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ORIGINAL RESEARCH ARTICLE

Critical appraisal of the instantaneous end-diastolic pulmonary arterial wedge pressures

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Abstract

Aims A substantial shift in the field of pulmonary hypertension (PH) is ongoing, as the previous practice of mean pulmonary arterial wedge pressure ($PAWP_M$) is no longer supported. Instead, aiming for a better estimate of end-diastolic pressures (EDP), instantaneous PAWP at mid-A-wave ($PAWP_{mid\text{-}A}$) or, in the absence of an A-wave, at 130–160 ms following QRS onset has recently been recommended. Electrocardiogram-gated PAWP ($PAWP_{QRS}$) has also been proposed. The quantitative differences as well as the diagnostic and prognostic utility of these novel PAWP measurements have not been evaluated. We set out to address these issues.

Methods and results Pressure tracings of 141 patients with PH due to left heart disease (PH-LHD) and 43 with primary pulmonary arterial hypertension (PAH) were analysed. PAWP was measured as follows: (i) mean pressure ($PAWP_M$); (ii) per the latest consensus approach [$PAWP_{mid\text{-}A}$, or in atrial fibrillation 130, 140, 150, and 160 ms following QRS onset ($PAWP_{130–160}$)]; (iii) at QRS onset ($PAWP_{QRS}$); and (iv) Z-point ($PAWP_Z$). For each PAWP, the corresponding pulmonary vascular resistance (PVR) and diastolic pressure gradient were calculated. The cohort comprised 45% female. Mean age was 66 ± 15. $PAWP_{mid\text{-}A}$ was in good agreement with $PAWP_Z$ (17.3 [14.5 to 21.2] vs. 17.6 [14.2 to 21.6] mmHg, $P = 0.63$), whereas $PAWP_{QRS}$ provided significantly lower values (15.3 [12.5 to 19.2] mmHg, $P < 0.001$). In atrial fibrillation, $PAWP_{130}$ and $PAWP_{QRS}$ yielded the optimal temporal and quantitative analyses of EDPs. The ability to differentiate PAH from PH-LHD was similar for the various PAWP measurements [$PAWP_M$: area under the curve (AUC) 0.98, confidence interval (CI) 0.96–0.99; $PAWP_{mid\text{-}A/130}$: AUC 0.94, CI 0.91–0.98; $PAWP_{QRS}$: AUC 0.96, CI 0.94–0.99, $P < 0.001$ for all]. PVR based on instantaneous PAWP measurements failed to provide superior prognostic information in PH-LHD as compared with conventional PVR.

Conclusions Although instantaneous PAWP measurement might better represent EDP, they nevertheless fail to yield incremental diagnostic or prognostic information in PH-LHD as compared with conventional measurements.

Keywords Pulmonary arterial wedge pressure; End-diastolic pressure; Pulmonary vascular resistance; Pulmonary hypertension; Heart failure

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Introduction

The pulmonary arterial wedge pressure (PAWP) entails a fundamental role in haemodynamic evaluation in heart failure (HF) as well as for the distinction between pulmonary hypertension (PH) due left heart disease (PH-LHD) and primary pulmonary arterial hypertension (PAH). However, despite its abundant utility in everyday practice, the lack of uniformity in the PAWP assessment remains considerable.[1,2] The mean PAWP ($PAWP_M$) averaged over the entire cardiac cycle is used as a surrogate of left sided end-diastolic pressure (EDP) in many instances with reasonable accuracy. However, particularly in the context of PH-LHD and atrial fibrillation (AF),[3,4] incorporation of large V-waves in the PAWP measurement ($PAWP_M$) might overestimate the EDP, while measuring instantaneous end-diastolic wedge pressure might yield more concordant results.[5,6] Recent guidelines proposed a classification system for PH-LHD on the basis of the diastolic pressure

gradient (DPG).[1] However, in case of DPG, the $PAWP_M$, being compared with the instantaneous end-diastolic pulmonary artery pressure (PAP) (PAP_D), would invariably yield misleading results. Moreover, augmented left atrial pressure (LAP) pulsatility, which impacts on $PAWP_M$,[7–9] further mitigates the potential information that DPG might otherwise provide. Recently, Wright and colleagues proposed the use of instantaneous electrocardiogram (ECG)-gated PAWP for DPG calculation.[10] Similarly, the latest consensus statement on PH-LHD advocates for instantaneous instead of mean PAWP measured, in case of sinus rhythm (SR), at the mid-A-wave, while in AF, at 130–160 ms after the QRS onset.[6] Additionally, with regards the controversies about the prognostic DPG value in PH-LHD,[7,11–17] pulmonary vascular resistance (PVR)—derived from instantaneous PAWP—has been introduced as the discerning marker of pre-capillary involvement.

The qualitative and quantitative discrepancies among the proposed PAWP measurements have not been investigated, leaving ambiguity regarding the optimal method. Also, in the recommended novel approach albeit relying on physiological rational, its diagnostic and prognostic utility have not yet been validated. We set out to address these issues.

