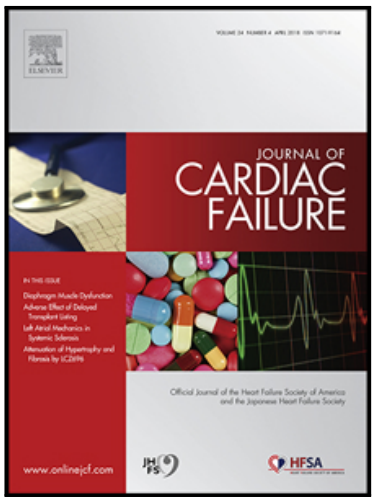
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The differential impact of the Left Atrial pressure components on Pulmonary Arterial Compliance-Resistance relationship in Heart Failure

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TITLE PAGE

The differential impact of the Left Atrial pressure components on Pulmonary Arterial Compliance-Resistance relationship in Heart Failure

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ABSTRACT

Purpose:

The pulmonary capillary wedge pressure (PAWP) rise has been shown to impact on the inherent relationship between the pulmonary arterial compliance (PAC) and pulmonary vascular resistance (PVR), thus augmenting the pulsatile relative to the resistive load of the right ventricle (RV). However, the PAWP comprises the integration of both the steady and the pulsatile pressure components. We sought to address the differential impact of the these distinct PAWP components on the PAC-PVR relationship in a cohort of heart failure (HF) patients.

Methods and results:

The study population consisted of 192 patients with hemodynamic findings diagnostic for HF. Off-line analysis was performed using the MATLAB software. The steady ($PAWP_S$) and pulsatile ($PAWP_P$) PAWP components were calculated as mid-A pressure and mean pressure during the V-wave oscillation, respectively. The PAC and PVR were hyperbolically and inversely associated and the subgroup of patients with PAWP above the median (>18 mmHg) displayed a significant left and downward shift of the curve fit ($p<0.001$). The shift in the PAC-PVR fit between patients with higher vs. low $PAWP_S$ was not significant ($p=0.43$). In contrast, there was a significant downward and leftward shift of the PVR-PAC curve fit for the subgroup with higher $PAWP_P$ ($p<0.001$). Furthermore, only $PAWP_P$ was significantly associated with the RC-time, assessed as the PAC × PVR product ($p<0.001$).

Conclusion:

In HF patients, the pulsatile rather than the steady PAWP component stands for the previously documented shift of the PAC-PVR relationship occurring at elevated PAWP.

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Key words: Heart failure, Pulmonary arterial compliance, Pulmonary vascular resistance, Pulmonary artery wedge pressure.

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New & Noteworthy:

Studying the steady and pulsatile PAWP components and their impact on PAC-PVR relationship

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INTRODUCTION

The prognostic role of pulmonary hypertension (PH) in left heart disease (LHD) is well established and reflects the various adverse effects of elevated RV afterload. (1) The RV afterload is comprised of the resistive as well as the elastic properties of the pulmonary vessels. The former reflects the opposition to forward flow and is commonly expressed in terms of pulmonary vascular resistance (PVR) representing the static element of the RV afterload. In turn, the pulmonary arterial compliance (PAC) signifies the elastic properties of the pulmonary vascular tree and reflects the energy required to overcome the pressure rise occurring during RV ejection. (2, 3)

The product of PAC and PVR denotes the pressure decay of the pulmonary pressure during diastole and is designated by the time-constant of the pulmonary circulation (RC-time). It has been suggested that the RC-time in the pulmonary circulation is rather constant, (4-7) which in turn would have the clinically important implication that quantification of PVR would allow for PAC estimation and vice versa. However, Tedford and colleagues have questioned the constancy of the RC-time and evaluated the impact of pulmonary capillary wedge pressure (PAWP) on the PAC-PVR relationship in patients with LHD. They demonstrated that elevation of the mean PAWP ($PAWP_M$) yields a leftward and downward shift of the PAC-PVR hyperbolic curve suggesting that higher $PAWP_M$ augments RV pulsatile relative to resistive load and may contribute to RV dysfunction.(8) Moreover, Dupont and colleagues(9) showed that lowering the left atrial pressure (LAP) in HF patients yielded a PAC rise at levels higher than one would predict from the corresponding decrease in PVR, thus implying an increase in RC-time. Accordingly, the notion of RC-time constancy was refuted.(8-10)

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Importantly, the PAWP comprises an integration of both the static (steady) and the pulsatile pressure occurring during the heart circle. There is evidence that the pulsatile element of the LAP entails differential effects on the pulmonary circulation as compared to the corresponding steady pressures. We have recently demonstrated that the pressure increase occurring during the V-wave impacts on the value of the diastolic pressure gradient (DPG), an index of pulmonary vascular function.(11) Furthermore, it has been shown that in the setting of prominent V-waves, retrograde propagation and superimposition of wave reflections on the pulmonary artery pressure (PAP) contour may occur.(12) Thus, in the current study we sought to address the differential impact of the steady and pulsatile components of PAWP on the RC time-constant.

