Clinical Investigation

Pulmonary Vascular Resistance Is Associated With Brachial-Ankle Pulse-Wave Velocity and Adverse Clinical Outcomes in Patients With Heart Failure With Preserved Ejection Fraction

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ABSTRACT

Background: The precise mechanisms underlying the high prevalence of pulmonary hypertension (PH) with increased pulmonary vascular resistance (PVR) in heart failure with preserved ejection fraction (HFpEF) remain largely unknown. Measurements of brachial-ankle pulse wave velocity (baPWV) have been shown to be useful for risk assessment in HF patients. Thus, this study sought to define the association of PVR with baPWV and clinical outcomes in HFpEF.

Methods and Results: Patients with HFpEF (n = 198) had measurements of baPWV and PVR by right heart catheterization, and were prospectively followed-up for <96 months or until the occurrence of a composite of all-cause death, hospitalization with worsening HF, and nonfatal acute coronary syndrome.

Results: Multivariate logistic analysis showed that baPWV was independently associated with PH with increased PVR ($P < .001$). During the follow-up period, 46 clinical events occurred. Multivariate Cox proportional hazards analysis showed that PH with increased PVR was a significant predictor of adverse outcomes after adjustment for conventional risk factors (HR 1.96, 95% CI 1.03−3.76, $P = .04$).

Conclusions: PH with increased PVR was associated with increased baPWV and adverse clinical outcomes in HFpEF. Thus, increased arterial stiffness may contribute to increased risk predictability of PVR for patients with HFpEF. (*J Cardiac Fail 2019;25:725−732*)

Key Words: HFpEF, PVR, baPWV, clinical outcomes.

Recent clinical studies showed that patients with heart failure with preserved ejection fraction (HFpEF) had a high incidence of adverse clinical outcomes that was equivalent to that in patients with heart failure with reduced ejection fraction (HFrEF).[1,2] However, treatments for HFpEF have been unsuccessful in improving long-term prognosis because multiple pathophysiological mechanisms that contribute to the disease severity make it difficult to find effective treatments.[3] A high prevalence of pulmonary hypertension (PH) has been observed in patients with HFpEF, leading to higher mortality.[4,5] Moreover, remodeling of the pre-capillary pulmonary arteries, as observed in pulmonary arterial hypertension (PAH) has also been shown to be involved in the development of PH in HFpEF.[6−8] The presence of pre-capillary PH can be distinguished from post-capillary PH by invasive measurement of increased pulmonary vascular resistance (PVR) using right heart catheterization (RHC). Patients with increased PVR have pulmonary vascular remodeling and persistent PH, even though left ventricular (LV) filling pressure is lower, and mortality is increased in these patients.[9,10] However, the precise mechanisms underlying the high prevalence of pre-capillary PH in HFpEF and effective treatment remain largely unknown.

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There are several clinical studies showing that assessment of arterial stiffness as an adjunct to traditional risk factors is useful to predict adverse clinical outcomes in patients with HF.[11–17] The measurement of brachial-ankle pulse wave velocity (baPWV) is easy to perform, and this parameter is closely correlated with aortic PWV and carotid-femoral PWV, which are well-established vascular tests for evaluation of arterial stiffness.[18,19]

Recently, systemic dysregulation of vascular tone through imbalances between nitric oxide (NO) and endothelin (ET) have been shown to contribute to both increased PVR in the pulmonary arteries and increased PWV in the systemic arteries.[20] However, the association between PVR and baPWV, and their effects on clinical outcomes have not been well studied in patients with HFpEF. Therefore, the purpose of this study was to examine the relationship between PVR and baPWV, and their prognostic value in patients with HFpEF.

