Comparative Prognostic Value of Parameters of Pulsatile Right Ventricular Afterload in Patients With Advanced Heart Failure Awaiting Heart Transplantation

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Right ventricular pulsatile afterload (RVPA) demonstrated a strong impact on survival of patients with advanced heart failure (HF) with reduced ejection fraction. The best prognostic parameter of RVPA is unknown. The aim of this work was to examine the prognostic relevance of pulmonary artery compliance (PAC), pulmonary artery elastance (PAE), and pulmonary artery pulsatile index (PAPi) in a consecutive cohort of patients with advanced HF evaluated for heart transplantation (HT).

A total of 149 patients with end-stage HF underwent right-sided cardiac catheterization and were clinically followed up until death or any censoring events, including HT, left ventricular assist device, and hospitalization for acute HF. The primary endpoint occurred in 29 patients (19.5%) during a median follow-up time of 12 (interquartile range 3 to 34) months. This cohort presented a worse hemodynamic profile than event-free survivors. PAC <1.9 mL/mm Hg (hazard ratio 3, 95% confidence interval 1.3 to 6.0, p= 0.007) and PAE >0.9 mmHg/mL (hazard ratio 2.5, 95% confidence interval 1.1 to 5.2, p= 0.02) were associated with the adverse outcome. On the contrary, PAPi was not associated with the outcome. PAC demonstrated a superior predictive value for the composite adverse outcome compared with pulmonary vascular resistance (area under the curve comparison p= 0.019) and PAPi (p= 0.03) but similar compared with PAE (p= 0.19) and mean pulmonary arterial pressure (p= 0.51). PAC, but not PAE, showed incremental prognostic value compared with cardiac index (p= 0.02). In conclusion, hemodynamic indexes of RVPA are associated with worse survival in patients with end-stage HF. PAC and PAE demonstrated superior prognostic value compared with PAPi and pulmonary vascular resistance. Moreover, PAC showed incremental prognostic value compared with cardiac index in patients awaiting HT. **(Am J Cardiol 2022;00:1−7)**

Abbreviations: RVPA, Right ventricular pulsatile afterload; HF, Heart failure; HT, Heart transplantation

Introduction

Right ventricular (RV) function is a major determinant of clinical outcome in patients with advanced heart failure with reduced ejection fraction (HFrEF).[1,2] Pulmonary venous pressure secondary to left ventricular (LV) dysfunction may trigger pulmonary vasoconstriction, reducing nitric oxide production and causing pulmonary vascular remodeling.[3−5] This mechanism can increase RV afterload and induce RV dysfunction. The afterload is defined as the pressure that the cardiac muscle needs to generate to eject blood during ventricular contraction. In particular, RV afterload is composed of a steady and a pulsatile component. The most commonly used RV pulsatile afterload parameters include pulmonary arterial compliance (PAC), pulmonary arterial elastance (PAE), and the pulmonary artery pulsatile index (PAPi). These indexes were associated with poor prognosis in patients with HFrEF.[6−9] However, the best marker of RV dysfunction and predictor of adverse outcome in patients with end-stage HFrEF enlisted for heart transplantation (HT) has not been determined. The purpose of this study was to assess the prognostic relevance of RV pulsatile afterload parameters in a large cohort of patients with advanced HFrEF evaluated for HT.

Methods

This was an observational and retrospective analysis including patients who underwent right-sided cardiac catheterization at Verona University Hospital, during the

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See page 6 for disclosure information.

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evaluation for HT between April 2007 and May 2021. The cohort of patients were followed up from the day of right-sided cardiac catheterization until death or any censoring events, including HT, LV assist device (LVAD) implantation, or new hospitalizations for acute heart failure. The inclusion criteria were patients aged older than 18 years and deemed to be at end-stage HFrEF at multidisciplinary team evaluation for the enlistment to HT or LVAD as a bridge to transplantation. The exclusion criteria were congenital heart disease, restrictive cardiomyopathy, intracardiac shunt, and non-group 2 pulmonary hypertension (PH). The study was conducted according to the Declaration of Helsinki and approved by our institutional review board (institutional review board approval number 1959CESC). All the patients provided their written informed consent to the anonymous data collection. Definitions of clinical and echocardiographic findings are reported in detail in Supplementary Material.

