg)						
At rest	89.6 ± 10.7	89.4 ± 10.7	90.4 ± 10.2	0.517	1.00 (0.97–1.02)	0.783
Peak exercise	100.1 ± 13.5	99.8 ± 13.5	101.5 ± 13.5	0.382	1.00 (0.98–1.02)	0.753
Mean BP (mmHg)						
At rest	109.1 ± 12.7	108.3 ± 12.7	113.2 ± 12.3	0.006	1.02 (1.00–1.04)	0.088
Peak exercise	129.3 ± 16.0	128.9 ± 16.2	131.5 ± 15.1	0.266	1.00 (0.98–1.01)	0.800
Peak watts	74.1 ± 32.6	78.0 ± 32.7	53.9 ± 23.8	<0.001	0.97 (0.96–0.98)	<0.001
Workload (W/kg)	0.97 ± 0.43	1.03 ± 0.43	0.70 ± 0.31	<0.001	0.08 (0.03–0.18)	<0.001
PCWP (mmHg)						
At rest	9.4 ± 4.1	9.1 ± 3.8	11.0 ± 5.0	0.001	1.12 (1.06–1.19)	<0.001
Peak exercise	22.9 ± 7.4	22.3 ± 7.4	26.0 ± 6.8	<0.001	1.07 (1.03–1.11)	0.001
PCWL (mmHg/W/kg)	30.7 ± 22.4	27.8 ± 20.4	45.0 ± 26.4	<0.001	1.35 (1.24–1.47)	<0.001
PCWP/Watts (mmHg/W)	0.40 ± 0.27	0.36 ± 0.24	0.60 ± 0.33	<0.001	15.58 (7.53–32.22)	<0.001
RAP (mmHg)						
At rest	5.7 ± 2.9	5.5 ± 2.7	6.7 ± 3.6	0.003	1.16 (1.07–1.26)	<0.001
Peak exercise	12.1 ± 5.7	11.4 ± 5.1	16.1 ± 6.7	<0.001	1.17 (1.12–1.22)	<0.001
PAPs (mmHg)						
At rest	28.3 ± 7.8	27.3 ± 6.6	33.6 ± 11.1	<0.001	1.08 (1.06–1.11)	<0.001
Peak exercise	54.5 ± 13.2	52.8 ± 12.5	63.0 ± 13.5	<0.001	1.06 (1.04–1.08)	<0.001
PAPd (mmHg)						
At rest	11.5 ± 4.6	11.1 ± 4.2	13.5 ± 5.8	<0.001	1.08 (1.04–1.12)	<0.001
Peak exercise	25.8 ± 7.2	25.1 ± 7.2	29.4 ± 6.3	<0.001	1.10 (1.06–1.14)	<0.001
PAPm (mmHg)						
At rest	18.3 ± 5.7	17.6 ± 5.1	21.7 ± 7.5	<0.001	1.10 (1.06–1.14)	<0.001
Peak exercise	38.7 ± 9.8	37.5 ± 9.5	44.8 ± 8.9	<0.001	1.08 (1.05–1.10)	<0.001
Cardiac index (L/min/m^2)	2.8 ± 0.6	2.9 ± 0.6	2.5 ± 0.6	<0.001	0.37 (0.22–0.61)	<0.001
SVI (mL/m^2)	41.4 ± 10.0	42.4 ± 9.6	36.1 ± 10.3	<0.001	0.92 (0.89–0.96)	<0.001
PVR (dyn*s*cm^{-5})	140.1 ± 67.3	130.7 ± 56.3	187.1 ± 93.4	<0.001	1.01 (1.06–1.12)	<0.001
SVR (dyn*s*cm^{-5})	1661.2 ± 446.5	1605.9 ± 414.0	1937.8 ± 500.9	<0.001	1.01 (1.01–1.02)	<0.001

Hazard ratio for PCWL is per 10 mmHg/W/kg increase; all other hazard ratios are per unit increase.
BP, blood pressure; PCWP, pulmonary capillary wedge pressure; PCWL, ratio of PCWP to Workload; RAP, right atrial pressure; PAPs, systolic pulmonary arterial pressure; PAPd, diastolic pulmonary arterial pressure; PAPm, mean pulmonary arterial pressure; SVI, stroke volume index; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

cohort, 10-year mortality was 17.3%. Compared with survivors, non-survivors were older, had a lower glomerular filtration rate and a higher prevalence of diabetes mellitus and hypertension as well as a higher left ventricular mass (*Table 1*).