Methods

Study Patients

This study screened 370 consecutive patients with congestive HF who were admitted to the cardiology section of Yamanashi University Hospital from April 2005 to March 2010. They all were examined with RHC after stabilization of HF symptoms before discharge. HF was defined by the cardiologist according to the Framingham criteria.[21] The patients included also fulfilled all of the following criteria: (1) clinical congestive heart failure defined by the Framingham criteria (21) with a disease history of at least 3 months; (2) stable heart failure with New York Heart Association class I-II after standard medications before discharge; and (3) LV ejection fraction (LVEF) >50% on echocardiography before enrollment. Patients were excluded based on the presence of any of the following criteria: (1) acute coronary syndrome, stroke, cardiogenic shock, major surgery, trauma, or serious infectious disease within 4 weeks prior to enrollment; (2) valvular heart disease; (3) neoplasm, chronic hepatic or inflammatory diseases; (4) chronic obstructive pulmonary disease; (5) chronic kidney disease (serum creatinine levels >2.5 mg/dL); (5) pulmonary embolism; (6) PAH; and (7) other serious systemic diseases. According to these inclusion and exclusion criteria, 204 patients were enrolled in this study. The characteristics of the study patients are shown in Table 1. Written informed consent was obtained from all study patients prior to enrollment. This study was in agreement with the guidelines approved by the ethics committee at our institution. The investigation conformed to the principles outlined in the 1975 Declaration of Helsinki.

Cardiac Catheterization

All study patients underwent standard RHC from the brachial venous approach before discharge. No medication changes were made before catheterization. The Swan-Ganz catheter technique was used for right heart catheterization, and pulmonary capillary wedge pressure (PCWP) and cardiac output were measured as in our previous studies.[22,23] Cardiac output was indexed to body surface area. Pulmonary vascular resistance (PVR) was calculated as [mean pulmonary arterial pressure (mean PAP)—PCWP]/cardiac output. Moreover, presence of pulmonary hypertension was defined as mean PAP >25mm Hg, and increased PVR was defined as PVR >3.0 Wood units, according to previous reports.[9,24]

Measurement of Brachial-Ankle Pulse-Wave Velocity

We measured baPWV after stabilization of heart failure symptoms before discharge by a volume plethysmographic method using an automatic waveform analyzer (VP-100; Colon Co. Ltd., Komaki, Japan), according to the manufacturer's instructions and our previously validated method.[18,19] The measurement of baPWV is easy to perform and this parameter is closely correlated with aortic PWV and carotid-femoral PWV.[18,19] Before measurement, patients were required to be in the supine position and resting for at least 5 min. Cuffs were wrapped around both upper arms and ankles. A phonogram, pulse volume waveform, blood pressure, and heart rate were recorded simultaneously. baPWV was calculated by measuring the time for the pulse wave to travel between the brachial and posterior tibial arteries. The mean value of left and right baPWV was used in the statistical analyses.

Follow-Up Study

After all baseline data including RHC, baPWV, and other clinical parameters had been obtained at our hospital, the 204 patients with HFpEF were followed-up prospectively every 3 months at various hospitals by the patients' primary physicians. The patients were followed-up for a period of <96 months or until the occurrence of one of following adverse clinical outcomes: all-cause death, hospitalization with worsening heart failure, and nonfatal acute coronary syndrome (nonfatal MI or unstable angina pectoris). If the first hospitalization for heart failure culminated in death from progressive heart failure during the follow-up period, the event was counted as a death. The time to the first event was evaluated prospectively. All-cause death was confirmed by hospital records. The follow-up data were obtained every 3 months from the patients' primary physicians and then collated by the investigators (J.D, K.N.), who were blinded to the patient characteristics at enrollment. All end point data were checked strictly for accuracy, consistency, and completeness of follow-up by the other investigators (D.F., Y.S.), who also had no knowledge of the baseline clinical characteristics. Additional information was obtained from the physicians as required. Two of the investigators (M.U., T.N.) were responsible for checking all the data, carrying out the analyses, and maintaining security of the data files.