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MATERIALS AND METHODS

Study population

A total of 416 patients (Supplemental figure 1) referred for diagnostic right heart catheterization (RHC) at the Karolinska University Hospital due to unexplained dyspnea, suspected pulmonary hypertension or for hemodynamic assessment prior to decision for heart transplantation (HTx) or left ventricular assist device (LVAD) eligibility were studied between 1-feb-2014 and 1-aug-2018. Of them, patients with pre-capillary pulmonary hypertension, constrictive pericarditis, arrhythmogenic right ventricular cardiomyopathy (ARVC), post heart transplantation, and patients with normal RHC findings were excluded. In total, the study population consisted of 192 patients with hemodynamic findings indicating HF defined as elevated LAP at rest or during exercise ($PAWP_{REST}$ >15 mmHg or $PAPW_{STRESS}$ ≥25 mmHg).(13)

All patients underwent a standard transthoracic echocardiographic examination 1-hour prior to RHC, and blood samples were collected in a fasting state. The glomerular filtration rate (eGFR) was estimated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration).(14) The study complies with the Declaration of Helsinki and was approved by the regional ethical review board.

Right Heart Catheterization

RHC was performed using a 6F balloon-tipped fluid-filled Swan-Ganz catheter (Edwards Lifesciences, Irvine, California, USA) through the jugular vein access. Mean right atrial pressure, pulmonary artery pressures, $PAWP_M$ and right ventricular systolic pressure were recorded under fluoroscopy after calibration with the zero-level set at the mid-thoracic line. Measurements were recorded at end-expirium during spontaneous breathing and stored in a connected hemodynamic recorder (Xper

Information Management, Philips Medical Systems, The Netherlands). From the PAP recordings, the peak of the ascending limb of the PAP curve (PAP_S) as well as the end diastolic pressure (PAP_D) were identified and marked manually, following which the software provided an automated calculation of PAP_S and PAP_D. Subsequently, mean PAP (PAP_M) was calculated by integration of PAP over the entire cardiac cycle. From the PAWP waveform the points signifying the peak of the V-wave and the trough of the X- and Y-descent were marked (**Figure 1**). Additionally, automated integration of the PAWP waveform over the entire cardiac cycle was also obtained ($PAWP_M$). All pressure measurements were averaged from a minimum of 3 heart cycles at end-expiration. Importantly, in order to ensure the uniformity of data acquisition and analysis the same investigator (AM) participated in the majority of RHC procedures and performed the analysis of all waveforms. Cardiac output (CO) was measured using the Fick's principle. The oxygen consumption was measured breath-by-breath (Jaeger Oxycon Pro, VIASYS™ Healthcare, Palm springs, California, USA) in mL/min. Arterio-venous oxygen difference was calculated from oxygen concentration in arterial and mixed venous blood from the pulmonary artery. In 10 cases thermodilution was employed.

Exercise Protocol. Following the assessment of resting hemodynamics, patients with normal $PAWP_M$ at rest (≤ 15 mmHg) in the absence of significant PAP_M elevation or those with clinical suspicion of heart failure with preserved ejection fraction (HFpEF), performed supine cycle ergometry. HFpEF was defined as LVEF ≥ 50%, elevated NT-proBNP, and relevant structural heart disease or echocardiographic diastolic dysfunction according to the current guidelines by the European Society of Cardiology (ESC) (15). Furthermore, patients with heart failure with reduced ejection fraction (HFrEF) underwent as well ergometry as part of the hemodynamic

evaluation. Patients cycled at 60 rpm starting at a 20 Watts workload and increasing by 10-Watt increments in 1-minute stages to maximum tolerated levels. $PAWP_M$ was determined at peak exercise. In line with prior studies and the current recommendations, $PAWP_M \geq 25$ mmHg during peak exercise denoted abnormal $PAWP_M$ response(13, 16).

Calculation of PAC and PVR

All hemodynamic tracings were reviewed by a single experienced invasive cardiologist (AM). Pressures at spontaneous end-expirations were analyzed. PVR was calculated as $(PAP_M - PAWP_M)/CO$ and expressed as mmHg•seconds•mL^{-1}. PAC was calculated as per the equation: $PAC = SV/PA_{PP}$ in mL•$mmHg^{-1}$; where: PA_{PP} : pulmonary arterial pulse pressure and SV: stroke volume (3, 17-20), $PAWP_M$ was obtained by digital analysis of a minimum of 3 consecutive beats at end-expiration.

