

Brachial pulse pressure in acute heart failure. Results of the Heart Failure Registry

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Abstract

Aims To investigate the still uncertain independent prognostic impact of pulse pressure (PP) in acute heart failure (HF), in particular across the left ventricular ejection fraction (EF) phenotypes, and the potential contribution of PP in outlining the individual phenotypes.

Methods and results We prospectively evaluated 1-year death and rehospitalization in 4314 patients admitted for acute HF grouped by EF and stratified by their PP level on admission. In HF with reduced (< 40%) EF (HFrEF), the highest quartiles of PP had the lowest unadjusted [hazard ratio (HR) 0.77, 95% confidence interval (CI) 0.61–0.98] and adjusted (HR 0.64 0.50–0.82) risk of 1 year all cause death compared to the lowest quartile. Its prognostic impact was partially mediated by systolic blood pressure (SBP). In HF with preserved (≥ 50%) EF (HFpEF), the intermediate quartile of PP showed the lowest 1 year all cause mortality in unadjusted (HR 0.598, CI 0.416–0.858) and adjusted (HR 0.55, 95% CI 0.388–0.801) models with no relationship with SBP. In a receiver operating characteristic analysis, a combination of PP > 60 mmHg and SBP > 140 mmHg was associated to a preserved EF with a high performance value. No prognostic significance of PP was found in the HF with mid-range EF subgroup.

Conclusions In acute HFrEF, there is an almost linear inverse relation between mortality and PP, partly mediated by SBP. In HFpEF, a J-shaped relationship between mortality and PP was present with a better prognosis at the nadir. A combination of PP > 60 mmHg with SBP > 140 mmHg may be clinically helpful as marker of a preserved left ventricular EF.

Keywords Pulse pressure; Heart Failure; Acute Heart Failure; Prognosis

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Listed in Appendix 1.

Introduction

Pulse pressure (PP) is the difference between systolic and diastolic blood pressure (BP) and reflects the complex interaction between left ventricular (LV) function and the elastic properties of the proximal large vasculature.¹ Particularly,

when the central arteries become stiffer, in aging as in heart failure (HF), the reflected wave arising from the peripheral arterial vessels travels faster and moves from diastole to systole increasing SBP (SBP), decreasing diastolic BP and widening PP.² The widening of PP imposes a greater burden on the LV affecting both systolic and diastolic function, favouring LV hypertrophy and impairing coronary blood flow.¹

Increased PP is associated with an increased risk of myocardial infarction and cardiovascular (CV) mortality in normotensive, hypertensive, and high-risk patients^{3,4} and with increased risk of HF in the elderly.⁵ Higher PP favours the development of coronary artery disease⁴ and is an independent prognosticator of re-infarction and all-cause mortality after myocardial infarction (MI) in patients with LV systolic dysfunction.⁶ Because a stiffening of the large elastic arteries determines a similar impairment in functional capacity in HF with reduced ejection fraction (EF) < 40% (HFrEF) and HF with preserved EF \geq 50% (HFpEF) LVEF,^{7,8} also a similar behaviour of PP could be expected in both EF phenotypes. However, data regarding the prognostic significance of PP in patients with acute HFrEF and HFpEF are unclear.^{9,10} Low PP has emerged as an independent predictor of mortality in patients with acute HFrEF,^{11,12} and in these patients it is believed to reflect mainly an excessive reduction in stroke volume rather being an index of arterial stiffening. In patients with acute HFpEF, and even more in those with HF mid-range EF (HRmEF), the prognostic role of PP is far less established,^{13,14} and inconsistent results were reported,^{9,13,14}

Apart its prognostic role, we also speculated the possible clinical utility of PP amplitude to discriminate the two HF phenotypes because in the acute setting they both present with similar clinical symptoms and signs.¹⁵ To address these clinical issues, we prospectively investigated a large multinational European cohort of acute HF (AHF) patients followed up for 1 year by considering distinctly the phenotypes according to the EF value.

Methods

Study design

The principles and procedures of the European Society of Cardiology (ESC)-Heart Failure Association EURObservational Research Programme (EORP) HF Long-Term Registry, a study of the EORP of the ESC and the ESC-Heart Failure Association have been previously described.¹⁶ The enrolling network of this prospective, multicentre, and observational study included 211 Cardiology centres of 21 European and Mediterranean ESC member countries. National network coordinators were identified by the participating National Societies of Cardiology, and several training meetings were organized for the study investigators to assure consistency in definition and data collection. A diagnosis of AHF (both de novo and worsening HF) was made by the clinician-investigators at initial presentation and required the presence of signs and symptoms of HF, evidence of cardiac dysfunction, and the need for intravenous therapy. From May 2011 to April 2013, all patients admitted for acute HF during the enrolment period (on 1 day per week for 12 consecutive months) were included in

this registry. The registry management, the central data quality control, and the statistical analysis were performed by the EORP Department of the ESC. For a random sample of 5% of centres, data source verification was performed by EORP monitors. There were no specific exclusion criteria, except for age \leq 18 years. Data were collected using a web-based system. The registry was approved by each local Institutional Review Board according to the rules of each participating country. All patients gave written informed consent before discharge.