As shown in *Table 2*, haemodynamic profiles on right heart catheterization differed substantially between survivors and non-survivors: Both, at rest and during exercise, non-survivors exhibited significantly higher left and right ventricular filling pressures than survivors, lower stroke-volumes and cardiac indices, and higher pulmonary vascular resistances. Systolic blood pressure at rest was higher in non-survivors.

Pulmonary capillary wedge pressure at rest and survival

Pulmonary capillary wedge pressure at rest was significantly associated with mortality. By univariable analysis, the HR for death per mmHg increase in PCWP was 1.12 (95% CI: 1.05–1.19, $P < 0.001$). Consistently, in the ROC analysis for prediction of death by PCWP at rest, the area under the curve was 0.60 (95% CI: 0.50–0.70) at 14 years (*Figure 2*). Dichotomizing the cohort in patients who did or did not meet the PCWP criterion for the diagnosis of HFpEF, i.e. PCWP at rest >12 mmHg, the HR for death in patients with established HFpEF ($n = 60$) was 2.44 (95% CI: 1.38–4.29, $P < 0.001$) (*Figure 3A*).

The association between PCWP at rest and subsequent mortality prevailed after adjustment for pertinent baseline variables, irrespective of whether PCWP at rest was considered as a continuous variable (HR: 1.09; 95% CI: 1.02–1.16; $P = 0.011$) or dichotomized according to the criterion for the diagnosis of HFpEF (HR: 2.21; 95% CI: 1.14–4.17; $P = 0.018$, *Figure 3B*). Other significant predictors of death were age (HR: 1.13; 95% CI: 1.09–1.18; $P < 0.001$) and left ventricular mass (HR: per 10 g increase 1.06; 95% CI: 1.01–1.12; $P = 0.026$; model with PCWP at rest as continuous variable) (*Figure 4*).

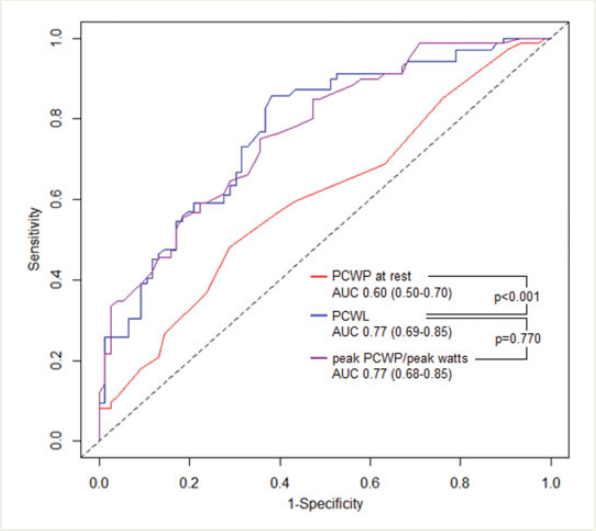


Figure 2 Receiver-operating characteristic analysis of pulmonary capillary wedge pressure at rest (red), PCWL (blue) and peak pulmonary capillary wedge pressure normalized to peak watts (purple) for the prediction of mortality through 14 years.