Assessment of the steady and pulsatile components of the pulmonary arterial load (Off-line analysis of RHC waveforms)

Of the 192 patients, 137 cases were accessible for further offline analysis in MATLAB software (R2018b, MathWorks, MA, USA). In these cases, the raw data of PAWP and PAP waveforms were extracted and transferred to MATLAB for subsequent analysis. This system allowed specific pressure integration of the various wave forms and thus comprehensive assessment of the various elements of PAWP waveform.

First, the pulsatile PAWP component ($PAWP_P$), representing the pulsatile load generated by the LA, was obtained by measuring the mean pressure during the V-wave (i.e. the time interval between the X and Y troughs), as illustrated in Figure 1a. In case of atrial fibrillation, the start of the pulsatile component was defined as the

beginning of the ascending limb of the V wave (Figure 1b). The steady PAWP component ($PAWP_S$) was calculated as the mid-A wave pressure in sinus rhythm or as the pressure 130 ms following the start of the QRS complex(16) in AF.

The average values of 3 beats were recorded. The reproducibility of the instantaneous PAWP measurements were determined in ten randomly selected patients.

Statistical Analysis

Normality was tested by the Shapiro-Wilk test. Continuous variables were expressed as median and lower and upper quartiles (Q1; Q3) as the distribution of PAC and PVR was asymmetric. To demonstrate the relationship between PAC and PVR, a non-linear curve was fitted according to the hyperbolic formula: $y = a/(b + x)$. Statistical analysis was performed using SPSS version 23.0 (SPSS Inc., Chicago, Ill. USA) while curve fits were generated using MATLAB (version 9.4, R2018a; 2018, The MathWorks, Natick, MA). All measurements are stated as median and lower and upper quartiles (Q1; Q3) if not stated otherwise. Categorical variables are presented as n (%). Continuous variables were compared using the Mann-Whitney U test (skewed variables). Chi-square test was performed when appropriate. The comparison between the various hyperbolic curves was performed using the methodology proposed by Armitage et al.(21) All tests were performed at 95% confidence intervals. A p-value of <0.05 was considered statistically significant.

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RESULTS

Baseline characteristics of the whole study cohort are shown in Table 1. In total 192 patients fulfilled the inclusion criteria. Of them 80 patients (42%) were classified as HFpEF. Median age was 64 [52; 74] years, 81 subjects were women (42%). As provided, the majority of the patients were significantly symptomatic with 75% of the cohort in New York Heart association (NYHA) functional class III.

Table 2 shows the baseline echocardiographic and hemodynamic data. Median EF was 46 (25; 60) %, CI 2.2 (1.8; 2.6) L/min/m^2, PVR (0.10; 0.22) 0.15 mmHg•seconds•mL^{-1}, and PAC 2.4 (1.7; 3.5) mL•mmHg^{-1}.

The impact of the $PAWP_M$ and the V-wave amplitude on the PAC-PVR relationship

In accordance with previous findings, the PAC and PVR were hyperbolically and inversely associated (curve fit: y=0.587/ (0.073 + x), R^2=0.56); (Supplemental Figure 2). As provided in Figure 2a, when the cohort was dichotomized based upon the $PAWP_M$, the subgroup of patients with $PAWP_M$ above the median (>18 mmHg) showed a statistically significant shift of the curve fit (p<0.001) as compared to the corresponding group with lower $PAWP_M$, such that PAC values were lower for similar PVR levels in patients with higher $PAWP_M$.

Similarly, the subgroup with V-wave above the median value for the whole cohort (V-wave > 24 mmHg) demonstrated a similarly significant shift of the curve fit downwards and to the left compared to the corresponding group with lower V-waves (y=0.56/(0.09 + x), R^2=0.53 vs. y=0.55/(0.05 + x), R^2=0.67), p< 0.0001 (Figure 2b).

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The impact of LAP pulsatility on the PAC- PVR relationship

A further detailed analysis was performed in order to elucidate whether the steady and the pulsatile PAWP components yield different effects on the PVR-PAC relationship. As illustrated in Figure 3a, the PAC-PVR curve fit of patients with $PAWP_S$ above the median of the whole group (>16.6 mmHg) was not significantly different (p= 0.43) compared to those with lower PAWPs values (y=0.639/(0.079 + x), R^2=0.59).