Clinical and laboratory data

Blood pressure was measured on hospital admission, and PP was calculated as the difference between systolic and diastolic BP. Patients were considered as having hypertension if their BP was \geq 140/90 mmHg or if they were taking antihypertensive drugs. Biochemical blood measurements were determined using local standard laboratory procedures. According to the pure observational nature of the study, the large involvement of many heterogeneous European countries and the urgency clinical status of patients enrolled the BP measurement technique was not predetermined by protocol. Conventional trans-thoracic echocardiography was used to measure EF according to international standard criteria. Patients were stratified according to LVEF as HF with preserved \geq 50% (HFpEF), reduced < 40% (HFrEF), and mid-range 40–49% EF (HFmEF).¹⁷

Statistical analyses

In the current analysis, we present the 1 year data from the ESC-EORP HF Long-Term registry concerning the rates of the cumulative (in-hospital and post-discharge) all cause of death, the post-discharge 1 year all cause mortality and 1 year CV-death, 1 year all cause re-hospitalization, and 1 year CV-rehospitalization in acute HFrEF, HFmEF, and HFpEF stratified by PP on admission. Descriptive statistics were used to summarize frequency tabulations (%) and distributions (mean \pm standard deviation). A Cox proportional hazards model was used to assess the association between PP quartiles and outcomes. In addition to unadjusted hazard ratios (HRs), adjusted HRs were estimated after adjustment for pre-specified potential confounding factors selected on the basis of their clinical or biological plausibility, namely age, gender, HF aetiology (ischemic vs. non-ischemic), renal dysfunction, and diabetes. The role of SBP on the prognostic impact of PP was also explored by dividing the population in three groups of SBP (< 100 mmHg, between 100–139 mmHg, and $>$ 140 mmHg) accordingly to the results of several studies.^{18–20} All conclusions were drawn separately by individual HF phenotype. A test for trend was also planned, but no

evidence of linear trend was found in the main analysis using the quartile of PP in categories. A ROC analysis to evaluate the ability of PP to discriminate a preserved or a reduced EF in AHF was also performed. A two-sided *P* value of < 0.05 was considered as statistically significant. All analyses were performed using SAS Statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Baseline characteristics of heart failure with reduced ejection fraction, heart failure with mid-range ejection fraction, heart failure with preserved ejection fraction groups and pulse pressure quartiles

Among the patients enrolled in the registry, 6629 were hospitalized with a primary diagnosis of AHF. Out of them, 6618 had PP available, but only 4314 had also the EF available; 217 died in-hospital (5%). Median follow-up time was 378 (288–415) days, during which 271 (6%) patients discharged alive were lost to follow-up, then 4097 patients were included in the present analysis.

According to a brachial SBP classification, 26.8% of patients presented within the range ≤ 80 –110 mmHg ($< 2\%$ with values < 85 mmHg), 42.9% with 110–140 mmHg, and 30.3% with > 140 mmHg, respectively. Then, on admission, $> 70\%$ of patients had a brachial SBP > 110 mmHg. The subjects distributed according to the EF-phenotypes were 2213 (51.3%) HFrEF, 818 (19.0%) HFmEF, and 1283 (29.7%) HFpEF. Main baseline characteristics of the EF-subtypes are reported in *Table 1*. Age was increasing along with the increase in EF among the considered three EF subgroups (from 65.8 [12.8] to 71.9 [13.1] years), whereas the male gender prevalence was decreasing (from 76.4% to 45.1%), and the prevalence of the New York Heart Association (NYHA) functional class III–IV was similar (88–83%). Ischemic aetiology was prevalent in HFrEF (62.6%) and HRmEF (65.4%) and not in HFpEF (37.6%). Hypertension was highly represented in all three groups, particularly in HFpEF (76.1%), in which the atrial fibrillation (AF) rate was also high (55%) whereas the prevalence was 38% and 44% in HFrEF and HFmEF, respectively. Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, aldosterone antagonists, beta-blockers, antiplatelets drugs, and lipid-lowering drugs were prevalent in HFrEF and HRmEF. Oral anticoagulants were more utilized in HFpEF (39.9%). The crude 1 year all-cause death, CV death, cumulative all-cause deaths, all cause re-hospitalization, CV rehospitalisation and in-hospital death in the three groups are reported in *Table 2*. All end-point events (except the in-hospital mortality, *P* 0.78) were significantly higher ($P < 0.001$) in patients with HFrEF.

The baseline characteristics of the PP quartiles in HFrEF, HRmEF and HFpEF are reported in Supporting Information *Table S1*. The patients of the highest PP quartile as compared to the patients of the lower PP quartiles were significantly and uniformly older, with higher proportion of female, higher BMI, and higher proportion of diabetes, hypertension, and ischemic heart disease. As expected, these patients were more likely to be treated with antihypertensive drugs as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and calcium channel blockers. In contrast, patients in the lowest PP quartile were shown to have lower systolic and diastolic BP, lower sodium plasma concentration, higher rate of AF and were more frequently treated with anticoagulant drugs, beta-blockers, aldosterone antagonists, digitalis, and diuretics as compared to the highest quartile. Interestingly, patients in NYHA III–IV functional class were significantly more represented in the lowest PP quartile in the HFrEF group, whilst no difference in NYHA functional class was observed across PP quartiles in HRmEF and HFpEF.