Table 1. Baseline Clinical Characteristics of the Study Patients

			Mean PAP >25 mm Hg		
		Mean PAP ≤25 mm Hg (n = 106)	PVR ≤3 Wood (n = 40)	PVR >3 Wood (n = 52)	*P* Value
Age (y)	69 (60, 74)	69 (59, 74)	67 (57, 73)	71 (61, 76)	.15
Male sex, n (%)	134 (67.7)	74 (69.8)	28 (70.0)	32 (61.5)	<.001
Current smoking, n (%)	43 (21.7)	16 (15.1)	12 (30.0)	15 (28.9)	.51
CAD, n (%)	104 (52.5)	59 (55.7)	21 (52.5)	24 (46.2)	.82
Diabetes mellitus, n (%)	87 (43.9)	34 (32.1)	26 (65.0)	27 (52.0)	.85
Hypertension, n (%)	119 (60.1)	58 (54.7)	25 (62.5)	36 (69.2)	.80
NHYA class II	85 (42.9)	24 (22.6)	20 (50.0)†	41 (78.9)*	<.001
Atrial fibrillation, n (%)	32 (16.2)	18 (17.0)	7 (17.5)	7 (13.5)	.83
Creatinine (mg/dL)	0.9 (0.7, 0.9)	0.8 (0.7, 1.2)	0.9 (0.7, 1.3)	0.8 (0.7, 1.3)	.63
HbA1c (%)	5.6 (5.2, 6.4)	5.5 (5.1, 5.9)	6.0 (5.4, 6.8)	5.8 (5.3, 7.3)	.67
LDL cholesterol (mg/dL)	116 (96, 144)	113 (92, 146)	116 (92, 132)	119 (99, 146)	.47
HDL cholesterol (mg/dL)	46 (39, 55)	46 (40, 54)	47 (38, 54)	45 (36, 55)	.10
BNP (pg/mL)	134 (105, 226)	134 (107, 210)	122 (103, 245)	170 (111, 292)*	.04
HR (bpm)	66 (60, 77)	65 (60, 78)	64 (60, 71)	70 (62, 77)	.74
Mean BP (mm Hg)	100 ± 17.4	100 ± 17	99 ± 16.9	101 ± 17.9	.22
baPWV (cm/sec)	1637 (1448, 1894)	1588 (1406, 1787)	1630 (1438, 1765)	1723 (1470, 1996)*	<.001
Medication use, n (%)					
Beta-blocker	59 (29.8)	27 (25.5)	13 (32.5)	19 (36.5)	.33
ACE-I/ARB	125 (63.1)	60 (56.6)	27 (65.5)	38 (83.1)	.11
Calcium antagonist	80 (40.4)	37 (34.9)	20 (50.0)	23 (44.2)	.20
Aspirin	108 (54.6)	57 (53.8)	25 (62.5)	26 (50.0)	.48
Loop diuretics	108 (54.6)	50 (47.2)	23 (57.5)	35 (67.3)	.05
Aldosterone antagonist	50 (25.3)	20 (18.9)	12 (30.0)	18 (34.6)	.08
Echocardiographic variables					
Left atrial diameter (mm)	36 (34, 39)	35 (31, 38)	36 (32, 40)	37 (35, 39)*	.03
Interventricular septal thickness (mm)	10 (9.0, 11.5)	9.8 (8.8, 11.0)	10.2 (8.9, 12.0)†	11.0 (10.0, 12.1)*	.01
Posterior wall thickness (mm)	10.7 (9.0, 11.8)	10.0 (8.9, 11.6)	11.0 (9.3, 12.1)†	11.0 (9.6, 11.7)*	.01
LV mass index (g/m^2)	127 (108, 155)	118 (97, 143)	137 (119, 155)†	142 (119, 169)*	.01
LVEF (%)	62 (54, 72)	62 (54, 71)	61 (54, 73)	62 (55, 76)	.32
E (cm/sec)	54 (43, 68)	52 (42, 66)	63 (45, 71)	55 (43, 70)	.10
A (cm/sec)**	71 (61, 81)	70 (60, 80)	66 (59, 80)	76 (66, 87)	.08
E/A ratio**	0.7 (0.6, 0.8)	0.7 (0.6, 0.8)	0.8 (0.6, 1.0)	0.7 (0.6, 0.8)	.08
Hemodynamic parameters					
Mean RAP, mm Hg	12 (10, 14)	11 (9, 13)	11 (9, 12)	13 (11, 15)*	.005
Mean PAP, mm Hg	22 (18, 25)	19 (17, 20)	25 (23, 26)†	25 (23, 27)*	<.001
PCWP, mm Hg	14 (12, 16)	12 (11, 14)	14 (12, 16)	14 (11, 16)	.24
Cardiac index, L/min/cm^2	2.9 (2.5, 3.4)	3.0 (2.5, 3.4)	2.8 (2.5, 3.2)	2.8 (2.6, 3.4)	.61