Methods

Study population

Patients referred for right heart catheterization (RHC) at Karolinska University Hospital between February 2014 and August 2018, due to unexplained dyspnoea or suspected PH or for haemodynamic assessment before heart transplantation or left ventricular (LV) assist device listing, were enrolled prospectively. Patients with constrictive pericarditis, arrhythmogenic right ventricular cardiomyopathy, previous heart transplantation, significant valvular disease, or normal haemodynamics were excluded. Consequently, 249 patients ($PAP_M \geq 20$ mmHg) were included in the final analysis. A total of 43 patients were classified as PAH ($PAWP_M \leq 15$ mmHg and consensus clinical board opinion) and 141 as PH-LHD, defined as elevated mean wedge at rest ($PAWP_{REST} > 15$ mmHg) or during exercise ($PAWP_{EX} \geq 25$ mmHg).[18] (*Figure S1*).

All patients underwent transthoracic echocardiography 1 h prior to RHC as per current recommendations.[19] The study complies with the Declaration of Helsinki and was approved by the regional ethical review board. Informed consent was provided.

Right heart catheterization

During RHC, all patients were in stable haemodynamic condition. RHC was performed through the jugular vein access using a 6F balloon-tipped fluid-filled Swan–Ganz catheter (Edwards Lifesciences, Irvine, CA, USA). Pressure measurements (in the right atrium, pulmonary artery, PAWP, and right ventricle) were performed under fluoroscopy after calibration with the zero-level set at the mid-thoracic line, at end-expirium during spontaneous breathing, and stored in dedicated software (Xper Information Management, Philips Medical Systems, The Netherlands). Cardiac output (CO) was assessed using the Fick principle. The oxygen consumption was measured breath by breath (Jaeger Oxycon Pro, VIASYS™ Healthcare, Palm Springs, CA, 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

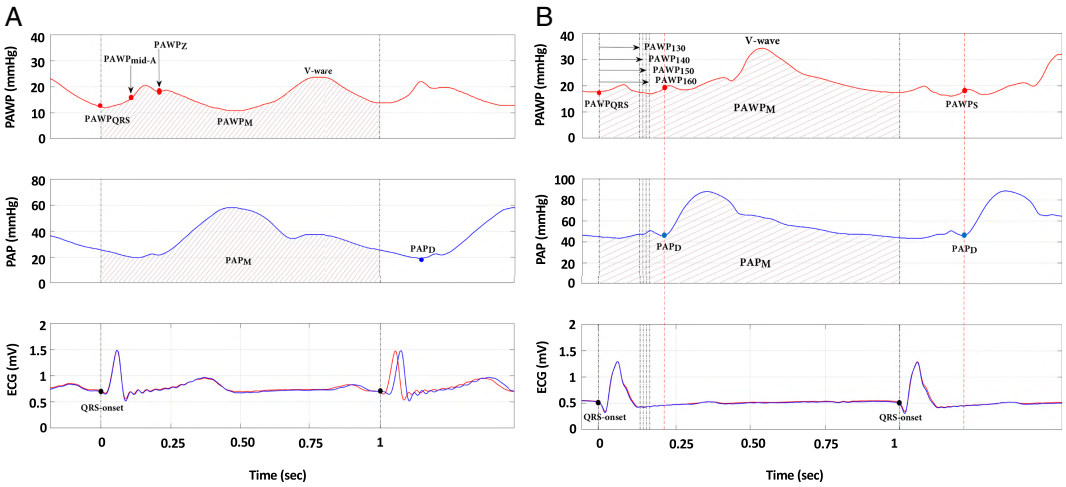
Following the assessment of resting haemodynamics, patients with $PAWP_M \leq 15$ mmHg at rest but with clinical suspicion of HF with preserved ejection fraction (HFpEF) underwent supine cycle ergometry as did patients with HF with reduced ejection fraction (HFrEF) as part of the haemodynamic evaluation. Patients cycled at 60 rpm in supine position for 2 min at 20 W before the workload was incrementally increased in ~1 min interval until maximal volitional exertion. $PAWP_M \geq 25$ mmHg during peak exercise denoted abnormal $PAWP_M$ response.[18]

Analysis of pulmonary arterial wedge pressure, pulmonary vascular resistance, and diastolic pressure gradient measurements

PAWP and PAP waveforms (n = 249) were analysed offline (MATLAB software; R2018b, MathWorks, MA, USA). First, the ECGs of the two measurements were synchronized manually so that despite non-beat-to-beat synchronous measurements, an optimal temporal harmonization was achieved. From the PAP recordings, the peak of the ascending limb of the PAP curve (PAP_S) and the EDP (PAP_D) were marked manually, and then the software automatically calculated PAP_S and PAP_D. Subsequently, mean PAP (PAP_M) was calculated by integration of PAP over the cardiac cycle. PAWP was measured in the following ways (*Figure 1*):

1 $PAWP_M$: Mean PAWP obtained by temporal integration of the instantaneous PAWP over the entire cardiac cycle.
2 Consensus statement's approach[6]: In SR, mid-A-wave pressure, that is, the mean value of the A-wave amplitude, was measured from the point just prior the ascending limb to the peak of the A-wave ($PAWP_{mid\text{-}A}$). In AF, pressures at 130, 140, 150, and 160 ms following the QRS onset were measured (four measurements: $PAWP_{130}$, $PAWP_{140}$, $PAWP_{150}$, and $PAWP_{160}$, respectively).