RV dilatation was defined as a RV basal diameter >41 mm and RV mid-diameter >35 mm. RV dysfunction was defined as tricuspid annular plane systolic excursion <17 mm Hg and/or tricuspid annular plane systolic velocity (S′) at pulsed wave Doppler (TDI) <9.5 cm/s.[10,11]

Right-sided cardiac catheterization was performed at rest under minimal sedation in the cardiac catheterization laboratory, using a balloon-tipped Swan−Ganz catheter (Edwards Lifesciences, Irvines, California), which was inserted from the femoral vein into the pulmonary artery as previously described.[12] Pressures were recorded at end-expiration. The following hemodynamic variable were collected: systolic pulmonary arterial pressure (sPAP), diastolic pulmonary arterial pressure (dPAP), pulmonary arterial wedge pressure (PAWP), and right atrial pressure. Mean pulmonary arterial pressure (mPAP) was calculated with the formula (sPAP + 2 × dPAP)/3 and pulmonary arterial pulse pressure (PP) with the difference between sPAP and dPAP. Transpulmonary gradient and diastolic pulmonary gradient (DPG) were calculated with the difference between mPAP or dPAP and PAWP (mPAP − PAWP, dPAP − PAWP) respectively. Cardiac output (CO) was evaluated using Fick oxygen method[13] and it allowed to measure cardiac index = CO/body surface area. The following hemodynamic formula were calculated: PAC = stroke volume (SV)/PP, PAE = sPAP/SV, PAPi = PP/right atrial pressure and pulmonary vascular resistance (PVR = transpulmonary gradient/CO). PH was defined when mPAP was ≥25 mm Hg. PH was considered postcapillary if PAWP was >15 mm Hg.[14] Postcapillary PH was defined isolated if DPG was <7 mm Hg and/or PVR was ≤3 Wood units (WUs) and combined (postcapillary and precapillary) if DPG was ≥7 mm Hg and or PVR was >3 WU.[14]

The primary endpoint was the composite adverse outcome, including all cause of death, urgent HT (defined according to United Network for Organ Sharing 1[15] heart allocation systems), LVAD implantation as bridge to transplantation, and new hospitalization for acute heart failure.

Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range), as appropriate. Categorical data are presented as number and percentages. Comparisons between continuous variables were performed using the Student's *t* test or Mann-