Increase in pulmonary capillary wedge pressure during exercise and survival

The response of PCWP to exercise described as PCWL also strongly predicted survival. The HR for death per 10 mmHg/W/kg rise in PCWL was 1.35 (95% CI: 1.24–1.47, $P < 0.001$) by univariable analysis. Likewise, in the time dependent ROC analysis for prediction of death by PCWL, the area under the curve was 0.77 (95% CI: 0.69–0.85) at 14 years which was significantly higher than that for PCWP at rest ($P < 0.001$) (*Figure 2*). Normalizing peak PCWP to peak watts without respecting patients weight retrieved virtually identical results as PCWL (AUC 0.77; 95% CI: 0.68–0.85; $P = 0.770$) (*Figure 2*) and by univariable analysis the HR for death was 15.58 (95% CI: 7.53–32.22, $P < 0.001$) per increase in mmHg/W. The optimal ROC curve derived cut-point of PCWL for mortality was 25.5 mmHg/W/kg. A PCWL >25.5 mmHg/W/kg was associated with a 5.44-fold increased risk of death (95% CI: 2.88–10.29; $P < 0.001$, *Figure 3A*).

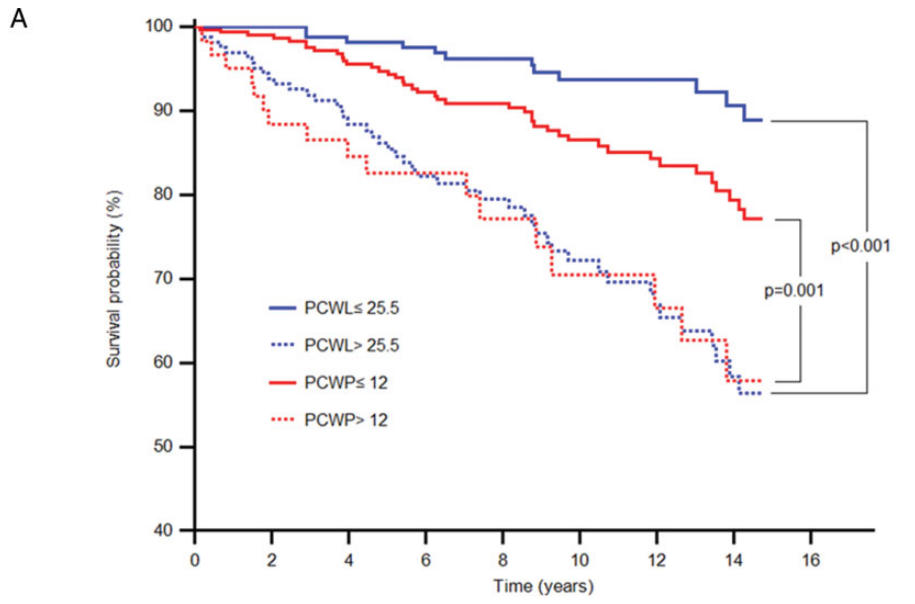
When added to PCWP at rest, PCWL significantly improved classification of patients into survivors and non-survivors with a NRI of 0.56 (95% CI: 0.29–0.83; $P < 0.001$) and an IDI of 0.07 (95% CI: 0.03–0.12, $P = 0.003$).

The prognostic value of PCWL was also confirmed by multivariable analysis. PCWL prevailed as an independent predictor of mortality in a multivariable model including PCWP at rest and pertinent baseline variables (HR: 1.16 per 10 mmHg/W/kg; 95% CI: 1.02–1.32; $P = 0.028$) and the goodness of fit of the model was improved by adding PCWL (increase in R^2 from 0.208 to 0.218). In this model, PCWP at rest lost its significant association with survival (HR: 1.06; 95% CI: 0.99–1.14; $P = 0.092$), whereas age (HR: 1.11; 95% CI: 1.07–1.16; $P < 0.001$) and left ventricular mass (HR: 1.07 per 10 g; 95% CI: 1.02–1.13; $P = 0.012$) were confirmed as significant independent predictors (*Figure 4*). Consistent results were obtained from the multivariable model with PCWL entered as a dichotomized variable (HR: 2.32; 95% CI: 1.08–4.96; $P = 0.031$) (*Figure 3B*).