Data are expressed as the mean ± SD, median (25th and 75th percentiles) or number (%) of patients. Hypertension was defined as >140/90mm Hg or use of antihypertensive medication; diabetes mellitus was defined according to the American Diabetes Association criteria or taking an antidiabetic medication.

Abbreviations: CAD, coronary artery disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; HR, heart rate; BP, blood pressure; baPWV, brachial-ankle pulse wave velocity; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; RAP, right atrial pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance.

†$P < .05$, vs patients with mean PAP ≤25mm Hg,

*$P < .05$, vs patients with mean PAP ≤25mm Hg.

**measured in patients without atrial fibrillation.

Statistical Analyses

Data are expressed as either means ± SD, medians and interquartile range (25th and 75th percentiles) or frequencies (%). The Shapiro-Wilk test showed that the continuous variables, except for mean blood pressure (BP), were not normally distributed. Therefore, these data were expressed as the median and interquartile range (25th and 75th percentiles) and were log-transformed for linear regression analyses. Continuous variables were compared among 3 groups using Kruskal-Wallis equality of populations rank test followed by a Dunn's test for post-hoc comparisons. Frequencies were compared using a Chi-square test. The associations of PH with increased PVR (>3WU) with the other hemodynamic and clinical parameters were examined using univariate and multivariate logistic regression analysis. The univariate analyses included age, male gender, current smoking, coronary artery disease, diabetes mellitus, hypertension, HbA1c, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, creatinine, brain natriuretic peptide (BNP), left ventricular ejection fraction (LVEF), LV mass index (LVMI), E/A, heart rate (HR), mean blood pressure (BP), beta blocker use, loop diuretic use, PWCP, and baPWV. The dichotomous variables were coded as 1 or 0 for the presence or absence of a factor, respectively. The multivariate logistic

regression analysis was performed using all variables which were significant in the univariate analyses. Kaplan-Meier survival analysis was performed in patients with PH with increased PVR (>3.0 Wood units), PH with decreased PVR (≤3.0 Wood units), and those without PH. The ability of the hemodynamic and other clinical parameters to predict adverse outcomes was assessed by univariate and multivariate Cox proportional hazards models. The univariate Cox analyses included age, male gender, current smoking, diabetes mellitus, coronary artery disease, hypertension, CAD, atrial fibrillation, creatinine, mean BP, HR, HbA1c, LDL cholesterol, HDL cholesterol, BNP, LVEF, PCWP, beta blocker use, loop diuretic use, baPWV, and PVR >3.0WU and PH. The multivariate Cox proportional hazards analysis included all variables which were significant in the univariate analyses. We also assessed the category-free net reclassification improvement (NRI) and integrated discrimination improvement (IDI) to analyze the predictive ability of PVR and baPWV when it was added to the baseline model of risk factors that included age, male gender, diabetes mellitus, hypertension, current smoking, coronary artery disease, atrial fibrillation, BNP, heart rate, and creatinine according to methods developed recently.[25–27] Statistical significance was defined as $P < .05$. All analyses were performed using STATA version 13.0 (Stata, College Station, TX).

Results

Association Between Increased Pulmonary Vascular Resistance and Clinical Parameters

At baseline, patients with PH with increased PVR (>3.0 Wood units) had higher levels of BNP, baPWV, but a lower frequency of male gender than those without PH (Table 1). Analysis of the echocardiographic and hemodynamic parameters showed that patients with PH with increased PVR had higher levels of left atrial diameter, interventricular septal thickness, posterior wall thickness, LV mass index, mean RAP, mean PAP (Table 1). Linear regression analysis showed that PVR levels were significantly correlated with baPWV (Fig. 1, upper panel). Moreover, univariate logistic regression analyses showed that PH with increased PVR was significantly associated with age, gender, BNP, LVMI, mean BP, beta-blocker use, and loop diuretic use, PCWP, and baPWV (Table 2). In addition, multivariate logistic regression analysis showed that baPWV was independently associated with PH with increased PVR after adjustment for age, male gender, BNP, LVMI, mean BP, beta-blocker use, loop diuretic use, and PCWP (Table 2).