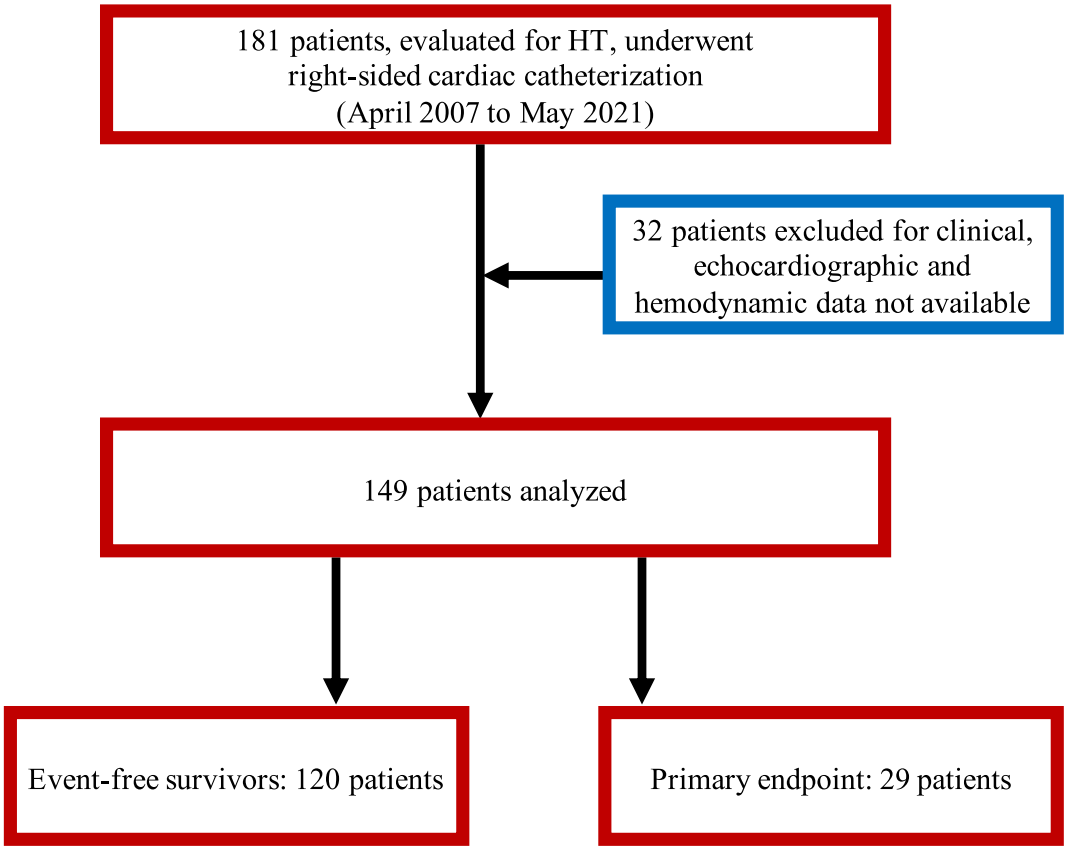


Figure 1. Study flow chart.

Whitney *U* test, as appropriate. Comparisons between categorical variables were evaluated using the Fisher's exact test or the Pearson's chi-square test, as appropriate. Survival was computed from the date of right-sided cardiac catheterization to the occurrence of death or any censoring events, using Kaplan−Meier analysis. HT and LVAD implantation were considered censoring events. Differences between the 2 groups were estimated using log-rank test. Multivariate Cox proportional hazards models were performed to test the independent prognostic value of variables that resulted significant at the univariate analysis. The hazard ratio (HR) with 95% confidence interval (CI) was provided. Area under the receiver-operating characteristic curve (AUC) was calculated and compared with the DeLong method. The statistical analysis was performed with SPSS version 26.0 (IBM Inc., New York, New York) and Stata (StataCorp LLC, 2018, College Station, Texas).

Results

Between April 2007 and May 2021, a total of 181 patients with advanced heart failure and left ventricle dysfunction were enlisted for HT at the Department of Cardiothoracic Surgery of Verona. Complete dataset, including right-sided cardiac catheterization, echocardiographic data, and clinical follow-up, were available for 149 patients who were included in this analysis (Figure 1).

The baseline characteristics of study cohort are shown in Table 1. The mean age was 56.6 ± 10.1 years and 85% were men. The most frequent etiology of HFrEF was ischemic cardiomyopathy (52%). Mean LV ejection fraction was 25.7 ± 10.2%. Chronic kidney disease was present in 40% and diabetes mellitus in 32% of the patients.

The median follow-up time was 12 (interquartile range 3 to 34) months. The primary endpoint occurred in 29 patients (19.5%): 9 patients died (6%), 4 patients (3%) underwent an urgent HT, 11 patients (7%) underwent