On the other hand, as illustrated in Figure 3b, there was a significant downward and leftward shift of the PVR-PAC curve fit in patients with higher $PAWP_P$ (> 3.5 mmHg) as compared to the corresponding group with lower levels of pulsatility [y=0.584/(0.102 + x); R^2=0.53 vs. y=0.683/(0.078 + x); R^2=0.54; p<0.0001]. Finally, employing linear regression analysis, of the two PAWP components, the $PAWP_P$ was the only predictor of the RC time (RC = 0.48 – 0.016 x [$PAWP_P$]; R=0.43; p< 0.0001)

We proceeded by dichotomizing the study cohort based upon the median value of the $PAWP_P/PAWP_S$ ratio. As provided in the Table 3, there was as barely significant difference in the $PAWP_M$ between the 2 groups. However, the RC-time was significantly lower in the subgroup with high $PAWP_P/PAWP_S$ ratio accompanied by significantly higher PA_{PP} (p<0.001).

To assess the differential impact of pulsatile vs. steady PAWP components on the PAC-PVR relationship we decided to separately investigate the impact of those two variables on the components of PAC and PVR. In case of PAC, SV and PA_{PP} are the two defining variables, while for PVR these are PAP_M, PAWP, SV and HR.

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While both PAWP components related similarly to the systolic PAP, [PAP_S= 16.4+ 1.3 x $PAWP_S$ +1.5 x $PAWP_P$; R= 0.62, p<0.001], in case of the diastolic PAP, only $PAWP_S$ was a significant predictor [PAP_D=2.4 +1.0 x $PAWP_S$; R= 0.77; p<0.001].

In effect, in a linear regression analysis including $PAWP_P$, $PAWP_S$ and SV, provided that the pulsatile PAWP component alone was significantly related to the PA_{PP} [PA_{PP} = 17+1.7 x $PAWP_P$; R=0.52; p<0.001].

Finally, both PAWP components were significantly albeit opposingly related to the SV, with $PAWP_P$ displaying a positive, $PAWP_S$ an inverse relationship [SV = 74+2.5 x $PAWP_P$ - 1.1 x $PAWP_S$; R=0.37; p<0.001].

In order to elucidate the physiologic factors that might differentially affect the PAWP curve morphology and amplitude we analysed the association of mitral regurgitation (MR) and LA-stiffness with the corresponding PAWP components. In our cohort 13 patients demonstrated severe MR. Using a chi-square test, we found a significant association between the degree of MR and the steady (p= 0.038) but not the pulsatile (p=0.169) PAWP component. Regarding LA stiffness, as assessed by the E/e' to LA-strain ratio, no significant association was found with either the steady (p=0.064) or the pulsatile (p=0.086) PAWP component**.**

Reproducibility. The intra- and interobserver intraclass correlation coefficients, respectively, were as follows: 0.95 and 0.96 for $PAWP_S$; 0.89 and 0.88 for $PAWP_P$; 0.93 and 0. 90 for PAC, finally 0.98 and 0.97 for PVR.

DISCUSSION

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In this prospective study of a hemodynamically rigorously characterized HF cohort we demonstrate that the previously shown PAWP influence on the hyperbolic PAC-PVR association is ascribed the pulsatile rather than the steady component of the PAWP.

The pulmonary circulation exhibits a rather tight coupling between its resistive and pulsatile properties which, as documented in previous studies and confirmed by the current results, is characterized by a hyperbolic and inverse relationship (4-6, 8, 22-24). Tedford et al. demonstrated that this constrained association between PVR and PAC is altered in the state of post-capillary PH; patients with elevated PAWP [>20 mmHg] exhibited a shift of the RC curve fit downwards and leftwards, as compared to those with low $PAWP_M$ [<10 mmHg].(8) In addition, Dupont and colleagues showed that lowering the PAWP in HF patients impacted on the RC-time, as described by the product of PVR and PAC, by displacing the curve right-and upwards.(9) Our results add on the aforementioned observations as we demonstrate in a hemodynamically thoroughly characterized and highly symptomatic HF cohort that at higher PAWP a steeper PAC reduction occurs for the same PVR values.(25)

The effects of LAP rise on the pulmonary circulation, might yet not be properly appreciated without considering both the steady and pulsatile LAP components. In particular, during systole the second phase of LA filling occurs, yielding the most prominent positive deflection of the PAWP waveform designated as the V-wave. The volume of blood together with the rate of filling and the LA compliance determine the V-wave's amplitude.(26, 27) Importantly, accentuated PAWP systolic pulsatility may arise not only in the presence of severe acute mitral regurgitation (28) but also in case of reduced left ventricular compliance resulting in an upward shift of the LA volume-pressure curve. In fact, in our cohort we found a significant association between the steady (but not the pulsatile) PAWP and the degree of MR (p= 0.038)

which might be ascribed to the fact that the relatively few MR cases where characterised by chronic functional valvular insufficiency in which condition hemodynamic LA adaptation had been established.