Incidence of Study End Points During Follow-Up

Of the 204 patients enrolled, 6 were withdrawn after enrollment because they could no longer be contacted, and the remaining 198 completed the follow-up study. During the median follow-up period of 2383 (1806, 2534) days,

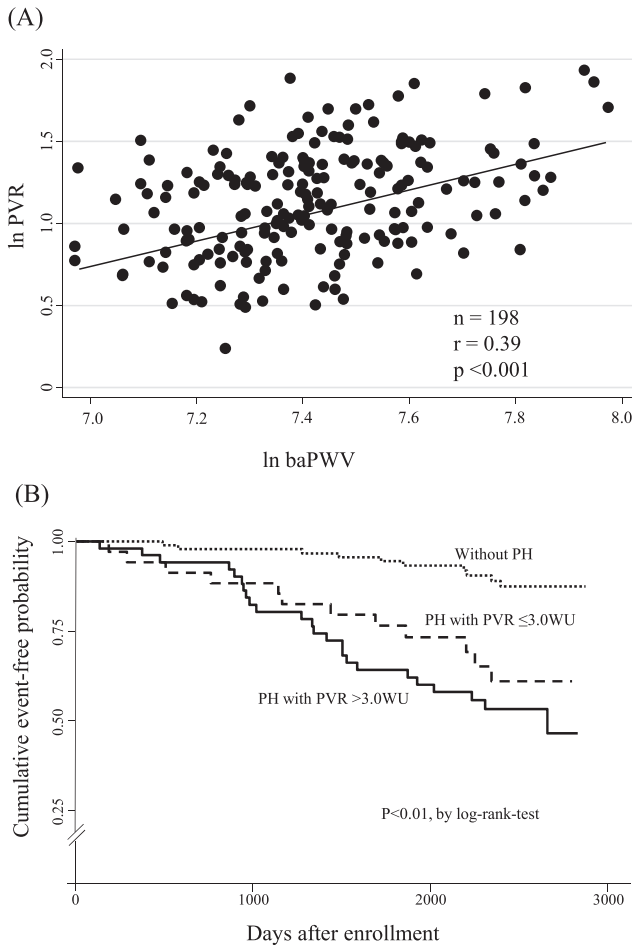

Fig. 1. Correlation of PVR with baPWV and Kaplan-Meier curves in 198 patients with HFpEF. (A, upper panel) Correlation of PVR with baPWV. (B, lower panel) Kaplan-Meier curves showing event-free probability of survival according to the presence of PH and increased PVR during follow-up.

there were 26 cases of death (16 due to cardiac death, 4 due to pneumonia, 4 due to cancer, and 2 due to stroke), 15 cases of hospitalization with worsening HF, and 5 cases of acute coronary syndrome. PVR was significantly higher in patients with than without adverse clinical outcomes (3.6 [2.5, 4.6] vs 3.1[2.4, 3.8] wood units, $P < .01$). In Kaplan-Meier analysis, patients with PH with increased PVR had a lower clinical event-free probability of survival over time than those with PH with decreased PVR and those without PH ($P < .01$, by log-rank test, Fig. 1, lower panel). In the univariate Cox proportional hazards model (Table 3), baPWV, PH with increased PVR, current smoking, diabetes mellitus, HbA1c, BNP, LVEF, PCWP, PVR, and loop diuretic use were significant predictors of adverse clinical outcomes. Moreover, the multivariate Cox proportional hazards model demonstrated that each baPWV and PH with increased PVR was an independent predictor of adverse clinical outcomes after adjustment for confounders (model 1 and 2, in Table 4). However, baPWV lost significance after adjustment for confounders including PH with increased PVR (model 3, in Table 4).

