Reliance on end-expiratory wedge pressure leads to misclassification of pulmonary hypertension

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ABSTRACT Current guidelines recommend measurement of pulmonary artery wedge pressure (PAWP) at end-expiration. However, this recommendation is not universally followed and may not be physiologically appropriate. We investigated the performance of end-expiratory PAWP in the evaluation of precapillary pulmonary hypertension patients.

329 spontaneously breathing patients undergoing right heart catheterisation were retrospectively classified as having a precapillary, post-capillary or mixed phenotype based on standardised clinical criteria. Tracings were reviewed to compare end-expiratory PAWP with PAWP averaged throughout the respiratory cycle; these values were correlated with the clinical classifications. Predictors of large respirophasic variation in PAWP were determined.

Elevated end-expiratory PAWP (>15 mmHg) occurred in 29% of subjects with precapillary phenotype. There were no differences in demographics or clinical history between those with elevated and normal end-expiratory PAWP. Those with elevated end-expiratory PAWP had greater right atrial pressure and respirophasic PAWP variation. Among all subjects, the magnitude of respirophasic variation in PAWP was positively correlated with body mass index and respirophasic variation in left ventricular end-diastolic pressure.

A significant proportion of precapillary pulmonary hypertension patients have end-expiratory PAWP >15 mmHg. Spontaneous positive end-expiratory intrathoracic pressure may contribute; in those cases, PAWP averaged throughout respiration may be a more accurate measurement.

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Introduction

Precapillary pulmonary hypertension is defined haemodynamically by right heart catheterisation as a mean pulmonary artery pressure (mPAP) $\geqslant$25 mmHg and pulmonary artery wedge pressure (PAWP) $\leqslant$15 mmHg [1]. This definition applies to a heterogeneous group of disorders associated with abnormalities in the pulmonary vasculature that restrict blood flow and can lead to right heart failure. World Health Organization (WHO) group 1 pulmonary arterial hypertension (PAH) describes those in whom pulmonary hypertension is not due to left heart disease (group 2), respiratory disease (group 3) or chronic pulmonary emboli (group 4), but is idiopathic or resulting from genetic predisposition, congenital heart disease, connective tissue disease, portal hypertension or drugs/toxins, among other causes [2]. Distinguishing precapillary pulmonary hypertension (groups 1, 3 and 4) from post-capillary or pulmonary venous hypertension is critical and requires accurate measurement of PAWP, as many patients present with risk factors for both PAH and pulmonary venous hypertension.

Appropriate measurement of PAWP requires careful thought about ventilation mode and timing within the respiratory cycle. Variation across respiratory phases can be profound and create measurement dilemmas and interobserver variability [3]. At the time of initial use of the Cournand catheter in the 1940s, right heart pressures were recorded as averages throughout the respiratory cycle [4, 5]; this approach was continued into the 1950s and 1960s [6, 7]. Conversely, current consensus statements recommend measurement of PAWP at the end of exhalation [8]. This recommendation, however, is not universally applied. In many catheterisation labs and intensive care units, a computer software-determined mean across multiple respiratory cycles is reported instead [9–11]. In spontaneously breathing patients, this leads to documentation of a PAWP that is lower than had it been measured manually at end-exhalation [12]. This practice could lead to misclassification of individuals with pulmonary venous hypertension as having PAH, though it is uncertain whether use of end-expiratory PAWP represents the most physiological approach. Direct measurement of left ventricular end-diastolic pressure (LVEDP) has been proposed to provide a more accurate assessment [13]. However, the effects of respiratory-related intrathoracic pressure shifts on LVEDP have not been previously well described.

We undertook this study to examine the performance of mean *versus* end-expiratory PAWP in the evaluation of precapillary pulmonary hypertension, using clinical characterisation as the comparison standard.

Methods

The study was approved by the Partners Human Research Committees, the institutional review board at Massachusetts General Hospital (Boston, MA, USA). All included patients had undergone right heart catheterisation at Massachusetts General Hospital between March 1, 2010 and December 31, 2011, with findings of precapillary pulmonary hypertension (mPAP $\geqslant$25 mmHg and PAWP $\leqslant$15 mmHg) on the finalised catheterisation report. Our experience in this laboratory has been the reporting of haemodynamic values as means across the respiratory cycle, thus our criteria was chosen to allow for identification of patients with ''controversial'' PAWP; $\leqslant$15 mmHg as a respiratory mean but $>$15 mmHg at end exhalation. Of those undergoing multiple catheterisations only a single catheterisation was included, which was chosen if it was performed with vasoreactivity testing or, if not, if it was the most recent. Patients receiving invasive or noninvasive positive pressure ventilation or continuous positive airway pressure (CPAP) during catheterisation were excluded.