We demonstrate that it is the pulsatile rather than the steady element of the PAWP curve that stands for the previously described PAWP-driven alteration in the RC relationship. There is evidence of retrograde propagation and occasionally superimposition of prominent V-waves on the PAP contour.(12) Our results indicate that the mechanism by which the phasic LAP oscillations impact on the PAC - PVR product might be related to a dissimilar impact of the two PAWP elements on pulmonary pressures. Indeed, the systolic pulmonary pressures did not differ between the groups of high and low $PAWP_P/PAWP_S$ ratio, and the two PAWP components were similarly associated with the PAP_S. In contrast, the PAP_D was related only with the $PAWP_S$, whereas the $PAWP_P$ lacked any significant impact on end-diastolic PAP. Accordingly, the correlation of $PAWP_P$ with the PA pulse pressure appears to emanate from the disparate effect of the two PAWP components on the pulmonary pressures, thus altering the mathematically coupled variables of PAC and PVR. Alternative explanations such as decreased elasticity of the lung parenchyma has previously been disproved.(8)

It should be emphasized that the current findings apply specifically to the PAC-PVR relationship and their product (i.e. RC), and not necessarily reflect the potential influence of the two different PAWP elements on the exact RC-time as defined by the diastolic pressure decay. Keeping this in mind, the clinical impact of the current observation is not less important when considering that under the assumption of a constant RC time, and for the same PVR, the extracted PAC values differ more than 2-fold. We may thus advocate that the curve shift observed in patients with

accentuated LAP pulsatility and elevated $PAWP_P/PAWP_S$ ratio might contribute to a better assessment of the state of pulmonary circulation, provided a stronger prognostic data and thus reinforce the decision making when tailoring the medical therapy and the follow up of patients. Nevertheless, further studies are warranted in order to strengthen the information provided in the current report.

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LIMITATIONS

Our study has limitations. Firstly, the size of our cohort is modest; however, it represents a hemodynamically thoroughly characterized HF population. The analysis of the PAWP curves was performed meticulously, but the measurements of compliance were based on the well-established albeit empirical formula (SV/PA_{PP}). This constitutes an important limitation as it has been shown that using this formula the total PAC is overestimated by up to 80%(5, 29, 30); Nevertheless, as the purpose of our study was to further investigate the observation that increased PAWP affects the PAC-PVR relationship,(8) by studying the differential impact of the steady and pulsatile PAWP components, we chose the same methodology of PAC assessment as the one used in the original publication by Tedford and colleagues.(8) Future studies using the semi-logarithmic approach for analysis of the RC-curve fit are warranted in order to validate the current results, as well as the observations concerning the impact of LAP on the RC-time. Finally, our study did not include a control group of healthy individuals, which confines our results to HF patients. However, considering the invasive nature of the presented measurements, the recruitment of a control cohort would raise major ethical issues.

CONCLUSION

Higher pulsatile rather than steady PAWP component alters significantly the PVR-PAC relationship in HF patients.

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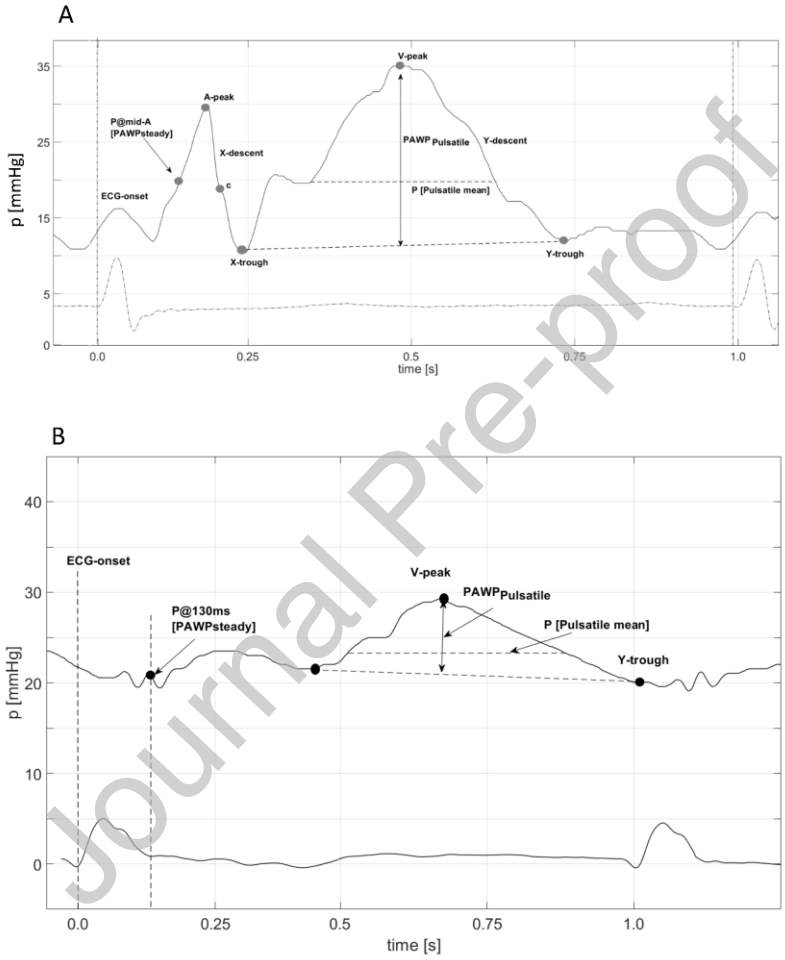
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FIGURE LEGENDS

Figure 1. PAWP waveform and the different points signifying the pulsatile and steady components (a) in sinus rhythm, (b) in atrial fibrillation.