Figure 1 Pulmonary artery wedge pressure measurements. The top panel shows the pulmonary artery wedge pressure (PAWP), the middle panel the pulmonary artery pressure (PAP) waveform, and the bottom panel the corresponding ECG traces for both measurements (ECG of the PAWP curve in red and ECG of the PAP curve in blue). In sinus rhythm (A), the instantaneous pressure values on the PAWP waveform were measured as follows: at mid-A-wave ($PAWP_{mid\text{-}A}$) and at the Z-point ($PAWP_Z$). In atrial fibrillation (B), the instantaneous pressure values on the PAWP waveform were measured at the time points 130, 140,150, and 160 ms after the QRS onset ($PAWP_{130}$, $PAWP_{140}$, $PAWP_{150}$, and $PAWP_{160}$, respectively). The following PAWP measurements were performed in both SR and AF: at QRS onset ($PAWP_{QRS}$) and at the time point simultaneous with PAP_D ($PAWP_S$). On the PAP waveform, the following instantaneous pressure values were measured: peak of the ascending limb of the PAP curve (PAP_S) and the point at the end of diastole (PAP_D). In addition, the software provided automated calculation of mean PAP (PAP_M) and PAWP ($PAWP_M$) by integrating the PAP and PAWP, respectively, over the entire cardiac cycle (lined area under the pressure curve).



3 $PAWP_{QRS}$: Instantaneous PAWP was measured at the QRS onset.[10]
4 $PAWP_Z$: Instantaneous PAWP at the Z-point (pre-C-wave) was measured in cases with evident C-wave.
5 $PAWP_S$: Instantaneous PAWP obtained simultaneously with PAP_D.

The corresponding PVR and DPG values were calculated using the following equations and applying the suitable PAWP value:

$$PVR = PAP_M - PAWP/CO;$$

$$DPG = PAP_D - PAWP.$$

All pressures were averaged from a minimum of three heart cycles at end-expiration.[1,6] To ensure the uniformity of data acquisition and analysis, the same investigator (A. M.) participated in the vast majority of RHC procedures and performed the analysis of all waveforms, blinded to patient data.

Details regarding the methodology used for MATLAB analysis are provided in *Data* S1.

Statistical analysis

Normality was tested by the Shapiro–Wilk test. Statistical analysis was performed using SPSS Version 26.0 (SPSS Inc., Chicago, IL, USA) Continuous variables were compared using the Mann–Whitney *U* test (skewed variables). All tests were performed at 95% confidence intervals. All measurements are stated as median and inter-quartile range or mean and standard deviation (SD) based on the Kolmogorov–Smirnov test. Correlations were tested by the Pearson two-tailed test. Intra-observer and inter-observer reproducibility of the instantaneous PAWP measurements was tested using the intraclass correlation coefficient in 10 randomly selected patients.[20] Survival was analysed with Kaplan–Meier non-parametric test and compared using a log-rank test. For survival analysis, patients who underwent cardiac transplantation or ventricular assist device implantation were censored at the time of the latter. Receiver operating characteristic (ROC) analysis was employed for diagnostic ability assessment of the various PAWP measurements. ROC curves were compared using the DeLong test. A *P*-value of <0.05 was considered statistically significant.

Results

Patient characteristics

Baseline clinical and haemodynamic characteristics of the study cohort are presented in *Table 1*. In total, 141 patients were classified as PH-LHD. Of them, 80 patients (57%) had

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Table 1 Demographic, echocardiographic, and haemodynamic data of the study population

	PAH (n = 43)	PH-LHD (n = 141)
Demographics		
Age (years)	56 [43–69]	66 [55–74]
HFpEF (n, %)	—	80 (57%)
Sinus rhythm	43 (100%)	113 (80%)
Female (n, %)	23 (54%)	62 (44%)
Diabetes mellitus (n, %)	2 (5%)	24 (17%)
Hypertension (n, %)	5 (12%)	80 (57%)
Hypercholesterolaemia (n, %)	3 (7%)	42 (30%)
BMI (kg/m^2)	24 [22–28]	27 [23–30]
Echocardiographic data		
EF (%)	61 [59–65]	54 [28–65]
E/e′	8 [7–10]	13.1 [10–19]
LAVi (mL/m^2)	27 [21–35]	48 [38–66]
TAPSE (mm)	19 [15–20]	16 [12–21]
Haemodynamic data		
SBP (mmHg)	119 [104–130]	119 [96–138]
DBP (mmHg)	70 [50–76]	65 [56–74]
CI (L/m^2)	2.4 [2.1–3.2]	2.3 [1.8–2.7]
HR (min^{-1})	71 [65–90]	67 [60–78]
PAP_M (mmHg)	36.6 [29.6–45.7]	30.8 [24.9–37.3]
PAP_D (mmHg)	23.8 [16.8–30.7]	20.1 [16–24.2]
$PAWP_M$ (mmHg)	10.8 [7.1–11.3]	18.7 [15.4–24.2]
PVR_M (WU)	5.5 [3.8–9.2]	2.6 [1.7–4.0]
DPG_M (mmHg)	−13.8 [8.9–20]	0.8 [−1.8 to 4.1]