Table 1
Baseline characteristics of patients

Variables	Overall population n:149	Event- free survivors n:120	Primary endpoint n:29	P value
Age (years)	56.6 ±10.1	55.5 ±10.3	61.2 ±7.8	0.006
Male	127 (85.2%)	104 (86.7%)	23 (79.3%)	0.31
Female	22 (14.8%)	16 (13.3%)	6 (20.7%)	0.31
BMI (Kg/m^2)	25.2±3. 7	25.2±3.8	25 ±2.94	0.75
Diabetes mellitus Type 2	48 (32.2%)	39 (32.5%)	9 (31%)	0.88
Arterial hypertension	59 (39.6%)	47 (39.2%)	12 (41.4%)	0.82
Smoker	22 (14.8%)	19 (15.8%)	3 (10.3%)	0.46
Chronic kidney disease	60 (40.3%)	43 (35.8%)	17 (58.6%)	0.025
Atrial Fibrillation	59 (39.6%)	46 (38.3%)	13 (44.8%)	0.52
Ischemic cardiomyopathy	78 (52.3%)	60 (50%)	18 (62.1%)	0.77
Non ischemic cardiomyopathy	71 (47.7%)	60 (50%)	11 (37.9%)	0.77
RAP (mmHg)	9.6 ± 6.2	9.4± 6.13	10.03 ±6.5	0.56
sPAP (mmHg)	46.7 ± 16.7	44.8±16.4	54.03±16.4	0.009
mPAP (mmHg)	30.2 ±11.2	29.3±11.0	33.5±11.3	0.05
PCWP (mmHg)	21.3 ±8.8	20.7±8.7	23.9±8.5	0.09
TPG (mmHg)	8.9 ± 5.9	8.7± 5.2	9.6± 8.3	0.31
DPG (mmHg)	-1.2 ±5.1	-1.1±5.0	-1.6±5.6	0.76
CO (L/min)	3.9 ±1.2	4.0±1.2	3.8±1.1	0.47
SV (mL)	54.8±20.2	55.4±21.2	52.4±15.08	0.62
Cardiac Index (L/min/m^2)	2.1±0.57	2.1±0.6	2.03±0.50	0.56
PVR (WU)	2.5±1.7	2.6±2.0	3.0±1.6	0.09
PAC (mL/mmHg)	2.5±1.9	2.7±2.0	1.8± 0.8	0.01
PAE (mmHg/mL)	1±0.1	0.1±0.6	1.1±0.5	0.04
PAPi (mmHg)	4.4± 4.4	4.1±3.6	5.7±6.7	0.32
Pulmonary hypertension	100 (67.1%)	76 (63.3%)	24 (82.8%)	0.04
Isolated post-capillary PH	91 (61.1%)	71 (59.2%)	20 (69%)	0.33
Isolated pre-capillary PH	4 (2.7%)	2 (1.7%)	2 (6.9%)	0.11
Combined PH	4 (2.7%)	3 (32.5%)	3.4 (1%)	0.77
LV ejection fraction (%)	25.7±10.2	26.0±10.5	24.6±8.5	0.66
ePAPs (mmHg)	45.9±18.8	43.7±16.8	52.5.±23.1	0.12
TAPSE (mm)	16.6±4.7	6.8±4.8	16.04±3.9	0.42
S'TDI (cm/sec)	12.1±19.8	13.9±24.03	8.2±1.7	1.0
Right ventricular dysfunction	66 (44.3%)	50 (41.7%)	16 (55.2%)	0.18

BMI = body mass index; RAP = right atrium pressure; sPAP = systolic pulmonary arterial pressure; mPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; TPG = transpulmonary gradient; DPG = diastolic pulmonary gradient; CO = cardiac output; SV = stroke volume; PVR = pulmonary vascular resistance; WU = Wood units; PAC = pulmonary artery compliance; PAE = pulmonary arterial elastance; PAPi = pulmonary artery pulsatile index; PH = pulmonary hypertension; LV = left ventricular; ePAPs = estimated systolic pulmonary arterial pressure; TAPSE = tricuspid annular plane systolic excursion; S'TDI = tricuspid annular plane systolic velocity tissue doppler imaging.