Table 2. Univariate and Multivariate Logistic Regression Analysis for the Relationships Between Higher Levels of Pulmonary Vascular Resistance With Pulmonary Hypertension and the Other Hemodynamic and Clinical Parameters

	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age (y)	1.49	1.08−2.07	.02	1.34	0.88−2.05	.18
Male sex	0.57	0.26−0.89	.02	0.51	0.34−1.08	.08
Current smoking	1.32	0.65−2.68	.44			
CAD	0.86	0.47−1.56	.62			
Diabetes mellitus	1.74	0.95−3.18	.07			
Hypertension	1.84	0.98−3.45	.06			
Atrial fibrillation	1.54	0.71−3.36	.28			
HbA1c	1.31	0.98−1.75	.07			
LDL cholesterol	1.10	0.80−1.45	.62			
HDL cholesterol	1.04	0.78−1.40	.78			
Creatinine	1.10	0.85−1.42	.52			
BNP	1.63	1.07−2.48	.02	1.33	0.86−2.07	.19
LVEF	1.22	0.90−1.64	.19			
LVMI	1.13	1.05−1.22	.01	1.12	1.02−1.23	.02
E/A*	0.82	0.55−1.24	.35			
HR	1.21	0.88−1.67	.24			
Mean BP	1.45	1.06−1.98	.02	1.01	0.99−1.03	.47
Beta-blockers	2.09	1.11−3.95	.02	2.64	1.24−5.64	.01
Loop diuretics	2.17	1.17−4.05	.01	1.79	1.03−4.67	.04
PCWP	1.63	1.17−2.26	.004	1.79	1.19−2.67	.005
baPWV	1.65	1.21−2.25	.001	1.83	1.23−2.74	.003

OR, odds ratio; CI, confidence interval; other abbreviations as in Table 1.
The OR and 95% CI for continuous variables were estimated by 1-SD increase of the variables.
*measured in patients without atrial fibrillation.

Incremental Effects of PVR on the Predictive Value of Traditional Risk Factors

Category-free NRI and IDI were evaluated in four different models where PVR and baPWV was added to 4 baseline traditional risk factors. These four models included the following risk factors: age, male gender, DM, hypertension (model 1); age, male gender, current smoking, coronary artery disease (model 2); age, male gender, BNP, atrial fibrillation (model 3); and age, male gender, heart rate, creatinine (model 4). The addition of PVR or baPWV to traditional risk models significantly improved category-free NRI and IDI. Moreover, the addition of PVR to traditional risk models with baPWV significantly improved only IDI. However, the addition of baPWV to traditional risk models with PVR did not improve category-free NRI and IDI (Table 5).

Table 3. Univariate Cox Proportional Hazards Analysis of Risk Factors for Adverse Clinical Outcomes

	Univariate Analysis		
	HR	95% CI	*P* Value
Age (y)	1.19	0.87−1.61	.28
Male sex	1.15	0.62−2.12	.67
Current smoking	1.95	1.05−3.61	.03
Diabetes mellitus	2.63	1.45−4.79	.002
Hypertension	1.20	0.66−2.15	.56
CAD	1.13	0.63−2.02	.68
Atrial fibrillation	1.58	0.80−3.18	.20
Creatinine (mg/dL)	1.18	0.93−1.51	.18
Mean BP (mm Hg)	1.01	0.75−1.34	.90
HR (bpm)	1.19	0.90−1.56	.23
HbA1c (%)	1.41	1.12−1.78	.008
LDL cholesterol (mg/dL)	0.8	0.6−1.05	.10
HDL cholesterol (mg/dL)	0.8	0.6−1.2	.34
BNP (pg/mL)	1.33	1.14−1.56	.004
LVEF (%)	0.65	0.47−0.90	.004
PCWP, mm Hg	1.32	1.04−1.67	.02
Beta-blocker use	0.9	0.47−1.68	.41
Loop diuretic use	2.24	1.18−4.26	.01
baPWV (cm/sec)	1.44	1.12−1.85	.005
Mean PAP >25mm Hg and PVR >3.0WU	2.24	1.18−4.26	.01

HR, hazard ratio; CI, confidence interval; other abbreviations as in Table 1.
The HR and 95% CI for continuous variables were estimated by 1-SD increase of the variables.