BMI, body mass index; CI, cardiac index; DBP, diastolic blood pressure; DPG_M, diastolic pressure gradient calculated from the $PAWP_M$; EF, left ventricular ejection fraction; HFpEF, heart failure with preserved ejection fraction; HR, heart rate; LAVi, left atrial volume index; PAH, pulmonary arterial hypertension; PAP_D, pulmonary arterial diastolic pressure; PAP_M, pulmonary arterial mean pressure; $PAWP_M$, mean value of the pulmonary arterial wedge pressure; PH-LHD, pulmonary hypertension due to left heart disease; PVR_M, pulmonary vascular resistance calculated from the $PAWP_M$; SBP, systolic blood pressure; TAPSE, tricuspid annular systolic excursion.
Continuous variables are given as median values, followed by the 25th and 75th percentiles in square brackets.

HFpEF (EF 63%; 57–65), and 61 (43%) had HFrEF (EF 25%; 19 to 36). In the HFrEF cohort, 21 patients (34%) had resynchronization therapy. The majority of the patients were highly symptomatic (78% in New York Heart Association III–IV). A total of 113 patients were in SR. At rest, 107 patients had $PAWP_M > 15$ mmHg; by using PVR_M, 38% of them were classified as having combined post-capillary and pre-capillary PH (Cpc-PH). The same figures for $PAWP_{QRS}$ and $PAWP_{mid\text{-}A/130}$ were 79 and 93 patients with 49% and 48% prevalence of Cpc-PH, respectively.

Pulmonary arterial wedge pressure and pulmonary vascular resistance measurements

In PH-LHD patients, $PAWP_{QRS}$ was lower than $PAWP_M$ ($P < 0.001$) (*Table 2*).

Sinus rhythm

As illustrated in *Figure 2A*, $PAWP_{mid\text{-}A}$ was significantly lower than $PAWP_M$ ($P = 0.009$), whereas both measurements yielded higher values than $PAWP_{QRS}$ ($P < 0.001$) and $PAWP_S$ ($P < 0.001$). The latter two measurements provided essentially similar results ($P = 0.81$).

Along with a lower mean value, at an individual level, $PAWP_{mid\text{-}A}$ was lower than $PAWP_M$ in 62% of the cases. Compared with the subgroup with $PAWP_{mid\text{-}A} < PAWP_M$, the cohort with $PAWP_{mid\text{-}A} > PAWP_M$ demonstrated significantly lower V-wave amplitude (18.7 [15.1 to 27–4] vs. 30 [22.3 to 38.3] mmHg, $P < 0.001$). The difference between $PAWP_{mid\text{-}A}$ and $PAWP_M$ was strongly related to the V-wave amplitude ($r = 0.69$, $P < 0.001$). In contrast, the A-wave amplitude did not differ between the two groups (20.6 [17.2 to 25.1] vs. 19 [15.7 to 26.0] mmHg; $P > 0.23$).

Accordingly, $PVR_{mid\text{-}A}$ was higher than PVR_M ($P < 0.001$), while PVR_{QRS} yielded higher values than $PVR_{mid\text{-}A}$ and PVR_M ($P < 0.001$ in both).

Atrial fibrillation

At the time of RHC, 28 patients were in AF. As illustrated in *Figure 2B*, in AF patients, $PAWP_{QRS}$ yielded similar figures to $PAWP_{130}$ and $PAWP_S$ ($P = 0.124$ and $P = 0.35$, respectively) but significantly higher compared with $PAWP_{140}$, $PAWP_{150}$, and particularly $PAWP_{160}$ ($P = 0.04$, $P = 0.002$ and $P < 0.001$, respectively). These relationships did not alter when the groups were dichotomized based on median hazard ratio (HR).

In line with the aforementioned observations, there was no significant difference between PVR_{130} and PVR_{QRS} ($P = 0.442$), whereas $PVR_{140–160}$ significantly overestimated PVR_{QRS} ($P < 0.001$).

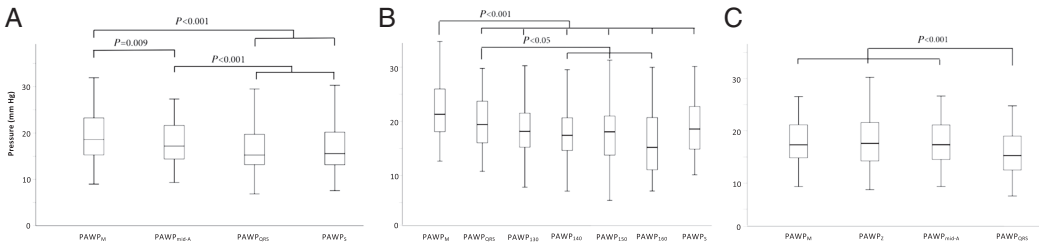
Accordingly, for comparative analyses based on the consensus proposal in AF, we used the 130 ms time point. When

Table 2 Instantaneous pulmonary arterial wedge pressure measurements and derived diastolic pressure gradient values in pulmonary hypertension due to left heart disease patients with sinus rhythm vs. atrial fibrillation