Haemodynamic measurements

Catheterisation tracings were individually reviewed to verify that mPAP and PAWP as a mean across the respiratory cycle ($PAWP_{mrc}$) were appropriate for inclusion. From this, $PAWP_{mrc}$ and an end-expiratory PAWP were recorded independently of the documented PAWP for the study. For inclusion, $PAWP_{mrc}$ had to be $\leqslant$15 mmHg. Studies in which haemodynamic tracings were not evident were excluded. From the catheterisation report, right atrial pressure (RAP), cardiac output and pulmonary vascular resistance (PVR) were recorded. All haemodynamic measurements were made prior to clinical characterisation of included patients. The zero reference level for the catheterisation laboratory was the mid-axillary line.

If performed, LVEDP was recorded from the catheterisation report. For studies in which left ventricular tracings were available on an appropriate scale (0–40 mmHg), tracings were similarly reviewed with independent recording of LVEDP at end expiration and as a respiratory cycle mean ($LVEDP_{mrc}$); defined as the average of the highest and lowest LVEDP within the saved tracing.

Clinical characterisation

Each subject's catheterisation report and medical record were reviewed to identify age, sex, body mass index (BMI) and relevant cardiopulmonary history. From medical notes and summaries, any documentation of

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clinical history of the following conditions was noted: WHO group 1 causes of PAH; congestive heart failure (CHF); obstructive lung disease (not including asthma); restrictive lung disease; chronic thromboembolic pulmonary hypertension (CTEPH); obstructive sleep apnoea (OSA); diabetes mellitus; coronary artery disease; and hypertension. Patients with PAH could be newly diagnosed or already on treatment at the time of catheterisation. Current echocardiography findings, if performed within 1 year prior to or 1 month following catheterisation, were recorded to include evidence of systolic dysfunction, diastolic dysfunction (left ventricular hypertrophy or Doppler evidence of impaired relaxation), aortic or mitral valvular disease (regurgitation, stenosis or replacement) and right ventricular abnormalities (hypertrophy, hypokinesis or dilation). Left atrial size was reported, with left atrial enlargement defined as a diameter >40 mm.

Clinical and echocardiographic data were used to classify patients as having a precapillary (isolated WHO group 1 PAH, CTEPH, obstructive lung disease or restrictive lung disease), post-capillary (isolated clinical diagnosis of CHF or systolic, diastolic, or valvular dysfunction on echocardiography), or mixed phenotype. Those with no specific precapillary or post-capillary phenotype were grouped separately. Specific phenotypic classification criteria are shown in table 1.

Statistical analysis

For all subjects, agreement between reported PAWP, end-expiratory PAWP and $PAWP_{mrc}$ was assessed to comment on reporting practices in our institution. Using ANOVA, Wilcoxon rank-sum and the Chi-squared test, clinical and haemodynamic parameters were compared between precapillary, post-capillary and mixed phenotype groups to comment on our algorithm's agreement with haemodynamic findings. Among those with the precapillary phenotype, the prevalence of end-expiratory PAWP >15 mmHg was calculated. The precapillary group was divided between those with end-expiratory PAWP >15 mmHg *versus* ⩽15 mmHg. Haemodynamic and clinical characteristics were compared between groups using the t-test, Wilcoxon rank-sum test or Chi-squared testing as appropriate. A p-value of 0.05 was used to assess for significance.

For all subjects, variables associated with magnitude of PAWP respiratory variation were assessed using the t-test or Pearson correlation coefficient. Multivariable linear regression modelling was used to estimate the association between PAWP respiratory variation and covariates including age, sex, BMI, obstructive lung disease, restrictive lung disease, CHF and OSA. For catheterisations associated with interpretable left ventricular tracings, the magnitude of LVEDP respiratory variation was also correlated with PAWP respiratory variation, and differences in respiratory variation between each LVEDP and PAWP pair were described by Bland–Altman analysis. A statistical software package (SAS version 9.3; SAS Institute Inc., Cary, NC, USA) was used for all analyses.

Results

Initial criteria identified 462 catheterisations involving 410 patients. 30 catheterisations were excluded due to positive pressure ventilation or CPAP and 33 due to inability to view tracings. 16 catheterisations were excluded due to PAWP tracings demonstrating elevated $PAWP_{mrc}$ and six catheterisations due to normal

TABLE 1 Definition of the phenotypes

	Definition	Study subjects n
Precapillary phenotype	Diagnosis of a precapillary disease[#] AND No clinical diagnosis of CHF AND No moderate/severe mitral or aortic valve disease or replacement, systolic dysfunction[¶] or diastolic dysfunction[+] on echocardiogram	93
Post-capillary phenotype	Clinical diagnosis of CHF OR moderate/severe mitral or aortic valve disease or replacement, systolic dysfunction[¶] or diastolic dysfunction[+] on echocardiogram AND No diagnosis of precapillary disease[#]	134
Mixed phenotype	Clinical diagnosis of CHF OR moderate/severe mitral or aortic valve disease or replacement, systolic dysfunction[¶] or diastolic dysfunction[+] on echocardiogram AND Diagnosis of a precapillary disease[#]	76

CHF: congestive heart failure. [#]: diagnosis of World Health Organization group 1 pulmonary hypertension, chronic thromboembolic pulmonary hypertension, obstructive lung disease or restrictive lung disease; [¶]: indicated by reduced ejection fraction (<50%) or wall motion abnormalities; [+]: indicated by left ventricular hypertrophy or Doppler evidence of impaired relaxation.