Stratifying patients into four groups according to cut-offs for PCWP at rest and PCWL demonstrated the prognostic potential of invasive exercise testing (*Figure 5*). In the adjusted Cox model, with individuals with low PCWP (≤12 mmHg) and low PCWL (≤25.5 mmHg) defined as a reference group, patients with PCWP ≤12 mmHg and a PCWL >25.5 mmHg/W/kg carried a 2.37-fold increased risk for death (95% CI: 1.09–5.17; $P = 0.029$). Patients with both PCWP at rest >12 mmHg and PCWL >25.5 mmHg/W/kg were at highest risk (HR: 4.75; 95% CI: 1.90–11.84; $P < 0.001$). Ten-year mortality was 6.6% in subjects with low PCWP at rest and low PCWL; 28.2% in patients with low PCWP at rest and high PCWL and 35.2% in patients with high PCWP and high PCWL. Owing to small group size ($n = 9$), a comparison of patients with high PCWP and low PCWL did not yield any meaningful results.

Discussion

The present study evaluating the prognostic utility of PCWP at rest and during exercise in patients with suspected HFpEF has two major findings: First, resting PCWP is strongly linked to long-term mortality; an elevated PCWP (>12 mmHg) is associated with a more than two-fold increased risk of death. Second, PCWL, i.e. the



Numbers at risk

Low PCWL	192	182	160	149	122	95	74	55	10
High PCWL	163	150	124	100	81	61	47	31	6
Low PCWP	295	279	241	214	176	137	104	74	16
High PCWP	60	53	43	35	27	19	17	12	0

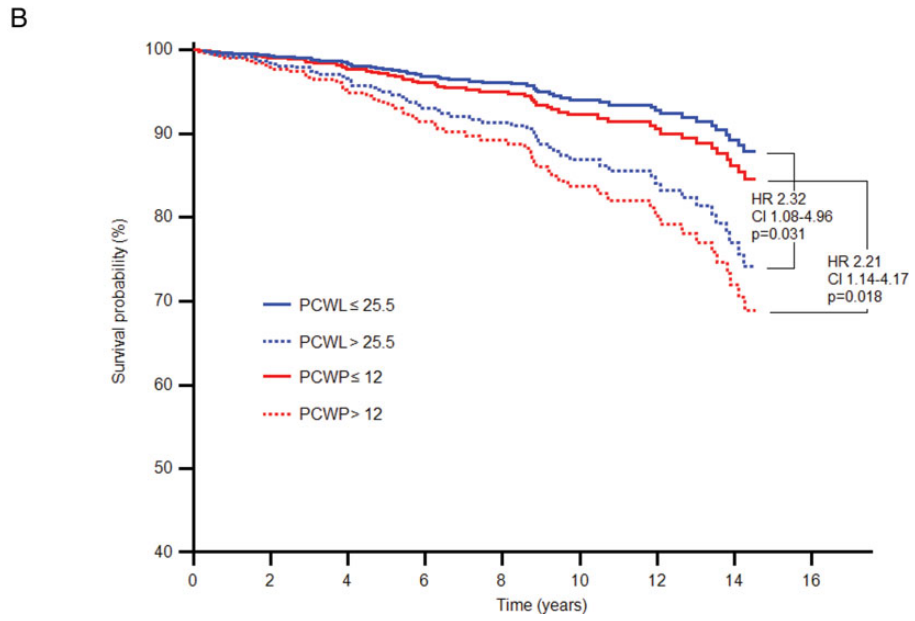


Figure 3 Unadjusted Kaplan–Meier survival curves (*A*) and adjusted survival curves (*B*) in various subgroups defined by pulmonary capillary wedge pressure at rest or PCWL. Blue solid line, PCWL ≤25.5 mmHg/W/kg; blue dotted line, PCWL >25.5 mmHg/W/kg; red solid line, pulmonary capillary wedge pressure at rest ≤12 mmHg; red dotted line, pulmonary capillary wedge pressure at rest >12 mmHg.

increase in PCWP with exercise (expressed as workload normalized to body weight), is even more closely linked to mortality and significantly improves the prediction of mortality by PCWP at rest alone. As such, PCWL is particularly useful for risk-stratification of patients with a normal resting PCWP. Based on our current findings, we identified a subgroup of patients with normal PCWP at rest but a steep rise of PCWP during exercise, which carries an increment in mortality of about two-fold compared with those with normal pressure at rest and normal rise of PCWP during exertion.