	Total (n = 141)	Sinus rhythm (n = 113)	Atrial fibrillation (n = 28)
HR (min^{-1})	67 (61–78)	66 (60–76)	73 (63–80)
$PAWP_M$ (mmHg)	18.7 (15.4–24.2)^{SQR}	18.5 (15.0–23.4)^{SQC}	21 (17.7–25.7)^{SQC}
$PAWP_S$ (mmHg)	16.7 (13.4–21.1)^{MQR}	15.6 (12.9–20.6)^{MQ}	18.3 (14.4–22.6)^{MQ}
$PAWP_{QRS}$ (mmHg)	15.8 (13.3–20.4)^{MSR}	15.2 (12.8–19.9)^{MC}	19.1 (15.5–23.6)^{MCS}
$PAWP_{mid\text{-}A}$ (mmHg)	—	17.2 (14.4–22.2)^{MSQ}	—
$PAWP_{130}$ (mmHg)	—	—	17.9 (14.6–21.8)^{M}
$PAWP_{140}$ (mmHg)	—	—	17.1 (14.3–20.7)^{M}
$PAWP_{150}$ (mmHg)	—	—	17.8 (13.4 – 20.8)^{MQ}
$PAWP_{160}$ (mmHg)	—	—	14.9 (10.8 – 20.6)^{MQ}
PVR_M (WU)	2.6 (1.7 – 4.0)^{QC}	2.5 (1.7 – 4.1)^{QC}	2.6(1.8 – 3.5)^{QC}
PVR_{QRS} (WU)	3.1 (2.2 – 4.6)^{MC}	3.0 (2.2 – 4.8)^{MC}	3.2 (2.7 – 4.3)^{M}
$PVR_{mid\text{-}A/130}$ (WU)	3.0 (1.9 – 4.4)^{MQ}	2.9 (1.7 – 4.4)^{MQ}	—
PVR_{130} (WU)	—		3.2 (2.7 – 4.5)^{M}
PVR_{140} (WU)	—	—	3.8 (2.7 – 4.9)[a]
PVR_{150} (WU)	—	—	3.5 (2.8 – 4.8)[a]
PVR_{160} (WU)	—	—	4.7 (2.7 – 6.2)[a]
PAP_D (mmHg)	20.2 (16.0 – 24.2)	19.7 (15.9 – 23.4)	23.0 (18.7 – 28.7)
PAP_M (mmHg)	31.2 (25.1 – 38.0)	30.8 (25.0 – 36.6)	33.3 (26.1 – 43.7)

Letters in superscript indicate statistically significant ($P < 0.05$) differences: S, simultaneous measurement; M, mean value; QRS, ECG-gated measurement; and C, according to the consensus paper's recommendation, i.e. mid-A-wave in sinus rhythm or 130 ms from QRS onset in atrial fibrillation.
HR, heart rate; PAP_D, pulmonary arterial diastolic pressure; PAP_M, pulmonary arterial mean pressure; PAWP, pulmonary artery wedge pressure; $PAWP_{130}$, instantaneous PAWP measured 130 ms after the QRS onset; $PAWP_{140}$, $PAWP_{150}$, $PAWP_{160}$, PAWP measured 140, 150 and 160 ms after the QRS onset, respectively; $PAWP_M$, mean PAWP; $PAWP_{mid\text{-}A}$, instantaneous PAWP measured at the mean of the A-wave; $PAWP_{QRS}$, instantaneous PAWP measured at the QRS onset; $PAWP_s$, instantaneous value of the PAWP pressure measured simultaneously with the time point of PAP_D; PVR, pulmonary vascular resistance; PVR_{130}, PVR calculated from the $PAWP_{130}$; PVR_{140}, PVR calculated from the $PAWP_{140}$; PVR_{150}, PVR calculated from the $PAWP_{150}$; PVR_{160}, PVR calculated from the $PAWP_{160}$; PVR_M, PVR calculated from the $PAWP_M$, PVR_{QRS}, PVR calculated from the $PAWP_{QRS}$; $PVR_{mid\text{-}A}$, PVR calculated from the $PAWP_{mid\text{-}A}$.
[a]Indicates that $PVR_{140–160}$ were significantly different from all the other reported PVR values, as well as from each other.

Figure 2 Comparison of the various PAWP measurements among patients (A) in sinus rhythm, (B) in atrial fibrillation, and (C) where C-wave was identifiable. $PAWP_{130}$, $PAWP_{140}$, $PAWP_{150}$, $PAWP_{160}$, and PAWP measured 130, 140, 150, and 160 ms after the QRS onset, respectively; $PAWP_M$, mean value of PAWP over the cardiac cycle; $PAWP_{mid\text{-}A}$, mid-A-wave pressure; $PAWP_{QRS}$, PAWP at QRS onset; $PAWP_S$, instantaneous PAWP measured at the time point simultaneous with PAP_D; $PAWP_Z$, PAWP at the Z-point.



patients with SR and AF were analysed together, these measurements are referred to as $PAWP_{mid\text{-}A/130}$.

Reproducibility measures of the instantaneous PAWP measurements have been published previously (intra-observer and inter-observer intraclass correlation coefficient: 0.98 and 0.97, respectively).[20]

Event timing

PAP_D occurred roughly 100 ms following the QRS onset, similarly in the SR and AF cohorts (99 ± 17 and 99 ± 30 ms, respectively) and was significantly associated with HR in both groups ($r = -0.75$, $P < 0.001$, and $r = 0.38$, $P = 0.043$).