Discussion

The present study demonstrated that pre-capillary PH due to increased PVR was associated with increased baPWV, a marker of increased systemic arterial stiffness, in patients with HFpEF. Moreover, the present study demonstrated that PH with increased PVR predicted a composite of adverse clinical outcomes including death, worsening HF, and acute coronary syndrome in patients with HFpEF. Thus, the present findings indicate that increased baPWV may contribute to the development of pre-capillary PH in HFpEF, and this may increase the ability of PVR to predict adverse clinical events in patients with HFpEF.

Recent clinical studies showed a high prevalence of PH in patients with HFpEF, and this was associated with increased mortality.[4,5] Moreover, pre-capillary PH, defined as increased PVR, was frequently observed in the process of developing PH in HFpEF.[8,28] In line with these studies, the present study showed that 46.5% of the study patients had PH, and increased PVR was a significant predictor of adverse clinical outcomes in patients with HFpEF.

Table 4. Multivariate Cox Proportional Hazards Analysis of Risk Factors for Adverse Clinical Outcomes

	Model 1			Model 2			Model 3		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Current smoking	1.58	0.81−3.06	.18	1.64	0.85−3.16	.14	1.68	0.87−3.24	.12
Diabetes mellitus	1.85	0.88−3.89	.10	2.05	0.99−4.23	.05	1.85	0.89−3.84	.10
HbA1c (%)	1,19	0.88−1.60	.27	1.11	0.83−1.49	.48	1.14	0.85−1.52	.39
BNP (pg/mL)	1.21	0.98−1.50	.07	1.27	1.05−1.54	.01	1.19	0.96−1.46	.11
LVEF (%)	0.79	0.56−1.11	.17	0.78	0.56−1.07	.12	0.76	0.54−1.05	.10
PCWP, mm Hg	1.28	1.01−1.62	.04	1.26	0.99−1.62	.07	1.21	0.95−1.54	.13
Loop diuretic use	1.83	0.95−3.53	.07	1.54	0.79−3.02	.21	1.61	0.82−3.16	.17
baPWV (cm/sec)	1.34	1.01−1.78	.04		–		1.21	0.94−1.67	.12
PH with PVR >3.0WU		–		2.17	1.15−4.08	.02	1.96	1.03−3.76	.04

HR, hazard ratio; CI, confidence interval; other abbreviations as in Table 1.
The HR and 95% CI for continuous variables were estimated by 1-SD increase of the variables.

However, the precise mechanisms underlying the high prevalence of PH in HFpEF patients has been largely unknown. Most recent studies of HFpEF patients focused on the role of left ventricular diastolic function; however, treatments that improve LV function have been unsuccessful in improving long-term prognosis. Therefore, the significant association of PVR with baPWV observed in this study suggests that increased systemic arterial stiffness may play partly an important role in the pathogenesis of the development of pre-capillary PH in HFpEF.

A possible explanation for the association of increased PVR with increased baPWV observed in the present study may be the consequences of adverse structural and functional alterations in the systemic vascular wall in HFpEF patients.[18] These structural and functional abnormalities are largely influenced by an impairment of endothelium-dependent dilation, medial hypertrophy, and elevated smooth muscle tone that are associated with NO availability in the vascular tree.[18] In the pulmonary arteries, as shown in the systemic arteries, the endothelium controls arterial tone through the regulated release of nitric oxide (NO) and endothelin (ET), and the impaired regulation of pulmonary vascular tone through imbalances between NO and ET leads to increased PVR.[20] These results suggest that systemic vascular dysfunction may be the link between increased baPWV and increased PVR in HFpEF patients. Moreover, baPWV was not significant in a multivariate Cox model that included PVR. These statistical results indirectly support a strong relationship between PVR and baPWV in patients with HFpEF. However, recent clinical study showed that J-shaped association of baPWV with adverse clinical events in HFpEF patients,[11] and these relationships might have influenced on our results that baPWV lost significance in the prediction of adverse clinical events in multivariate analysis. However, it still remains unclear that there is a discrepant finding regarding the predictive value of baPWV between previous and present study. Therefore, a larger clinical trials is needed to assess the relationships between baPWV and PVR in HFpEF patients.