Prognostic impact of pulse pressure in ejection fraction subgroups

Cox proportional hazard models of PP quartiles or continuous PP value at hospital admission with the individual endpoints in acute HFrEF, HFmEF, and HFpEF are shown in *Table 3*. In HFrEF, patients in the intermediate and highest quartile compared to patients in the lowest quartile had a 33.9% and 22.6% significantly lower unadjusted relative risk of death, respectively. This association was strengthened after adjusting for age, gender, HF aetiology, diabetes, and renal dysfunction with a 39.5% and 35.9% significant reduction in relative risk of death, respectively. All the other endpoints showed similar lower event rates either in unadjusted or in adjusted models for intermediate and higher PP quartiles. This was confirmed also when PP was considered as a continuous variable. In both the analyses of crude 1 year events and of the PP quartile in categories, no evidence of linear trend was found.

The association of PP for different levels of SBP was also explored and it was found that a BP between 100 and 139 mmHg conferred a 11.8% and 16.6% significant relative risk reduction in all-cause deaths for every 10 mmHg increase of PP in the unadjusted and adjusted models, respectively, whereas no relationship with outcomes was found for SBP below and above these thresholds (*Table 3*). The estimated cumulative incidence of all-cause death according to PP quartiles in HFrEF showed an increase of probability of a fatal event with the decline in PP amplitude ($P = 0.0006$). In contrast, no prognostic measurable differences among PP quartiles were observed in the HFmEF group. Similar neutral results were seen by combining PP and SBP (*Table 4*). In HFpEF, Cox proportional hazard models showed a 40.2% and 44.3% significantly lower unadjusted and adjusted

Table 1 Baseline clinical characteristics in acute HFpEF (ejection fraction < 40%), HFmEF (40% ejection fraction 49%) and HFpEF (ejection fraction >=50%)

Phenotypes n	All 4314	HFpEF 2213	HFmEF 818	HFpEF 1283	P value
Demographic and anthropometric					
Age (years) [mean (SD)]	68.1 (13.0)	65.8 (12.8)	68.5 (12.1)	71.9 (13.1)	< 0.001
Caucasian	3352 (79.3%)	1652 (76.4%)	606 (75.0%)	1094 (87.2%)	< 0.001
Men	2785 (64.6%)	1690 (76.4%)	516 (63.1%)	579 (45.1%)	< 0.001
NYHA class III-IV	3694 (86.0%)	1945 (88.2%)	675 (83.0%)	1074 (84.1%)	< 0.001
Body Mass Index (kg/m ²) Median [Q1-Q3]	27.8 [25.1; 31.6]	27.7 [24.6; 30.9]	28.4 [25.5; 32.0]	28.4 [25.4; 32.7]	< 0.001
Systolic Blood Pressure (mmHg) Median [Q1-Q3]	130.0 [110.0; 150.0]	120.0 [110.0; 140.0]	130.0 [117.0; 150.0]	135.0 [120.0; 159.0]	< 0.001
Diastolic Blood Pressure (mmHg) Median [Q1-Q3]	80.0 [70.0; 90.0]	75.0 [70.0; 85.0]	80.0 [70.0; 90.0]	80.0 [70.0; 90.0]	< 0.001
Heart Rate (b.p.m) Median [Q1-Q3]	86.0 [72.0; 102.0]	88.0 [72.0; 100.0]	90.0 [75.0; 106.0]	83.0 [70.0; 102.0]	< 0.001
Pulse pressure (mmHg) Median [Q1-Q3]	50.0 [40.0; 62.0]	47.0 [40.0; 60.0]	50.0 [40.0; 66.0]	59.0 [45.0; 70.0]	< 0.001
Haemoglobin (g/l) Median [Q1-Q3]	12.6 [11.0; 14.0]	12.9 [11.3; 14.1]	12.6 [10.9; 13.9]	12.0 [10.5; 13.6]	< 0.001
eGFR (mL/min/1.73m ²) Median [Q1-Q3]	55.8 [38.8; 73.6]	56.3 [39.5; 73.6]	54.8 [38.5; 73.2]	55.1 [38.2; 73.7]	0.555
NT-proBNP (pg/dL) Median [Q1-Q3]	3801.0 [1665.0; 8612.1]	4570.0 [2088.0; 9110.0]	3250.5 [1372.0; 8505.5]	2553.0 [1200.0; 6799.0]	< 0.001
Total cholesterol (mg/dL) Median [Q1-Q3]	156.0 [123.0; 190.0]	161.0 [129.3; 196.0]	156.0 [126.7; 190.0]	156.0 [126.7; 190.0]	0.029
Glycemia (mg/dL) Median [Q1-Q3]	110.0 [92.7; 150.0]	108.0 [91.0; 147.0]	111.7 [93.0; 163.3]	111.0 [95.0; 149.0]	0.008
Sodium (mEq/L) Median [Q1-Q3]	139.0 [135.0; 141.0]	138.0 [135.0; 141.0]	139.0 [136.0; 142.0]	139.0 [136.0; 141.0]	
Risk factors and comorbidities					
Diabetes mellitus	1766 (40.9%)	907 (41.0%)	345 (42.2%)	514 (40.1%)	0.629
Hypertension	2860 (66.3%)	1335 (60.4%)	549 (67.1%)	976 (76.1%)	< 0.001
Smoking status (never)	676 (15.7%)	401 (18.1%)	143 (17.5%)	132 (10.3%)	< 0.001
Ischaemic HF aetiology	2403 (55.7%)	1385 (62.6%)	535 (65.4%)	483 (37.6%)	0.002
Previous stroke	558 (12.9%)	262 (11.8%)	95 (11.6%)	201 (15.7%)	< 0.001
Previous MI/angina	2407 (55.8%)	1356 (61.3%)	522 (63.8%)	529 (41.2%)	< 0.001
COPD	861 (20.0%)	412 (18.6%)	144 (17.6%)	305 (23.8%)	< 0.001
Atrial fibrillation	1916 (44.4%)	847 (38.3%)	361 (44.1%)	708 (55.2%)	< 0.001
Type of atrial fibrillation					
Paroxysmal	478 (11.1%)	210 (9.5%)	84 (10.3%)	184 (14.3%)	< 0.001
Permanent	1167 (27.1%)	518 (23.4%)	227 (27.8%)	422 (32.9%)	
Persistent	271 (6.3%)	119 (5.4%)	50 (6.1%)	102 (8.0%)	
Medications					
Previous revascularization (percutaneous/surgical)					
Statins	973 (22.6%)	580 (26.2%)	181 (22.1%)	212 (16.5%)	< 0.001
ACE-inhibitors	2085 (48.4%)	1148 (52.0%)	422 (51.6%)	515 (40.1%)	< 0.001
ARBs	2425 (56.3%)	1363 (61.7%)	474 (57.9%)	588 (45.8%)	< 0.001
Beta-blockers	607 (14.1%)	259 (11.7%)	102 (12.5%)	246 (19.2%)	< 0.001
Aldosterone antagonists	2647 (61.4%)	1478 (66.9%)	499 (61.0%)	670 (52.2%)	< 0.001
Diuretics	1782 (41.4%)	1159 (52.5%)	317 (38.8%)	306 (23.9%)	< 0.001
Calcium channel blockers	3117 (72.3%)	1744 (79.0%)	538 (65.5%)	837 (65.2%)	< 0.001
Digitalis	668 (15.5%)	204 (9.2%)	144 (17.6%)	320 (24.9%)	< 0.001
Antiplatelets	948 (22.0%)	576 (26.1%)	155 (18.9%)	217 (16.9%)	< 0.001
Anticoagulants (vitamin K antagonists/NOACs)	2274 (52.8%)	1302 (58.9%)	443 (54.2%)	529 (41.2%)	< 0.001
	1547 (35.9%)	785 (35.5%)	250 (30.6%)	512 (39.9%)	< 0.001