Table 2
Univariate Cox regression analysis

Variable	HR (95% CI)	P value
PAC	0.60 (0.41−0.88)	0.01
PAE	1.43 (0.88−2.32)	0.14
PAPi	1.03 (0.98−1.09)	0.17
sPAP	1.02 (1−1.04)	0.007
mPAP	1.03 (1−1.06)	0.05
PCWP	1.04 (0.99−1.08)	0.06
TPG	1.27 (0.96−1.09)	0.42
DPG	0.99 (0.92−1.07)	0.98
PVR	1.14 (0.96−1.3)	0.131
Age	1.07 (1.02−1.13)	0.005
Arterial hypertension	0.86 (0.41−1.81)	0.70
Smoker	1.14 (0.75−1.72)	0.52
Chronic kidney disease	2.13 (1.01−4.46)	0.04
Atrial fibrillation	1.18 (0.56−2.45)	0.65
Diabetes mellitus type 2	0.83 (0.38−1.83)	0.65
LV ejection fraction	0.97 (0.85−1.12)	0.75

PAC = pulmonary artery compliance; PAE = pulmonary arterial elastance; PAPi = pulmonary artery pulsatile index; sPAP = systolic pulmonary arterial pressure; mPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; TPG = transpulmonary gradient; DPG = diastolic pulmonary gradient; PVR = pulmonary vascular resistance; LV = left ventricular.

LVAD implantation, and 5 (3%) were hospitalized for heart failure. A total of 64 patients (43%) underwent HT, whereas 67 patients (45%) were alive without HT or LVAD at the end of the study period. Patients who met the primary endpoint were significantly older (61.2 ± 7.8 vs 55.4 ± 10.3, p = 0.006), with worse hemodynamic profile than the event-free survivors. In particular, the primary endpoint occurred more frequently in patients with higher mPAP (33.5 ± 11.3 vs 29.3 ± 11.0, p = 0.05), PVR (3.0 ± 1.6 vs 2.6 ± 2.0, p = 0.09), and PAE (1.1 ± 0.5 vs 0.1 ± 0.6, p = 0.04) and lower PAC (1.8 ± 0.8 vs 2.7 ± 2.0, p = 0.01). At the univariate Cox regression, PAC (HR 0.6, CI 0.41 to 0.88, p = 0.01) and mPAP (HR 1.03, CI 1 to 1.06, p = 0.05) were associated with primary endpoint, Table 2. On the contrary, PAE, PAPi, PVR, and DPG did not show a significant correlation at this analysis. At a multivariate Cox regression analysis, PAC (HR 0.62, CI 0.41 to 0.93, p = 0.02) but not mPAP (HR 1.02, 95% CI 0.96 to 1.08, p = 0.40) was significantly associated with the composite adverse outcome after adjustment for potential confounding factors (Table 3).

PAC <1.9 mL/mmHg was associated with a threefold increased risk of adverse composite outcome (HR 3, 95% CI 1.3 to 6.0, p = 0.007, log-rank chi-square = 7.9, p = 0.005; Figure 2, Table 4). Similarly, PAE >0.9 mmHg/mLwas associated with the risk of adverse outcome (HR 2.5, 95% CI 1.1 to 5.2, p= 0.02; Figure 2). Conversely, PAPi was not significantly associated with the outcome (Table 4). PH was associated with significant increased risk of adverse outcome (HR 3, 95% CI 1.0 to 7.5, p= 0.03; Supplementary Figure 1, Table 4). Importantly, the time of enrollment was not associated with the clinical outcome (Supplementary Figure 2).

A total of 97 patients (65%) presented low PVR (<3 WU). In this subgroup, the primary endpoint occurred in 16 patients (16%). At the univariate Cox regression, PAC (HR 0.61, 95% CI 0.4 to 0.9, p= 0.04, mPAP (HR 1.06, 95% CI 1.0 to 1.1, p= 0.02), and PCWP (HR 1.07, 95% CI 1.0 to 1.1, p= 0.01) were associated with the adverse outcome in patients with low PVR (Supplementary Table 1). On the contrary, PAE (HR 1.60, 95% CI 0.8 to 2.8, p = 0.12) and PAPi (HR 1.03, 95% CI 0.9 to 1.1, p = 0.54) were not associated with the adverse outcome in this subgroup.