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Figure 2. Effects of elevated mean pulmonary artery wedge pressure ($PAWP_M$) (2a) and peak V-wave pressure (2b) on the PAC-PVR relationship.

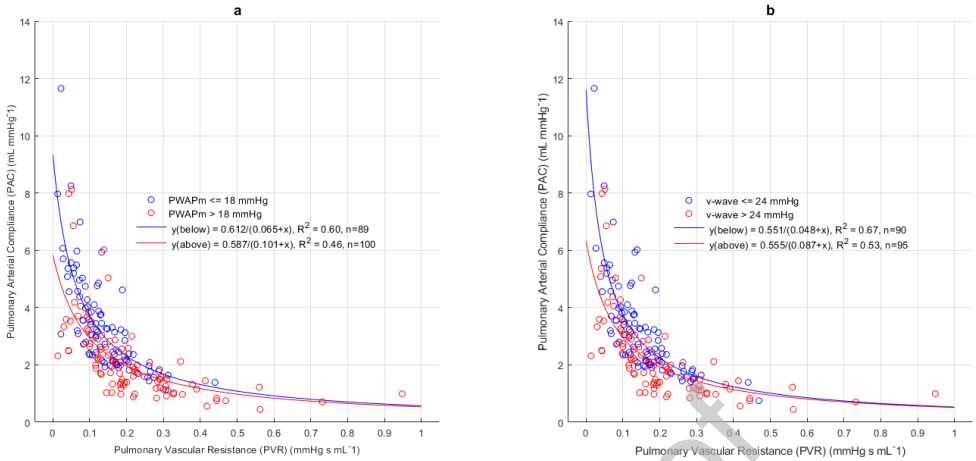
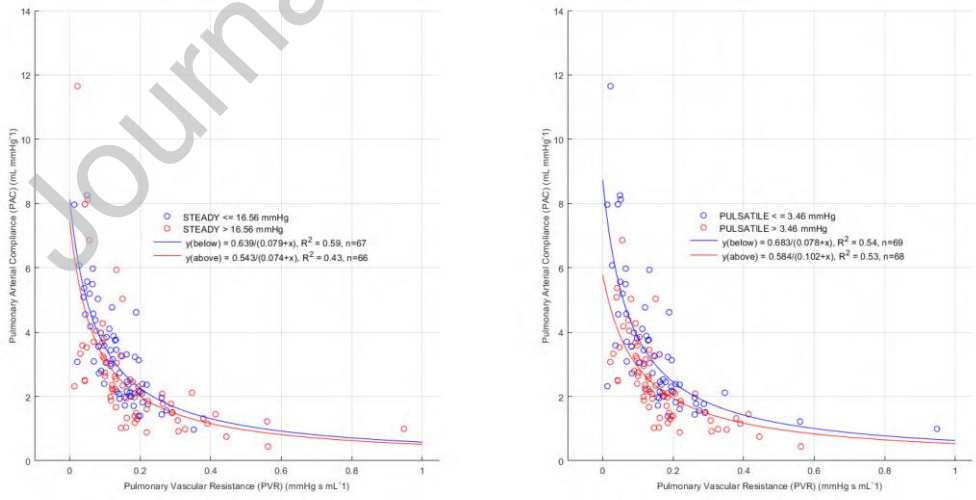


Figure 3. Effects of elevated pulmonary artery wedge pressure PAWP steady (3a) and pulsatile (3b) components on the PAC-PVR relationship.



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TABLE LEGENDS

Table 1. Baseline clinical characteristics of the entire cohort; continuous variables are given as median followed by lower and upper quartiles [Q1; Q3] in brackets.
HFpEF, heart failure with preserved ejection fraction; NYHA, New York Heart Association functional class; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; ARB, angiotensin receptor blocker; ACE-I, angiotensin converter enzyme inhibitor; MRA; mineralocorticoid receptor antagonist; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate.