ACE: Angiotensin converting-enzyme; ARB: angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; eGFR, estimated Glomerular Filtration Rate; HF, heart failure; HFmEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFpEF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal prohormone of BNP; NOAC, new oral anticoagulant; NYHA, New York Heart Association; MI, myocardial infarction.

All variables were available in > 98% of the cases, except for total cholesterol (n 2883), glycemia (n 3679), Na (n 4082), and NT-proBNP (n 984).
Categorical variables are reported as n(%).

Table 2 Outcomes at 1 year according to the left ventricular ejection fraction phenotypes

Phenotypes <i>n</i>	HFrEF 2213	HFmEF 818	HFpEF 1283	<i>P</i> value
1 year all cause death	534/1944 (27.5%)	141/730 (19.3%)	244/1151 (21.2%)	< 0.001
1 year cardiovascular death	270/1731 (15.6%)	68/682 (10.0%)	113/1071 (10.6%)	< 0.001
Cumulative (in-hospital + 1 year) all cause death	643/2053 (31.3%)	180/769 (23.4%)	313/1220 (25.7%)	< 0.001
In-hospital death	109/2212 (4.9%)	39/818 (4.8%)	69/1283 (5.4%)	0.782
1 year all cause rehospitalization (at least 1)	887/1777 (49.9%)	288/694 (41.5%)	524/1081 (48.5%)	< 0.001
1 year cardiovascular rehospitalization (at least 1)	754/1744 (43.2%)	239/687 (34.8%)	386/1066 (36.2%)	< 0.001

HFmEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

relative risk of death respectively in the intermediate quartile of PP compared to patients in the lowest quartile, in which the probability of a fatal event is slightly more elevated. ($P = 0.031$). This was confirmed also for the cumulative all-cause deaths. As shown in the *Table 4*, we did not find any relationship between PP and different levels of SBP in both unadjusted and adjusted models. As shown in the Supporting Information, *Tables S2* and *S3*, the number of patients, particularly in the category of SBP < 100 mmHg in HFmEF and in HFpEF, is relatively low that may have weakened the statistical power of this SBP subgroup analysis.