Table 3
Multivariate analysis for hemodynamic determinants of composite adverse outcome

Variable	HR (95% CI)	P value
PAC	0.62 (0.41−0.93)	0.02
Age	1.05 (1.00−1.10)	0.04
Chronic kidney disease	1.7 (0.80−3.64)	0.16

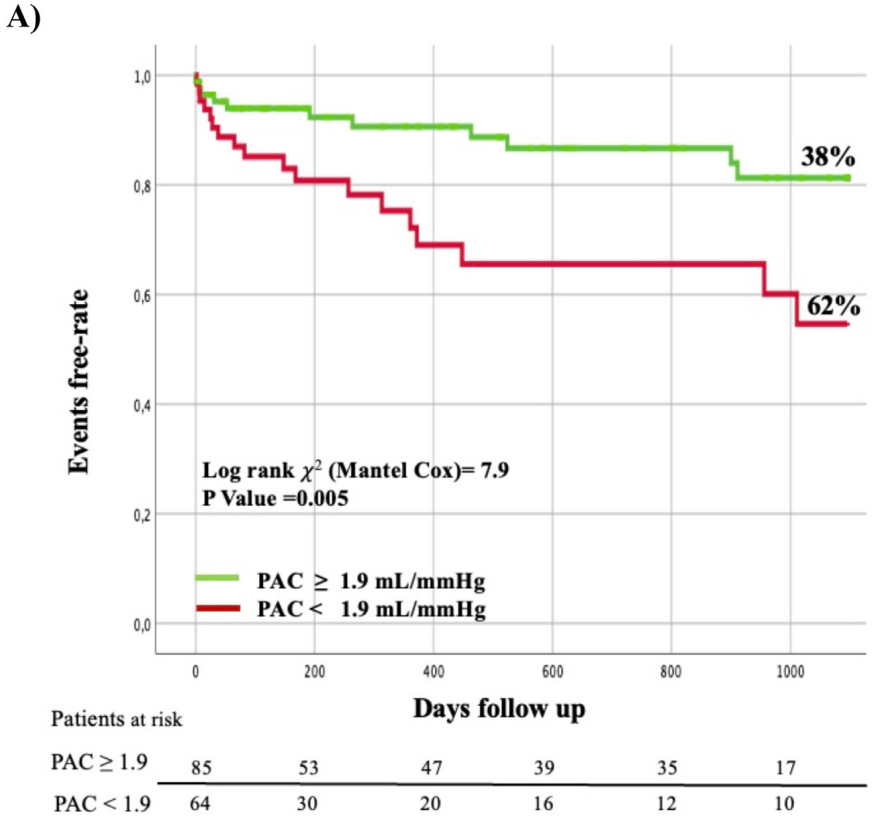
PAC = pulmonary artery compliance.

PAC was superior compared with PVR (AUC_{PAC} 0.64 vs AUC_{PVR} 0.42, p= 0.019) and PAPi (AUC_{PAC} 0.64 vs AUC_{PAPi} 0.47, p= 0.03) in predicting the primary end point. Conversely, no significant difference was observed between the prognostic value of PAC and mPAP (AUC_{PAC} 0.64 vs AUC_{mPAP} 0.62, p= 0.51) and PAE (AUC_{PAC} 0.64 vs AUC_{PAE} 0.62, p= 0.19). Notably, PAC demonstrated a stronger association with the primary end point compared with cardiac index (AUC_{PAC} 0.64 vs $AUC_{Cardiac\ Index}$0.53, p = 0.02). In multivariate regression models, PAC (p = 0.02) but not PAE showed incremental prognostic value compared with cardiac index. Conversely, mPAP was not superior to the cardiac index in predicting the primary end point (AUC_{mPAP} 0.62 vs $AUC_{Cardiac\ Index}$ 0.53, p= 0.28).

Discussion

The main results of our analysis are as follows: (1) determinants of pulsatile RV afterload are strongly associated with adverse outcome in patients with end-stage HFrEF awaiting HT. (2) In particular, PAC but not mPAP demonstrated to be independently associated with the composite end point. (3) PAC provided superior prognostic performance compared with conventional parameters, including cardiac index and PVR.