The A-wave onset occurred 52 ± 7 ms, while the A-wave peak 150 ± 6 ms after the QRS onset. In all cases, the time point for PAP_D befell during the ascending limb of the A-wave in the corresponding PAWP curve.

Z-point-derived measurements

A distinct Z-point was identified in 48 cases (43%) in the SR cohort, occurring around 180 ms (179 ± 7 ms) after the QRS

Table 3 Diastolic pressure gradient values based on various instantaneous pulmonary arterial wedge pressure measurements in pulmonary hypertension due to left heart disease patients with sinus rhythm vs. atrial fibrillation

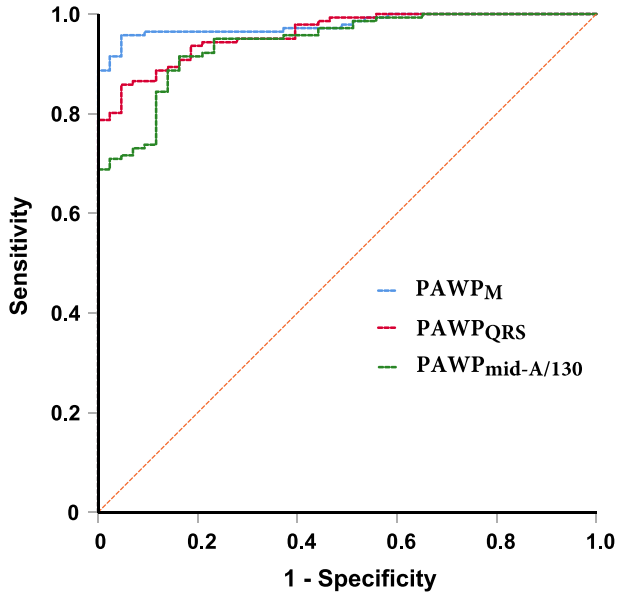
	Total (n = 141)	Sinus rhythm (n = 113)	Atrial fibrillation (n = 28)
DPG_M (mmHg)	0.8 (-1.8 – 4.1)	0.8 (-1.8 – 4.2)^{SQC}	0.9 (-1.7 – 4.1)^{MQ}
DPG_S (mmHg)	3.7 (1.1– 6.8)	3.7 (0.8 – 6.6)^{MC}	3.7 (1.9 – 7.4)^{MC}
DPG_{QRS} (mmHg)	3.6 (1.6– 6.7)	3.5 (1.6 – 7.4)^{MC}	3.9 (0.8 – 6.0)
$DPG_{mid\text{-}A}$ (mmHg)		1.8 (-0.6 – 5.8)^{MSQ}	—
DPG_{130} (mmHg)	—	—	5.0 (1.2 – 10.3)
DPG_{140} (mmHg)	—	—	6.2 (1.6 – 9.9)
DPG_{150} (mmHg)	—	—	5.6 (2.0 – 9.7)
DPG_{160} (mmHg)	—	—	8.5 (1.1– 12.5)

Letters in superscript indicate statistically significant ($P < 0.05$) differences: S, simultaneous measurement; M, mean value; QRS, ECG-gated measurement; C, according to the consensus paper's recommendation, i.e. mid-A-wave in sinus rhythm or 130 ms from QRS onset in atrial fibrillation.
DPG, diastolic pressure gradient; DPG_S, DPG_{QRS}, $DPG_{mid\text{-}A}$, DPG_{130}, DPG_{140}, DPG_{150}, and DPG_{160} stand for DPG calculated from the $PAWP_S$, $PAWP_{QRS}$, $PAWP_{mid\text{-}A}$, $PAWP_{130}$, $PAWP_{140}$, $PAWP_{150}$, and $PAWP_{160}$, respectively; PAP_D, pulmonary arterial diastolic pressure; PAP_M, pulmonary arterial mean pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance.

onset, the time delay being inversely associated with the V-wave amplitude (−0.47, P = 0.002). As illustrated in *Figure 2C*, $PAWP_{QRS}$ (15.3 [12.5 to 19.2] mmHg) was significantly lower than all the other pressure measurements ($P < 0.001$). In contrast, there was no significant difference between $PAWP_Z$ (17.6 [14.2 to 21.6] mmHg), $PAWP_{mid\text{-}A}$ (17.3 [14.5 to 21.2] mmHg; P = 0.63), and $PAWP_M$ (17.3 [14.7 to 21.2] mmHg; P = 0.49).

The mean difference between $PAWP_{mid\text{-}A}$ and $PAWP_Z$ was barely discernible with rather narrow limits of agreement and the in-between difference significantly associated with the rate of A-wave pressure decay (r = 0.5, P = 0.002), but not related to the A-wave or V-wave amplitude or the $PAWP_M$ ($P > 0.05$, for all).

Figure 3 Receiver operating characteristic (ROC) curve comparing the diagnostic ability of the mean pulmonary artery wedge pressure ($PAWP_M$) with the two proposed instantaneous PAWP measurements ($PAWP_{QRS}$ at QRS onset and $PAWP_{mid\text{-}A/130}$ at mid-A-wave in sinus rhythm or 130 ms after QRS onset in atrial fibrillation) for the differential diagnosis of primary pulmonary arterial hypertension and pulmonary hypertension due to left heart disease.