Pulse pressure as marker of preserved vs. reduced left ventricular ejection fraction

We conducted a ROC analyses to evaluate the potential role of PP as marker of a preserved LVEF ($\geq 50\%$), measured on hospital admission, in individual AHF patients (*Figure 1*). When only PP > 60 mmHg was considered and analysed as a continuous variable, its ability in detecting an EF $\geq 50\%$ was low (the ROC area under curve was 66.6%). On the other hand, when the highest quartile of PP > 60 mmHg was combined with SBP > 140 mmHg, the ROC curve area coefficient was 76.1% suggesting a remarkable sensitivity and specificity of this combination to suggest a preserved LVEF in this clinical context.

Discussion

The salient findings of our study, performed in patients with acute HF, are the following: (i) in HFrEF, intermediate and highest quartiles of PP showed a lower mortality as compared to the lowest quartile with an almost inverse linear relationship, at least in part mediated by SBP; (ii) in HFmEF, PP did not show any relationship to prognosis; (iii) in HFpEF, intermediate quartiles of PP showed a better prognostic value suggesting a J-curve with a more favourable PP value at the nadir of the curve, with no relationship with SBP; (iv) the combination of PP > 60 mmHg and SBP > 140 mmHg was associated with a preserved LVEF suggesting a clinical relevance of this combination in discriminating these HF phenotypes.

Longitudinal community studies like the Framingham Heart study²¹ and the Multiethnic Study of Atherosclerosis²² showed that the brachial PP, in particular the pulse wave velocity and the pulse reflection magnitude respectively, were strong predictors for incident HF. Several studies on the prognostic role of PP in established chronic HF were conducted with non-consistent results.^{6,9–14,23–25} In acute HF, most of the work focused on the prognostic impact of the SBP, a meaningful indicator, and the potential prognostic role of PP has been less explored.^{26–30}

Our data in HFrEF are in line with the results of both Vasodilation in the Management of Acute-HF study¹¹ and (Meta-Analysis Global Group in Chronic Heart Failure) MAGGIC meta-analysis¹² on the prognostic value of PP in acute HFrEF (with a cut-off value of EF < 40% and < 50% respectively) that found that the patients in the lowest PP had the worst prognosis with an association more pronounced if PP was measured within 24 hours after admission¹¹ (with EF).¹² Similarly to our results, the prognostic role of PP was interpreted according to corresponding SBP values.¹² Higher PP was associated to higher SBP and higher LVEF suggesting that stroke volume and SBP are probably the major determinants of its amplitude in this setting.^{11,12}

Differently from our data, the Get With The Guidelines (GWTG) Registry¹³ reported a U-shaped association between PP at discharge and mortality in patients with HFrEF (EF cut-off at 50%) with a risk nadir at PP of 50 mmHg. Risk decreased as PP increased up to 50 mmHg, whereas risk increased as PP increased ≥ 50 mmHg suggesting that for lower PP the LV function is the main determinant of its amplitude, whereas for higher PP arterial stiffness plays a major role. In our population, although intermediate quartiles of PP showed the best prognosis, this significant positive trend was maintained also for higher PP quartiles suggesting an almost linear relation between PP amplitude and reduced mortality further supporting the predominant role of LV pump in determining the PP amplitude in HFrEF. No data were reported in the above studies about the role of PP in the “grey” zone of HFmEF patients. We did not observe any relationship between PP and mortality in this intermediate cohort, and even by comparing the EF subgroups obtained by a single cut-off value of 50%, the results of PP interaction in HFrEF and HFpEF did not change substantially (data not shown). The lack of

Table 3 Hazard Ratios of PP quartiles or continuous PP value at hospital admission with the individual endpoints in acute HFref (n 2213), HFmEF (n 818), and HFpEF (n 1283) (Cox proportional hazards model).