To the best of our knowledge, the present study presents the largest cohort of patients evaluated for suspected HFpEF with invasively assessed exercise haemodynamic data. The median follow-up

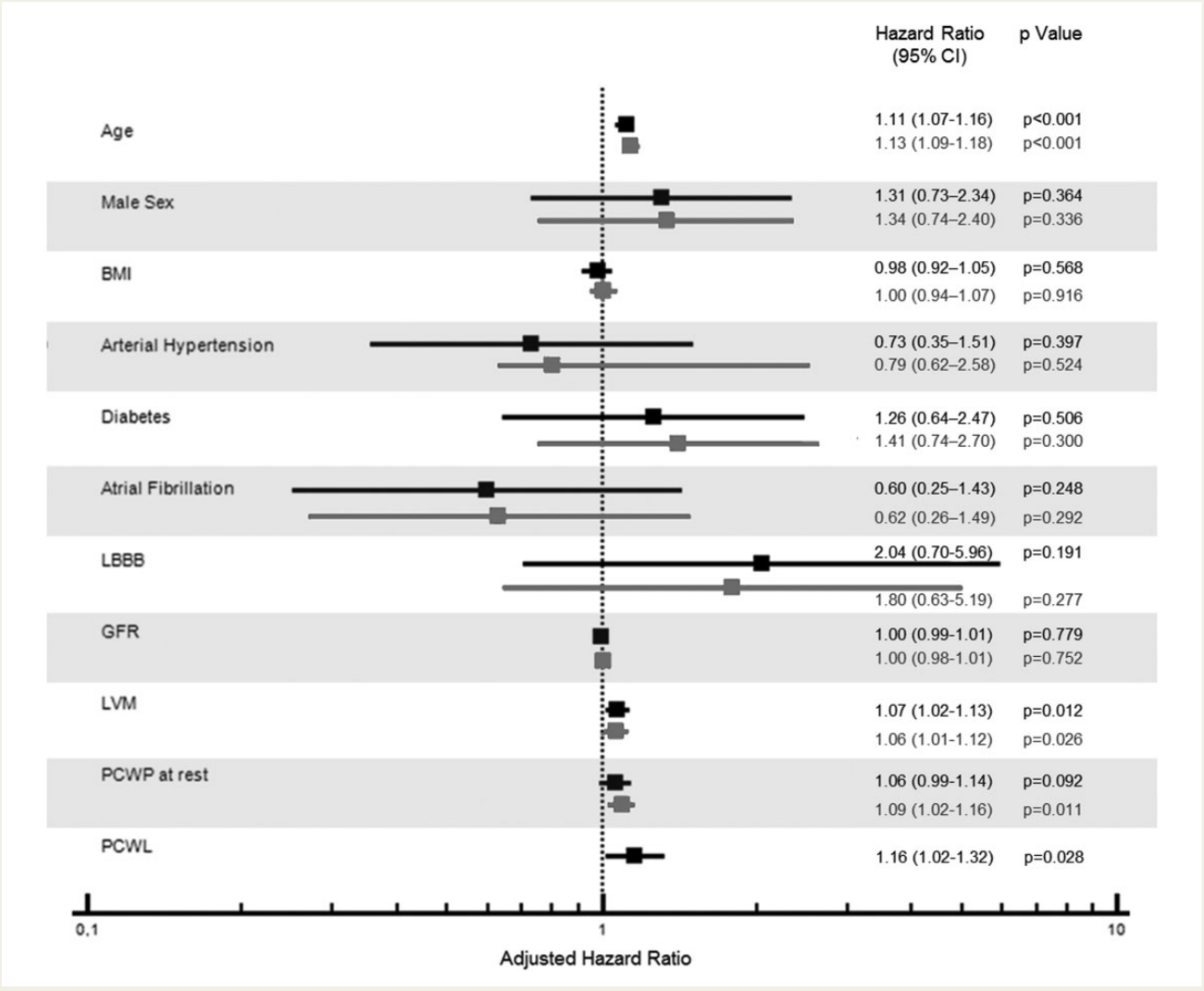


Figure 4 Forest plot of adjusted hazard ratios for mortality in different cox regression models. Grey boxes: model with pulmonary capillary wedge pressure at rest as continuous variable adjusted for pertinent baseline variables. Black boxes: PCWL as continuous variable added to the same model.