Diastolic pressure gradient calculations

$DPG_{mid\text{-}A}$ was higher than DPG_M ($P < 0.001$) and significantly associated with the A-wave pressure decay rate (r = 0.43, $P < 0.001$) while inversely related to the rate of the A-wave pressure rise (r = −0.39, $P < 0.001$). DPG_{QRS} yielded higher values than both $DPG_{mid\text{-}A}$ and DPG_M, and it was also significantly associated with A-wave pressure rise and fall (r = 0.36 P = 0.003 and r = −0.25, $P < 0.02$; respectively). DPG_Z was slightly, yet not significantly, higher than DPG_M and $DPG_{mid\text{-}A}$, whereas DPG_{QRS} was significantly higher than all three other DPG measurements (*Table 3*). In patients with AF, DPG_{130} was similar to DPG_{QRS}, whereas $DPG_{140–160}$ was significantly higher ($P < 0.001$).

Regarding DPG_{NEG}, among DPG_M, a rather high prevalence of 42% was observed, whereas the corresponding numbers for DPG_{QRS} and $DPG_{mid\text{-}A/130}$ were significantly lower (16% and 28%, respectively).

Differentiation between pulmonary arterial hypertension and pulmonary hypertension due to left heart disease

We tested the diagnostic ability of $PAWP_M$, $PAWP_{mid\text{-}A/130}$, and $PAWP_{QRS}$ measurements for distinguishing between PAH and PH-LHD. ROC analysis revealed similar diagnostic ability for the three variables [$PAWP_M$: area under the curve (AUC) 0.98, CI 0.96–0.99, SE 0.009, optimal cut-off limit at ≥13 mmHg, sensitivity 92%, and specificity 95%; $PAWP_{mid\text{-}A/130}$: AUC 0.94, CI 0.91–0.98, SE 0.017, optimal cut-off limit

at ≥13 mmHg, sensitivity 89%, and specificity 86%; $PAWP_{QRS}$: AUC 0.96, CI 0.94–0.99, SE 0.012, optimal cut-off limit at ≥12 mmHg, sensitivity 87%, and specificity 93%; $P < 0.001$ for all] (*Figure 3*).

Prognostic value

PH-LHD patients were followed up over 17 (8–27) months. During this period, 25 deaths occurred, and 27 patients were transplanted. ROC analysis for the prediction of death revealed similar AUC for the three PVR measurements (PVR_M: AUC 0.67, CI 0.54–0.80, SE 0.068 $P = 0.008$; $PVR_{mid\text{-}A/130}$: AUC 0.66, CI 0.53–0.78, SE 0.064, $P = 0.016$; PVR_{QRS}: AUC 0.64, CI 0.51–0.77, SE 0.067, $P = 0.029$). At the cut-off limit of 3 WU, by using Kaplan–Meier analysis, only PVR_M was significantly prognostic for death ($P = 0.016$), while PVR_{QRS} and $PVR_{mid\text{-}A/130}$ did not reach statistical significance ($P = 0.151$ and $P = 0.061$, respectively). However, when the ROC curves of PVR_M and $PVR_{mid\text{-}A}$ for the prediction of death were compared, no statistically significant difference was found in the discriminating power between PVR_M and $PVR_{mid\text{-}A/130}$ ($P = 0.36$).

In case of DPG, none of the DPG_M, DPG_{QRS}, and $DPG_{mid\text{-}A;130}$ was prognostic at any of the tested cut-off values (5, 6, 7, 8, and 9 mmHg) ($P > 0.05$ for all).

Discussion

Our study provides important insights into the various approaches for PAWP assessment. Firstly, we show that the mid-A-wave pressure comprises a more accurate EDP estimate as compared with $PAWP_{QRS.}$ In regard to AF, our results advocate for PAWP measurements at the lower end of the time interval proposed by the consensus statement, and in this particular setting, even ECG-gated measurements seem to comprise a feasible alternative. We demonstrate that the diagnostic ability of the various instantaneous PAWP measurements for differentiating PH-LHD from PAH is at best similar to that of $PAWP_M$. Finally, PVR derived from momentary PAWP, in contrast to conventional PVR, failed to provide prognostic information.

A precise wedge-derived EDP assessment requires to account for the transmission time from the LAP as well as for the electromechanical time delay.[21] Consequently, the EDP is expected to occur 130–200 ms following the QRS onset,[21,22] in line with the current findings of a median 180 ms time delay for the Z-point. Braunwald *et al*. demonstrated that the Z-point pressure comprised a more accurate EDP estimate compared with $PAWP_M$[5]; however, its utility is limited owing to its rather infrequent demarcation on the PAWP waveform. Recently, the mid-A-wave pressure has been proposed as a preferable EDP estimate.[6] Indeed, we found that $PAWP_{mid\text{-}A}$ reliably represents $PAWP_Z$ and thus EDP. Nevertheless, as currently demonstrated, $PAWP_{mid\text{-}A}$ might occasionally overestimate the $PAWP_Z$ particularly in cases of steep A-wave pressure decay, which can occur with increased LV end-diastolic stiffness.[23]