Variable	Modality	HFref			HFmEF			HFpEF				
		Unadjusted HR (95% CI)	P value	Adjusted HR** (95% CI)	Unadjusted HR (95% CI)	P value	Adjusted HR** (95% CI)	Unadjusted HR (95% CI)	P value	Adjusted HR** (95% CI)		
1 year all-cause death	Q1 (PP < =40) Ref											
	Q2 (40.0 < PP < =47.0)	0.92 (0.64-1.31)	0.650	0.81 (0.57-1.16)	0.251	1.00 (0.64-1.57)	0.982	1.11 (0.71-1.75)	0.637	0.72 (0.509-1.023)	0.067	0.68 (0.48-0.96)
	Q3 (47.0 < PP < =60.0)	0.66 (0.54-0.81)	<0.001	0.60 (0.49-0.74)	<0.001	1.06 (0.66-1.71)	0.800	1.15 (0.71-1.86)	0.574	0.59 (0.416-0.858)	0.005	0.56 (0.39-0.80)
	Q4 (PP > 60.0)	0.77 (0.60-0.98)	0.037	0.64 (0.50-0.82)	<0.001	0.93 (0.58-1.48)	0.764	0.90 (0.56-1.44)	0.657	0.85 (0.615-1.189)	0.351	0.77 (0.55-1.07)
1 year CV death*	Continue PP value	0.99 (0.98-0.99)	0.016	0.98 (0.98-0.99)	<0.001	1.00 (0.99-1.00)	0.527	0.99 (0.99-1.00)	0.302	1.00 (0.990-1.002)	0.230	0.99 (0.99-1.00)
	Q1 (PP < =40) Ref											
	Q2 (40.0 < PP < =47.0)	0.83 (0.50-1.38)	0.483	0.73 (0.44-1.22)	0.232	0.54 (0.27-1.08)	0.081	0.59 (0.29-1.19)	0.139	0.71 (0.43-1.18)	0.189	0.68 (0.41-1.13)
	Q3 (47.0 < PP < =60.0)	0.57 (0.43-0.76)	<0.001	0.53 (0.39-0.71)	<0.001	0.66 (0.32-1.34)	0.249	0.70 (0.33-1.43)	0.320	0.61 (0.36-1.02)	0.061	0.56 (0.33-0.93)
Cumulative in-hospital + 1 year all cause death	Q4 (PP > 60.0)	0.68 (0.48-0.96)	0.030	0.56 (0.39-0.80)	0.001	0.97 (0.53-1.76)	0.929	0.92 (0.50-1.69)	0.803	0.72 (0.44-1.19)	0.199	0.66 (0.40-1.08)
	Continue PP value	0.99 (0.98-0.99)	0.009	0.99 (0.97-0.99)	<0.001	1.01 (0.99-1.01)	0.843	1.00 (0.98-1.01)	0.573	0.99 (0.98-1.00)	0.167	0.99 (0.98-1.00)
	Q1 (PP < =40) Ref											
	Q2 (40.0 < PP < =47.0)	0.88 (0.63-1.21)	0.432	0.78 (0.56-1.09)	0.142	0.97 (0.66-1.43)	0.889	1.08 (0.73-1.60)	0.707	0.68 (0.50-0.91)	0.011	0.65 (0.48-0.87)
1 year all cause re-hospitalization	Q3 (47.0 < PP < =60.0)	0.65 (0.54-0.78)	<0.001	0.60 (0.50-0.72)	<0.001	0.98 (0.64-1.49)	0.918	1.04 (0.68-1.60)	0.853	0.53 (0.40-0.73)	<0.001	0.50 (0.36-0.69)
	Q4 (PP > 60.0)	0.69 (0.55-0.87)	0.002	0.59 (0.46-0.74)	<0.001	0.87 (0.58-1.32)	0.524	0.83 (0.55-1.26)	0.391	0.73 (0.54-0.97)	0.032	0.65 (0.49-0.88)
	Continue PP value	0.99 (0.98-0.99)	<0.001	0.99 (0.98-0.99)	<0.001	1.00 (0.99-1.00)	0.365	0.99 (0.99-1.00)	0.155	0.99 (0.98-1.00)	0.004	0.99 (0.98-0.99)
	Q1 (PP < =40) Ref											
1 year all cause re-hospitalization	Q2 (40.0 < PP < =47.0)	1.02 (0.75-1.38)	0.895	1.01 (0.74-1.36)	0.969	0.95 (0.68-1.32)	0.748	0.93 (0.67-1.30)	0.693	0.94 (0.73-1.22)	0.659	0.95 (0.73-1.23)
	Q3 (47.0 < PP < =60.0)	0.89 (0.76-1.05)	0.163	0.89 (0.75-1.05)	0.163	1.33 (0.93-1.90)	0.116	1.27 (0.88-1.84)	0.200	0.87 (0.68-1.11)	0.262	0.87 (0.67-1.11)
	Q4 (PP > 60.0)	0.99 (0.81-1.21)	0.930	0.96 (0.78-1.18)	0.711	1.10 (0.80-1.52)	0.549	1.07 (0.77-1.49)	0.676	1.12 (0.89-1.43)	0.358	1.02 (0.79-1.31)
	Continue PP value	1.00 (0.99-1.00)	0.390	1.00 (0.99-1.00)	0.265	1.00 (0.99-1.00)	0.540	1.00 (0.99-1.00)	0.886	1.00 (0.99-1.00)	0.804	1.00 (0.99-1.00)
Q1 (PP < =40) Ref		0.271		0.232			0.511		0.656		0.039	0.033

(Continues)

Table 3 (continued)

Variable	Modality	HFrEF			HFmEF			HFpEF					
		Unadjusted HR (95% CI)	P value	Adjusted HR** (95% CI)	P value	Unadjusted HR (95% CI)	P value	Adjusted HR** (95% CI)	P value	Unadjusted HR (95% CI)	P value	Adjusted HR** (95% CI)	P value
1 year CV re-hospitalization	Q2 (40.0 < PP < =47.0)	0.83 (0.60-1.15)		0.82 (0.60-1.13)		0.90 (0.63-1.26)		0.92 (0.65-1.31)		0.73 (0.54-0.98)		0.72 (0.53-0.98)	
	Q3 (47.0 < PP < =60.0)	0.76 (0.64-0.89)	0.001	0.76 (0.64-0.90)	0.002	0.86 (0.58-1.27)	0.448	0.90 (0.61-1.34)	0.616	0.94 (0.72-1.24)	0.685	0.90 (0.68-1.18)	0.440
	Q4 (PP > 60.0)	0.63 (0.50-0.79)	<0.001	0.63 (0.50-0.79)	<0.001	1.02 (0.72-1.45)	0.888	0.95 (0.66-1.36)	0.774	0.87 (0.66-1.16)	0.347	0.80 (0.60-1.06)	0.117
	Continue PP value	0.99 (0.99-1.00)	<0.001	0.99 (0.98-0.99)	<0.001	1.00 (1.00-1.01)	0.403	1.00 (0.99-1.00)	0.788	1.00 (0.99-1.00)	0.671	1.00 (0.99-1.00)	0.258

CI; confidence interval; CV, cardiovascular; HFmEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; PP, pulse pressure. Fisher's test.