Table 2. Baseline echocardiographic data and hemodynamics of the entire cohort; median and lower and upper quartiles (Q1; Q3).
LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; LVMi, Left ventricular mass index; LAVi, Left atrial volume index; E, transmitral early diastolic filling velocity; A, transmitral late diastolic filling velocity; E', average value of lateral and septal early diastolic myocardial velocity; E/A, ratio between the early transmitral diastolic filling velocity to late diastolic filling velocity; E/E', ratio of the transmitral early diastolic filling velocity to the early diastolic myocardial velocity; RA , right atrium; RVSP, right ventricular systolic pressure; TAPSE, Tricuspid annular plane systolic excursion; CI, cardiac index; DPG, diastolic pulmonary pressure gradient; TPG, transpulmonary pressure gradient; PVR, pulmonary vascular resistance; PAC, pulmonary arterial compliance ; PAWP, Pulmonary artery capillary wedge pressure; PAP, pulmonary artery pressure; RAP, right atrial pressure.

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Demographics (n=192)	
Age, (years)	64 (52;74)
Gender, (male/female)	111/81 (58/42)

Table 3. Baseline characteristics stratified according to pulsatile and steady PAWP pressures below and above median and according to low and high $PAWP_P/PAWP_S$ ratio; median and lower and upper quartiles (Q1; Q3) and n (%).CI, cardiac index; SVi, stroke volume index; PAWP; Pulmonary artery capillary wedge pressure; PVR, pulmonary vascular resistance; PAC, pulmonary arterial compliance; PAP, pulmonary artery pressure; DPG, diastolic pulmonary gradient; TPG, total pulmonary gradient; PAPP, pulmonary artery pulse pressure; LAVi, Left atrial volume index.

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Medical history	
Ischemic heart disease	50 (26)
Diabetes mellitus	39 (20)
Hypertension	109 (57)
Atrial fibrillation/flutter	104 (54)
Smoking	7 (4)
NYHA I	7 (3.5)
NYHA II	32 (17)
NYHA III	144 (75)
NYHA IV	9 (4.5)
Diagnosis	
HFpEF	80 (42)
Ischemic cardiomyopathy	33 (17.2)
Dilated cardiomyopathy	51 (26.6)
Hypertrophic cardiomyopathy	5 (2.6)
Restrictive cardiomyopathy	16 (8.3)
Other causes	7 (3.6)
Clinical measurements	
BMI, (kg/m^2)	27 (23;30)
SBP, (mmHg)	110 (95;134)
DBP, (mmHg)	63 (57;72)
HR, (beats/min)	69 (59;79)
Treatment	
ARB/ACE-I	149 (78)
Beta blocker	163 (85)
MRA	116 (60)
Loop diuretic	162 (84)
Calcium channel blockers	29 (15)
CRT-P/CRT-D	34 (18)
Laboratory	
NTproBNP, (ng/L)	2120 (868;3580)
eGFR, ($mL/min/1.73m^2$)	58 (41;79)
Hemoglobin, (g/L)	132 (117;146)

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Table 1. Baseline clinical characteristics of the entire cohort; median and lower and upper quartiles (Q1; Q3) and n (%).

HFpEF, heart failure with preserved ejection fraction; NYHA, New York Heart Association; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; ARB, angiotensin receptor blocker; ACE-I, angiotensin converter enzyme inhibitor; MRA;

mineralocorticoid receptor antagonist; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate.

Echocardiographic measurements	
LVEF, (%)	46(25;60)
LVEDD, (mm)	53(45;65)
LVMi, (g/m²)	108 (80;150)
LAVi, (mL/m²)	53 (40;67)
E, (cm/sec)	94 (73;117)
A, (cm/sec)	49 (27;76)
E',(cm/sec)	7 (5.5;8.5)
E/A	1.7 (1.3;2.2)
E/e' (average)	13 (10;18)
RA area, (cm²)	22 (17;27)
RVSP, (mmHg)	45 (37;58)
TAPSE, (mm)	15 (11;19)
Hemodynamic measurements	
CI , (L/min/m²)	2.2 (1.8;2.6)
DPG, (mmHg)	0 (-2;3)
TPG, (mmHg)	10 (7;15)
PVR, (mmHg•seconds/mL)	0.15 (0.096;0.216)
PAC, (mL/mmHg)	2.4 (1.7;3.5)
PAWP-mean, (mmHg)	18 (14;24)
PAWP-A, (mmHg)	19 (15;25)
PAWP-V, (mmHg)	24 (17;32)
PAP-mean, (mmHg)	30 (22;37)
PAP-systolic, (mmHg)	44 (35;57)
PAP-diastolic, (mmHg)	18 (13;24)
RAP-mean, (mmHg)	8.5 (5;14)