Study Limitations

The first limitation of this study was the timing of measurements of hemodynamic parameters. It is difficult to completely distinguish patients in a stable state from patients without symptoms but clinically not stable using our protocol. It may be possible that a favorable change in hemodynamics could have occurred after the hemodynamic measurements. Therefore, serial assessments of hemodynamic parameters and biomarkers are needed to confirm whether patients are stable or not. The second limitation of this study was the relatively small number of patients with HFpEF, which reduced the statistical power of the study. Therefore, a larger clinical trial using a single clinical end point is needed to assess the precise mechanisms for the development of HFpEF. The third limitation of this study is that we did not focus on ventricular-arterial stiffening, an important pathophysiological process as shown in previous studies.[16,17] The significant association of baPWV with PVR observed in the present study may be the results of ventricular-arterial stiffening, and this could lead to the progression of PH and adverse clinical outcomes. Therefore, complete echocardiographic analysis including E/e', a standard method for evaluation of diastolic function, is needed for further evaluation of involvement of ventricular-arterial stiffening in progression of pre-capillary PH in HFpEF patients. The fourth limitation of this study is that we analyzed patients with a history of HFpEF. Therefore, it remains unclear that increased arterial stiffness is the primary mechanism for the development of HFpEF and PH. Moreover, we could not deternine the effects of antiatherosclerotic such as antidiabetic, lipid lowering, and antihypertensive therapies on baPWV, and whether these changes might influence the incidence of PH and adverse clicanical outcomes in HFpEF patients. However, our results suggest that it is important to measure baPWV to detect HFpEF in patients at high risk of pre-capillary PH and adverse clinical outcomes.

In conclusion, increased PVR was associated with increased baPWV and adverse clinical outcomes in patients

Table 5. Incremental Effects of Pulmonary Vascular Resistance on the Predictive Value of Traditional Risk Factors

	Category-Free NRI		IDI	
	Index	*P* Value	Index	*P* Value
Traditional risk model 1 (age, gender, diabetes mellitus, hypertension)				
Traditional risk model 1 + baPWV	0.42	.01	0.03	.03
Traditional risk model 1 + PVR	0.41	.01	0.09	.001
(Traditional risk model 1 + baPWV) + PVR	0.25	.13	0.07	.001
(Traditional risk model 1 + PVR) + baPWV	0.27	.12	0.01	.09
Traditional risk model 2 (age, gender, current smoking, CAD)				
Traditional risk model 2 + baPWV	0.44	.01	0.05	.006
Traditional risk model 2 + PVR	0.37	.02	0.09	.001
(Traditional risk model 2 + baPWV) + PVR	0.28	.09	0.06	.002
(Traditional risk model 2 + PVR) + baPWV	0.23	.18	0.02	.05
Traditional risk model 3 (age, gender, BNP, atrial fibrillation)				
Traditional risk model 3 + baPWV	0.46	.01	0.03	.01
Traditional risk model 3 + PVR	0.41	.02	0.05	.01
(Traditional risk model 3 + baPWV) + PVR	0.24	.15	0.04	.02
(Traditional risk model 3 + PVR) + baPWV	0.25	.13	0.22	.06
Traditional risk model 4 (age, sex, heart rate, creatinine)				
Traditional risk model 4 + baPWV	0.53	.002	0.05	.005
Traditional risk model 4 + PVR	0.46	.006	0.09	.001
(Traditional risk model 4 + baPWV) + PVR	0.33	.05	0.06	.01
(Traditional risk model 4 + PVR) + baPWV	0.29	.09	0.23	.07

NRI, net reclassification improvement; integrated discrimination improvement.

All continuous variables were estimated for a 1-SD increase.

with HFpEF. Thus, increased baPWV may partly contribute to the development of pre-capillary PH in HFpEF, and this may increase the ability of PVR to predict adverse clinical events in patients with HFpEF.

Disclosures

None.

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