^aA composite endpoint of cardiovascular death comprising death because of stroke, myocardial infarction (MI) or other cardiovascular aetiology, including deaths because of pulmonary embolism. Any MI or stroke followed by death in the next 28 days (regardless of the cause) was considered to be a fatal MI or fatal stroke.

^bCovariates: age, gender, heart failure aetiology, diabetes, renal function.

relation between PP and any of the prognostic outcomes considered in the intermediate EF group remains unexplained, but it could be related to the very narrow range of EF and a too low number of patients and events.

In acute HFpEF, the prognostic impact of PP is more complex. In our study and in another recent report,¹⁴ the intermediate quartiles of PP showed a better prognosis compared to the lowest and the highest quartiles with no relationship with the level of SBP. This suggests that in HFpEF attributing the relative weight of PP amplitude to arterial stiffness or to LV systolic function may be harder than in HFrEF, and probably, the better prognostic impact of intermediate values of PP is associated with a more favourable ventricular-vascular coupling compared to higher or lower values of PP. Differently from our results, in the GWTG Registry,¹³ the patients with HFpEF showed increasing risk of mortality as PP increases, and this was mediated by increasing SBP suggesting a predominant role of arterial stiffening over LV systolic function. On the contrary, in the acute HFpEF patients of the MAGGIC meta-analysis,¹² those in the lowest quintile of PP had the worst outcome irrespective of the level of SBP, suggesting a prevalent role of a transient alteration in LV systolic performance during the acute episode.

The relative contribution of the single determinants of PP amplitude is dynamic and varies in relation to the clinical situation and the precise timing at which the measurement is performed. In fact, changes over time of its amplitude during hospital stay have been described.³⁰ Of course PP measured on admission is not the same as PP taken days after or at discharge from the initial acute episode, and PP taken early on admission showed the worst prognostic impact.¹¹ Our determinations of PP are on hospital admission whereas in the GWTG Registry¹³ were taken at hospital discharge, and in both the MAGGIC meta-analysis¹² and the Tokitsu study,¹⁴ data of PP were measured at variable time during hospital stay. This might help to explain the apparent discrepancy observed in the literature regarding its prognostic behaviour.

The fact that a lower PP is associated with a worse prognosis does not exclude a major role also of arterial stiffening in determining its narrowing rather than its widening. In fact under stress conditions such as during physical exercise, HFrEF patients with stiffer arteries had lower PP amplitude compared to those with more distensible elastic arteries.⁷ Similarly, in HFpEF, an altered ventricular-vascular coupling reserve may determine a lesser increase in LVEF and in PP amplitude compared to normal subjects.³¹ This increased burden on the left ventricle related to a stiffer vascular system observed during exercise in both HFrEF, and HFpEF may resemble what happens during an acute episode of HF leading to a narrower PP. This may also explain the opposite negative prognostic behaviour of low PP and high pulse wave velocity, a direct measure of arterial stiffness, observed in patients with chronic HFrEF.³² In a recent study comparing 22 hypertensive control subjects and 98 HFpEF patients during hemodynamic

Table 4 Hazard ratios for association of pulse pressure with 1 year all-cause death in A HFrEF (n 2213), B HFmEF (n 818) and C HFpEF (n 1283) for different level of SBP (Cox proportional hazard models)

Variable	SBP level, mmHg	Unadjusted HR (95% CI)	P value	Adjusted HR ^a (95% CI)	P value
A 1 year all-cause death	SBP < 100	0.95 (0.71–1.27)	0.748	0.83 (0.618–1.13)	0.241
	100 ≤ SBP < 140	0.88 (0.79–0.98)	0.023	0.83 (0.748–0.93)	0.001
	SBP ≥ 140	1.12 (1.00–1.25)	0.046	1.08 (0.961–1.21)	0.201
B 1 year all-cause death	SBP < 100	1.09 (0.54–2.22)	0.803	1.28 (0.64–2.53)	0.484
	100 ≤ SBP < 140	1.15 (0.92–1.43)	0.230	1.16 (0.92–1.46)	0.202
	SBP ≥ 140	1.10 (0.94–1.28)	0.229	0.97 (0.83–1.14)	0.711
C 1 year all-cause death	SBP < 100	0.87 (0.47–1.63)	0.663	0.72 (0.36–1.41)	0.335
	100 ≤ SBP < 140	1.05 (0.90–1.21)	0.552	0.94 (0.81–1.09)	0.441
	SBP ≥ 140	1.09 (0.98–1.20)	0.105	1.04 (0.94–1.15)	0.469

CI, confidence interval; HFmEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; SBP, systolic blood pressure.

Fisher's test.

HRs Adjusted per every 10 mmHg increase of PP.