RV function is an important prognostic determinant in patients with advanced HFrEF.[16] The RV works against a low pressure and resistance and high compliance and elasticity circulation. The alteration of one or more components of RV afterload impacts on RV function. Therefore, RV afterload parameters may be used to predict RV dysfunction when kinetic alteration has not been presented yet. Interestingly, Carluccio et al[17] demonstrated subclinical RV dysfunction using strain analysis in patients with preserved tricuspid annular plane systolic excursion. In particular, RV pulsatile afterload parameters have the potential to detect abnormalities in RV function earlier in the natural history of end-stage HFrEF. Indeed, PAC was also significantly associated with the primary end point in the subgroup with low PVR. RV pulsatile afterload parameters can be easily derived from standard right-sided cardiac catheterization measurements, which is a recommended exam in patients evaluating for HT or mechanical circulatory support.[18] Importantly, the analysis of hemodynamic



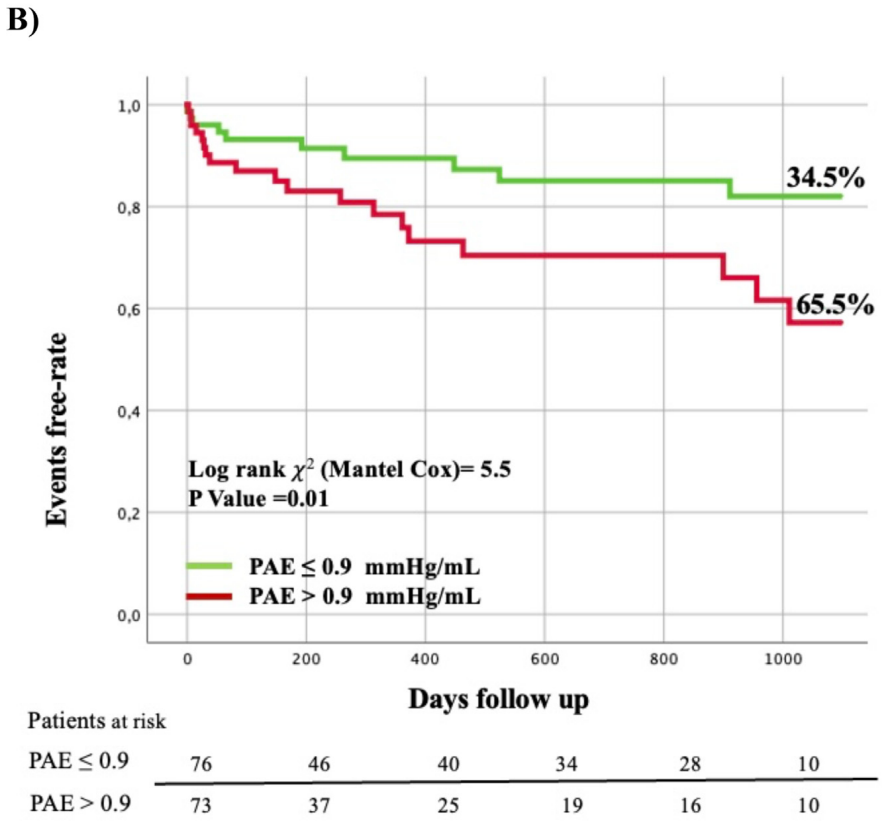


Figure 2. Survival analysis of patients according to different hemodynamic determinants cutoff at follow-up. (*A*) green line indicates PAC ≥1.9 mL/mm Hg and red line PAC <1.9 mL/mm Hg; (*B*) green line PAE ≤0.9 mmHg/mL and red line PAE >0.9 mmHg/mL.

Table 4
Univariate Cox regression for specific hemodynamic determinants cut-off of composite adverse outcome

Variable	HR (95% CI)	P value
PAC <1.9 mL/mmHg	3 (1.3−6.0)	0.007
PAE >0.9 mmHg/mL	2.5 (1.1−5.2)	0.02
PAPi <1.37 mmHg	1.03 (0.4−2.1)	0.93
PVR ≥ 3 WU	2 (0.9−3.9)	0.08
mPAP ≥ 25 mmHg	3 (1−7.5)	0.03

PAC = pulmonary artery compliance; PAE = pulmonary arterial elastance; PAPi = pulmonary artery pulsatile index; PVR = pulmonary vascular resistance; WU = Wood units; mPAP = mean pulmonary arterial pressure.

indexes of RV pulsatile afterload might improve the risk stratification of severely ill patients with HFrEF.