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Table 2. Baseline echocardiographic data and hemodynamics of the entire cohort; median and lower and upper quartiles (Q1; Q3). LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; LVMi, Left ventricular mass index; LAVi, Left atrial volume index; E, transmitral early diastolic filling velocity; A, transmitral late diastolic filling velocity; E', average value of lateral and septal early diastolic myocardial velocity; E/A, ratio between the early transmitral diastolic filling velocity to late diastolic filling velocity; E/E', ratio of the transmitral early diastolic filling velocity to the early diastolic myocardial velocity; RA , right atrium; RVSP, right ventricular systolic pressure; TAPSE, Tricuspid annular plane systolic excursion; CI, cardiac index; DPG, diastolic pulmonary pressure gradient; TPG, transpulmonary pressure gradient; PVR, pulmonary vascular resistance; PAC, pulmonary arterial compliance ; PAWP, Pulmonary artery capillary wedge pressure; PAP, pulmonary artery pressure; RAP, right atrial pressure.

	Low Steady PAWP n = 68	High Steady PAWP n = 66	P	Low pulsatile PAWP n = 66	High pulsatile PAWP n = 68	P	Low PAWPp/PAWPs ratio n = 65	High PAWPp/PAWPs ratio n = 69	P
CI (L/min/m²)	2.32 (1.89; 2.63)	2.18 (1.72; 2.62)	0.54	2.20 (1.80; 2.48)	2.33 (1.88; 2.66)	0.239	2.25 (1.8; 2.5)	2.31 (1.9; 2.7)	0.112
SVi, (mL/min/ m²)	36 (29; 45)	31 (24; 37)	**0.01**	33 (27; 41)	34 (27; 41)	0.749	31 (26; 40)	35 (29; 44)	0.072
PAWP-mean, (mmHg)	14 (12; 16)	24 (19; 27)	**< 0.001**	15 (12; 19)	21 (17; 26)	**< 0.001**	16.5 (13; 23)	19.4 (15; 25)	**0.046**
PVR, (mmHg•seconds/ mL)	0.12 (0.09; 0.19)	0.14 (0.09; 0.29)	0.24	0.14 (0.1; 0.21)	0.14 (0.08; 0.23)	0.84	0.14 (0.10; 0.21)	0.14 (0.08; 0.20)	0.245
PAC (mL/mmHg)	3.3 (2.1; 4.6)	2.1 (1.5; 3.3)	**0.001**	3.3 (2.1; 4.5)	2.3 (1.6; 3.3)	**0.003**	2.9 (2.0; 4.1)	2.4 (1.7; 3.7)	0.1
PAP-systolic, (mmHg)	36 (30; 43)	50 (43; 62)	**< 0.001**	36 (31; 47)	49 (38; 63)	**< 0.001**	39 (33; 52)	45 (36; 61)	0.07
PAP-diastolic, (mmHg)	13 (11; 16)	23 (18; 28)	**< 0.001**	16 (12; 21)	20 (15; 25)	**0.008**	19 (15; 24)	18 (14; 24)	0.529
PAP-mean, (mmHg)	23 (19; 26)	35 (30; 39)	**< 0.001**	24 (20; 30)	32 (26; 38)	**< 0.001**	30 (25; 36)	31 (28; 36)	0.346
DPG (mmHg)	-1 (-2; +2)	-1 (-3; +2)	0.542	0 (-2; +3)	-1 (-4; +1)	**0.004**	1 (-1.5; +3)	-1 (-3; 0.5)	**< 0.001**

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TPG, (mmHg)	9 (6; 13)	10 (7; 15)	0.065	10 (5; 12)	10 (7; 15)	0.106	10 (6; 13)	9 (7; 15)	0.633
PAPP (mmHg)	23 (17; 26)	26 (20; 38)	**0.003**	21 (17; 27)	27 (22; 41)	**< 0.001**	21 (17; 26)	25 (21; 38)	**0.001**
LAVi, (mL/m²)	44 (37; 63)	54 (43; 68)	0.082	46 (37; 66)	54 (40; 64)	0.317	46 (38; 67)	53 (39; 65)	0.581
RC time (seconds)	0.40 (0.33; 0.48)	0.32 (0.23; 0.41)	**0.001**	0.43 (0.33; 0.52)	0.31 (0.23; 0.40)	**<0.001**	0.42 (0.33; 0.53)	0.33 (0.23; 0.40)	**<0.001**

Table 3. Baseline characteristics stratified according to pulsatile and steady PAWP pressures below and above median; median and lower and upper quartiles (Q1; Q3) and n (%). CI, cardiac index; SVi, stroke volume index; PAWP; Pulmonary artery capillary wedge pressure; PVR, pulmonary vascular resistance; PAC, pulmonary arterial compliance; PAP, pulmonary artery pressure; DPG, diastolic pulmonary gradient; TPG, total pulmonary gradient; PAPP, pulmonary artery pulse pressure;LAVi, Left atrial volume index.

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