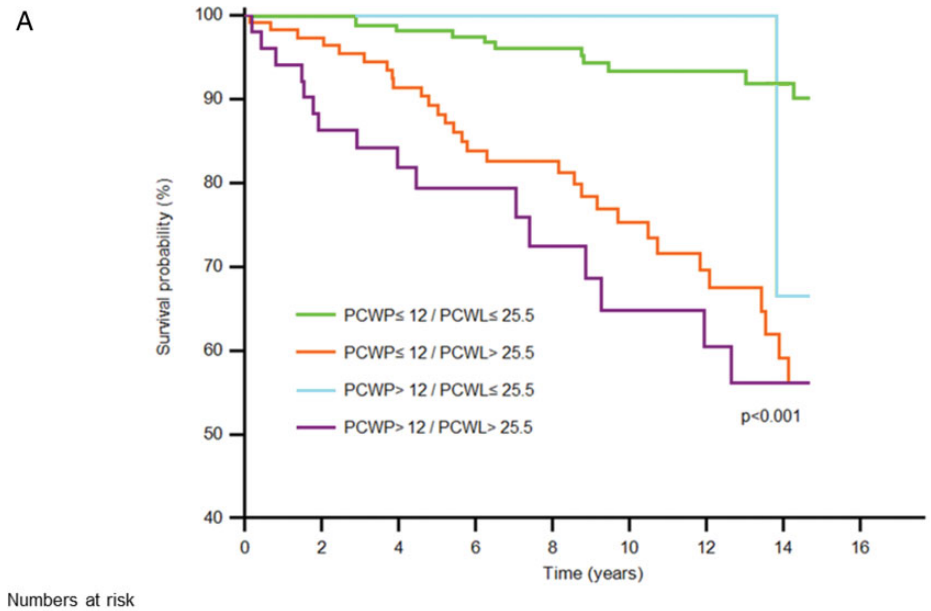
reaching almost 10 years was considerably long, and no patient was lost to follow-up. Although recently there has been much interest in echocardiographic assessment of left ventricular filling pressure, invasively assessed PCWP can still be considered the diagnostic gold standard and has been the reference value in a substantial number of echocardiographic studies.[9–11] Adequate determination of PCWP is of particular importance, especially since *E*/*e*′ (ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity), a key element of current diagnostic recommendations,[2] has lately been questioned as a reliable estimate of filling pressure at rest and during exercise.[5,12,13]

Prognostic impact of established heart failure with preserved ejection fraction

As suggested in a consensus paper, a PCWP >12 mmHg substantiates the clinical diagnosis of HFpEF in the absence of other causes.[2] However, data on the prognostic relevance of this criterion were limited so far. To our knowledge, the present study applied this diagnostic criterion for the first time for the prediction of long-term mortality in a larger cohort of patients evaluated for HFpEF. We confirmed the prognostic impact of established HFpEF and demonstrated that PCWP at rest is associated with mortality in patients with preserved left ventricular EF. This endorses and extends results from a prior non-invasive study which showed that a restrictive transmitral filling pattern, indicative of elevated left ventricular filling pressure, is an important prognostic factor in patients hospitalized for heart failure, independent of left ventricular EF.[14]

The concept of early heart failure with preserved ejection fraction

Pathophysiology of HFpEF is still a matter of debate. Diastolic dysfunction might not solely be responsible for exercise intolerance since several other mechanisms, such as subtle systolic dysfunction, impaired ventriculoarterial coupling and chronotropic incompetence have been