In this analysis, PAC demonstrated to provide advantages compared with other RV pulsatile afterload parameters. In particular, PAC was superior compared with PAPi in predicting the primary end point. Moreover, PAC yielded better prognostic stratification than PAE, providing incremental risk stratification to the cardiac index. PAC expresses the distensibility of arterial pulmonary vessels and describes the capability of pulmonary vessels to dilate during systole and recoil during diastole. The contribute of compliance of pulmonary artery in the afterload of the RV is superior to the role of compliance in the systemic circulation.[19] Indeed, in the pulmonary circulation, compliance depends both on the proximal and distal pulmonary vessels.[12,20] On the contrary, in the systemic circulation compliance concerns only the proximal aorta.[21] In patients with HFrEF, the combination of increased pulmonary arterial pressure and arterial remodeling of pulmonary vascular system determines a gradual reduction of PAC.[22]

Dupont et al[7] analyzed a large cohort of 724 patients with HFrEF described PAC as the best predictor of all cause of mortality and HT compared with PVR and PCWP. A recent meta-analysis investigated the prognostic role of PAC in patients with PH secondary to left heart disease,[23] showing that per 1-unit mL/mm Hg decrease of PAC, the risk of mortality increases by nearly 30% (HR 1.29, 95% CI 1.07 to 1.56, p = 0.019).

PVR describes the steady component of RV afterload and reflects the opposition to forward blood flow in pulmonary circulation. PVR is related to PAC, with an inverse hyperbolic relation, with a constant product.[6,24] Interestingly, in patients with normal or modestly abnormal PVR, PAC may be significantly impaired. Consistently, in our analysis, PAC demonstrated a significant prognostic value in patients with normal PVR, (Supplementary Table 1).[6,25] PVR was previously significantly associated with adverse prognosis in patients awaiting HT, regardless the value of pulmonary pressure.[26] However, in our series, PVR >3 WU did not demonstrate a significant correlation with the adverse outcome.

Augmented values of PAE expresses increased pulmonary artery stiffness and it is related to consequently higher level of energy required by the RV to maintain forward flow.[27] Wright et al[28] showed that elevated PAE (>0.5 mm Hg/mLl) was associated with an increased risk of mortality in patients with advanced HF. Similarly, we observed that PAE higher than 0.9 mm Hg/mL was associated with adverse outcome in patients with end-stage HFrEF awaiting HT.

PAPi is a RV pulsatile afterload index independent from SV.[29] A retrospective analysis of ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial demonstrated a significant correlation between low PAPi and mortality and new hospitalization.[30] In particular, PAPi <3.65 demonstrated a high positive predictive value for 6-month mortality and hospitalization. In our cohort, PAPi was not associated with the adverse outcome and demonstrated inferior prognostic value compared with PAC in patients with HFrEF awaiting HT.

The present analysis has several limitations. The main limitation is the retrospective nature of the data collection. Moreover, this was a single-center, observational study, conducted over a long period of time. Therefore, potential inaccuracies in data collection and confounders cannot be excluded. In particular, the retrospective data collection prevented advanced imaging technique analysis, including RV free wall strain analysis. Nevertheless, this was a highly selected cohort of patients, in which every case was discussed into multidisciplinary meetings and underwent standardized assessment, including echocardiography and right-sided cardiac catheterization. Furthermore, the clinical outcome was assessed using records of dedicated outpatient clinic or hospital records and collected into a dedicated database.

In conclusion, hemodynamic indexes of pulsatile RV afterload are associated with event-free survival in patients with end-stage HFrEF. In particular, PAC and PAE demonstrated a superior prognostic value compared with PAPi and steady-state PVRs in a cohort of patients enlisted for HT.

Disclosures

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.08.010.

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