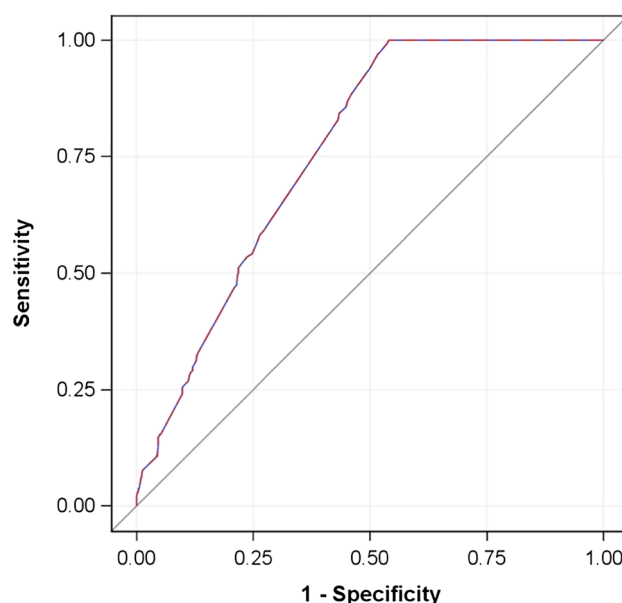
^aCovariates: age, gender, heart failure aetiology (ischemic/non-ischemic), diabetes, renal function

exercise testing with invasively measured radial artery pressure waveform, the HFpEF subjects displayed reduced total arterial compliance and higher effective arterial elastance at similar mean arterial pressures in control subjects. This was directly correlated with higher ventricular filling pressures and depressed cardiac output reserve.³³

Also, the presence of atrial fibrillation may at least in part contribute to a narrower PP in acute HF probably because of a reduction in atrial contribution to LV filling with a consequent further reduction in stroke volume. This may reconcile the apparent discrepancy with earlier studies showing that higher PP is a predictor of incident AF whereas in our study

as well as in the MAGGIC meta-analyses¹² a lower PP relates to higher prevalence of AF.

Finally, the results of our study also suggest a potential clinical role of PP. Acute HFrEF and HFpEF present with similar clinical symptoms and signs, and only imaging techniques can really differentiate the LVEF phenotypes.¹⁵ In previous studies, a low proportional PP index (PP/SBP) has shown to correlate with LV systolic performance in HFrEF.³⁴ In our study, a combination with PP > 60 mmHg and a SBP > 140 mmHg has been shown to discriminate a preserved EF providing a support for a phenotypic diagnosis and some insight in the pathogenetic pattern of these two clinical entities.

Figure 1 Receiving operator characteristics (ROC) curve of PP > 60 mmHg combined with SBP > 140 mmHg in predicting a preserved ejection fraction (>50%) in AHF (ROC curve area 0.761).

Study limitations

Several issues regarding our study must be acknowledged. First, by considering the presumable high proportion of patients needing immediate treatment at enrollment (in fact 88% were in NYHA functional class III–IV), and to foster the consecutiveness of enrollment, specific modalities of BP measurements were not mandated by protocol. This may expose to some imprecision in the BP-reported values. However, the reported level of BP was that used by the attending physicians to take the clinical decisions for patients' management. Second, the observational, pragmatic methodology of our large study does not allow a definite proof of a direct link between PP amplitude and outcome. Third, a recent comprehensive technical, pathophysiological, and clinical review on pulsatile hemodynamics in various HF conditions also outlines the limitation of inferring the PP between two points measured at the clinical bed.²⁹ However, some information can be drawn by this simple measurement, and we tried to explore this area of clinical knowledge. Fourth, we have only one time-point measurement, and we cannot evaluate the potential—likely relevant—prognostic role of changes over time of PP, and we cannot exclude unmet or unknown confounding factors that may have influenced its prognostic impact. Fifth, we do not have information about central PP, found to be a stronger prognostic marker than brachial PP in various conditions.^{21,35} Sixth, we also lack of direct measurements of arterial stiffness like the aortic pulse wave velocity that showed prognostic impact in chronic HFrEF^{32,36} and HFpEF.¹⁴ However, though warranted, central PP and aortic pulse wave velocity have never been measured in any large trial in acute HF and cannot be implemented in a large multinational setting of non-tertiary cardiology centres like the present registry.

Conclusions

Brachial PP has a prognostic value and a potential contributory diagnostic role in acute HF. In HFrEF, an almost linear, inverse relationship between mortality and PP, partly mediated by SBP, was shown. In HFpEF, a J-shaped relationship between mortality and PP was observed with no evident relationship to the level of SBP. A combination of PP and SBP may result as clinically helpful to discriminate the two different major phenotypes of HF.

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All investigators listed in the Supporting Information Appendix 1.

Conflicts of interest

Stefano Bonapace, Andrea Rossi, Cécile Laroche, Massimo Piepoli, Philip Malek, Cezar Macarie, Pierluigi Temporelli, conflict of interest: none declared;

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Clinical characteristics of acute HFrEF, HFmEF and HFpEF groups stratified by baseline PP quartiles.

Table S2. The number of patients in each SBP category of in the HF phenotypes.

Table S3. Distribution of HF subgroups according to SBP category

Appendix S1. List of investigators.

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