Numbers at risk

Low PCWP / Low PCWL	183	173	152	141	115	92	71	53	10
Low PCWP / High PCWL	112	106	89	73	61	45	33	21	6
High PCWP / Low PCWL	9	9	8	8	7	3	3	2	0
High PCWP / High PCWL	51	44	35	27	20	16	14	10	0

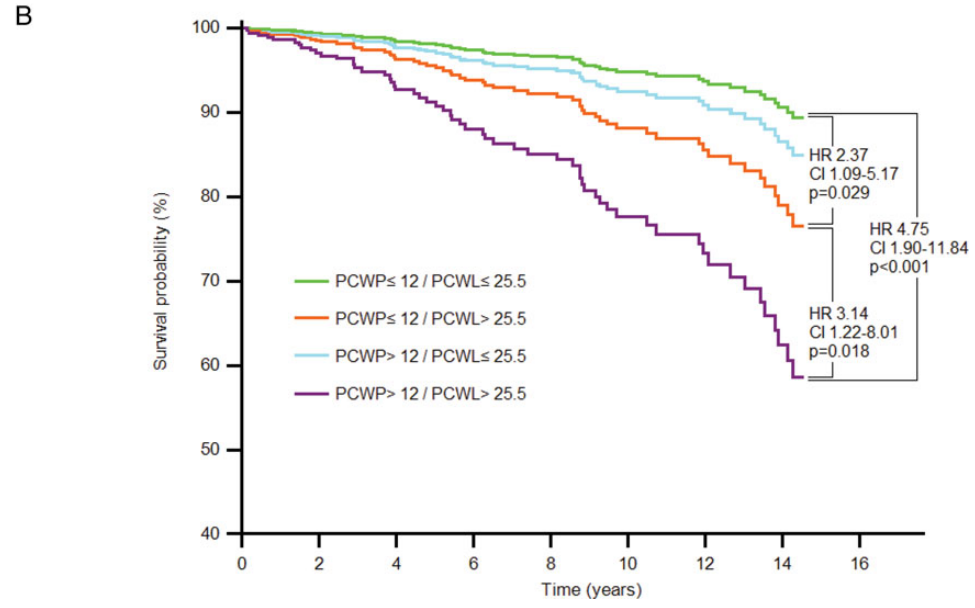


Figure 5 Unadjusted Kaplan–Meier survival curves (*A*) and adjusted survival curves (*B*) for patients stratified in four groups according to pulmonary capillary wedge pressure and PCWL. Green line, PCWP ≤12 mmHg and PCWL ≤25.5 mmHg/W/kg ($n = 183$); orange line, PCWP ≤12 mmHg and PCWL >25.5 mmHg/W/kg ($n = 112$); blue line, PCWP >12 mmHg and PCWL ≤25.5 mmHg ($n = 9$); purple line, PCWP >12 mmHg and PCWL >25.5 mmHg/W/kg ($n = 51$).

discussed to play a contributing role.[15–17] However, it is commonly accepted that increased ventricular stiffness with a consecutive left- and upward shift of the left ventricular pressure–volume curve is one of the haemodynamic key mechanisms of HFpEF.[4,18] Additionally, a recent study showed that in patients with newly diagnosed HFpEF, inadequate enhancement of relaxation and acute escalation of left ventricular chamber stiffness, above and beyond changes at rest, contributed to rise of filling pressures during exercise.[19] In consequence, depending on volume load PCWP can still be normal at rest, while exercise may result in a substantial increase in filling pressure.