The absence of coordinated atrial contraction might accentuate the disparity between $PAWP_M$ and EDP, and it has been shown that in AF, $PAWP_M$ significantly overestimates EDP.[3] Accordingly, in AF, the latest consensus statement recommends instantaneous wedge pressure measurements at 130 to 160 ms following the QRS onset.[6] The lack of LV pressure recordings in our study does not allow for a direct comparison between PAWP at the aforementioned recommended time intervals and the corresponding LVEDP. Nonetheless, our results indicate that measurements at the earliest part (i.e. 130 ms) of the suggested time-period are more justifiable considering that PAP_D befell roughly 100 ms after the QRS onset. Furthermore, case-by-case analysis of the instantaneous PAWP occurring concurrently with the PAP_D revealed good agreement with the corresponding $PAWP_{130}$. Of note, ECG-gated PAWP measurements provided similar values to the corresponding simultaneous pressures as well as to $PAWP_{130}$. Considering the superior feasibility of the ECG-gated approach in clinical practice, our results support the use of $PAWP_{QRS}$ as the measurement of choice in AF.

The preferential employment of instantaneous end-diastolic PAWP measurements is currently supported even in the context of differentiation between PH-LHD and PAH.[6] It is however debatable whether this new approach could provide superior results in this setting. Indeed, it is commonplace for any experienced invasive cardiologist that patients with PAH do not exhibit substantial pressure pulsatility on PAWP recordings, an observation most probably ascribed to the dampening effect of significantly elevated PVR. In contrast, significant pressure pulsatility (the presence of large V-waves) is suggestive of PH-LHD. Accordingly, evasion of the pulsatile component of the PAWP, by employing instantaneous measurements, would preferentially impact on PH-LHD cases and by yielding lower PAWP values might perplex the differentiation between PH-LHD and PAH[24] as corroborated by our results showing that end-diastolic PAWP measurements provided lower specificity than $PAWP_M$ in this regard. $PAWP_M > 15$ mmHg has historically been employed for differentiation between PAH and PH-LHD. Of note, in our cohort, lower values (for $PAWP_M$ and $PAWP_{mid\text{-}A/130}$ an optimal diagnostic cut-off of 13 mmHg, and for $PAWP_{QRS}$ of 12 mmHg) have been identified, in line with the ongoing discussion for lower differentiating PAWP levels.

Along with the studies refuting the utility of DPG[7,13,14,16,25–27] arose the concept that the prognostic inconsistencies associated with this measurement originated, at least partially from an inappropriate approach to DPG derivation, not taking into account the temporal occurrence of the applied pressures.[7,9,14] Wright and colleagues first

attempted to standardize DPG calculation proposing instantaneous PAWP at QRS onset, thereby limiting the distorting effects of pressure pulsatility on DPG.[10] Temporal adjustment of PAWP assessment is also suggested in the current consensus statement,[6] which furthermore proposes that even PVR used for PH classification should also be based on instantaneous PAWP. Although the suggested instantaneous PAWP do indeed evade some physiological incongruencies of $PAWP_M$, these adjustments did not render improved prognostic or diagnostic information in our study. This might not be surprising, considering what exactly the PAWP is expected to represent in the specific setting. For DPG calculation, approximation of the end-diastolic LV pressure is important; thus, end-diastolic PAWP is likely the method of choice. However, for PVR, accounting for both the pulsatile and the static pressures as provided by $PAWP_M$ might better represent the haemodynamic load imposed on the right ventricle. In light of the current findings, before introducing momentary PAWP in place of $PAWP_M$, cautious consideration and most probably more data are required to clarify whether the use of instantaneous PAWP measurements should really be generalized.

Limitations

Our investigation has limitations. The study cohort was relatively small; however, it is still among the largest of its kind considering the detailed analysis of invasive pressure waveforms. Conductance catheters would have provided better accuracy than fluid-filled catheters; on the other hand, the current approach represents everyday clinical practice. We did not perform LV catheterization, which hampers the comparability of our data; however, that would not have been ethically defendable.

In accordance with guideline recommendations, we measured PAWP at end-expiration.[1] This approach may lead to an overestimation of pulmonary vascular pressures in case of hyperventilation and/or obstructed airways.[28] Whether averaging pulmonary pressure measurements over multiple respiratory cycles would be the preferred method was not addressed in the present study.

Our study did not include a control group of healthy individuals, which confines our results to HF and PAH; however, regarding that all participants underwent invasive testing, the recruitment of such control cohort would also raise major ethical issues.

Conclusions

Instantaneous PAWP measurements evade the distorting effect of pressure pulsatility and reliably represent EDPs. Nevertheless, these adjustments failed to translate into diagnostic or prognostic superiority compared with conventional mean PAWP-derived indices.

Conflict of interest

None.

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Supporting information

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

Figure S1. Flowchart explaining patient composition of the study cohort. RHC, right heart catheterisation; HF, heart failure; ARVC, arrhythmogenic right ventricular cardiomyopathy; PH, pulmonary hypertension; PAP_M, mean pulmonary artery pressure; $PAWP_M$, mean pulmonary artery wedge pressure.

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