Though exercise intolerance and exertional dyspnoea are main symptoms of HFpEF, cardiopulmonary exercise testing is not included in current diagnostic recommendations.[2] Mainly, this is due to limited or missing data regarding haemodynamic alterations during exertion in HFpEF. One of the largest study so far investigating exercise haemodynamics in typical elderly HFpEF patients ($n = 22$), demonstrated that despite normal filling pressure at rest, an excessive rise of PCWP is a key element of exercise limitation.[5] Pathological changes during exercise testing such as reduced peak oxygen consumption and a steep VE/VCO_2 (minute ventilation/carbon dioxide production relationship) slope have been described to correspond with this inadequate PCWP response.[20] A recent study reported that an impaired CO reserve in relation to metabolic needs is a further exertional haemodynamic abnormality in HFpEF, additional to increases in filling pressure.[21] In line with our findings, these data imply that cardiopulmonary stress testing might reveal a haemodynamic response consistent with HFpEF, at a level when measurements at rest still appear to be normal. Based on this, Borlaug *et al.*[3] recently proposed that an elevation of PCWP $\geq$25 mmHg at peak exercise identifies early stages of HFpEF. However, uncertainty remained about the prognostic relevance of haemodynamic changes during exercise. Subsequent data showed that a stress-induced increase in LV filling pressure, derived by an elevation of E/e', was associated with a higher rate of cardiovascular hospitalizations within 13 month of follow-up, while mortality was not affected.[22] Another analysis reported that exercise-induced pulmonary hypertension is a predictor of a worse clinical outcome, but only in patients with increased estimated left ventricular filling pressure (E/e') during stress echocardiography.[23] Our data demonstrate that a steep rise of PCWP during exercise is a strong independent predictor of mortality in patients with unexplained dyspnoea even if haemodynamics at rest are normal. Since systolic dysfunction, ischaemia and other cardiac diseases were ruled out by patient selection and no difference in the mean arterial pressure at maximum exercise was seen between the groups, the disproportionate elevation of PCWP during exercise must be attributed to diastolic dysfunction. Based on these findings, we suggest that a normal resting PCWP with a PCWL >25.5 mmHg/W/kg represents HFpEF at an early stage.

Study limitations

Even if all data were carefully assessed, there is the inherent limitation of potential bias of unmeasured confounding factors. Additionally, since catheterization in this population was based on decision of the treating physicians, a potential referral bias cannot be ruled out. Given the long follow-up period of this study cohort, we did not record and include medication at enrolment in our analysis because these variables show usually profound changes over time which are difficult to include in a statistical model. Thus, this lack of information might represent a potential bias. However, the close association of PCWL with survival despite this limitation underscores the prognostic value of this variable. Owing to this limitation, we cannot completely rule out that HFpEF patients treated with diuretics had 'pseudonormal' PCWP at rest. Nevertheless, this would not alter the results regarding the prognostic impact of exercise haemodynamics. The error introduced by using PAPd for missing values of PCWP may be considered small, especially since the proportion of missing values was similar across the various strata. Cardiac output during right heart catheterization was determined by the Fick method using estimated oxygen uptake for calculation. Though it is common clinical practice to use estimated values, concerns about accuracy of this method have recently been raised.[24] In particular during exercise, the use of assumed values for oxygen consumption might inherit an unpredictable error. Therefore, we did not further analyse CO-related data from RHC. Finally, we had information only on all-cause mortality. Because we cannot differentiate between cardiac and non-cardiac causes of death, we potentially underestimate the true association of PCWL with cardiac mortality, since left ventricular filling pressures at rest and during exercises may not be related to non-cardiac causes of death.

Clinical implications

Pulmonary capillary wedge pressure at rest is a predictor of mortality in HFpEF patients. Moreover, in individuals with unexplained dyspnoea and normal filling pressure at rest, exercise haemodynamics identifies a subgroup of patients with an inadequate rise of PCWP in response to physical exertion. These patients have impaired prognosis and a higher risk of death. Our data suggest classifying these patients as having HFpEF in an earlier stage, before pathological haemodynamic findings at rest become apparent. Thus, haemodynamic stress testing should be considered in particular if measurements at rest are normal, because it provides not only the unique opportunity to rule out a cardiac cause of dyspnoea in uncertain cases, but also to identify patients at risk.

Since up to now, no therapeutic intervention could demonstrate a positive effect on mortality in HFpEF, our findings also provide new options for future trials. Interventions in the early course of HFpEF may be more effective than those later in the course of the disease and may be capable of preventing progression to more advanced stages of HFpEF, thus improving survival.

Conflict of interest: none declared.

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