TABLE 2 Characteristics of precapillary, post-capillary and mixed phenotype groups

	Precapillary	Post-capillary	Mixed	p-value[#]
Subjects n	93	134	76	
End-expiratory PAWP mmHg	12.8±4.0	16.0±3.1	14.0±3.4	<0.0001
PAWPmrc mmHg	9.4±3.2	12.5±2.2	11.0±2.7	<0.0001
PVR dyn·s·cm^{-5}	379 (280–639)	240 (178–309)	320 (234–541)	<0.0001
Left atrial diameter >40mm[¶]	5.8	62.1	43.7	<0.0001

Data are presented as mean±SD, median (interquartile range) or %, unless otherwise stated. PAWP: pulmonary artery wedge pressure; PAWPmrc: PAWP as mean across the respiratory cycle; PVR: pulmonary vascular resistance. [#]: comparisons between all three groups; for pairwise comparisons there was no difference in PVR between precapillary and mixed patients, for all other pairwise comparisons $p<0.05$; [¶]: results only for those with echocardiogram data (precapillary: n=52; post-capillary: n=124; mixed: n=71).

mPAP on tracings. 48 additional catheterisations were excluded as they were multiple catheterisations involving a single patient. After the detailed exclusions, 329 catheterisations were included in the study.

Reported PAWP for the entire population was mean±SD 11.6±2.9 mmHg. Reported PAWP was similar to measured PAWPmrc (11.3±2.9) but significantly lower than end-expiratory PAWP (14.6±3.7). Reported PAWP and PAWPmrc agreed in 50% of cases and were within ±1 mmHg 80% of the time. In comparison, reported PAWP and end-expiratory PAWP agreed 9% of the time and were within ±1 mmHg 28% of the time. Of the entire population, 141 (42.9%) had end-expiratory PAWP >15 mmHg.

Clinical phenotypes

93 (28.3%) subjects met the criteria for the precapillary pulmonary hypertension phenotype, 134 (40.7%) for the post-capillary phenotype, 76 (23.1%) for the mixed phenotype, and 26 did not meet criteria for either pre- or post-capillary pulmonary hypertension. The precapillary pulmonary hypertension group contained subjects with obstructive lung disease (n=22), restrictive lung disease (n=15), WHO group 1 PAH (n=21), CTEPH (n=16), or more than one disease (n=19; most commonly obstruction combined with restriction (n=12)).

Significant differences in PAWPmrc and end-expiratory PAWP were detected when comparing the precapillary, post-capillary and mixed phenotype groups (table 2); although substantial overlap existed (fig. 1). Consistent with the phenotypes, PVR was greater in precapillary and mixed subjects compared to post-capillary subjects. Left atrial enlargement was uncommon in precapillary subjects, present in only three (5.8%) out of the 52 subjects for whom echocardiography data were available.

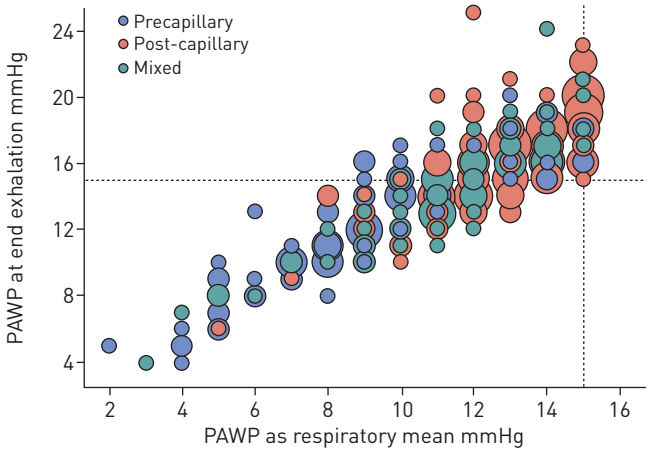

FIGURE 1 Distribution of pulmonary artery wedge pressure (PAWP) at end exhalation *versus* respiratory mean, as grouped by clinical phenotype. Larger circles represent identical observations in multiple patients. The standard cut-off of 15 mmHg (·····) yields poor phenotype separation, regardless of where PAWP is measured in the respiratory cycle. Blue circles above the standard cut-off represent phenotypically precapillary patients who would have been misclassified as pulmonary venous hypertension using end-expiratory PAWP.

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Precapillary phenotype by end-expiratory PAWP

End-expiratory PAWP >15 mmHg was seen in 27 (29.0%) phenotypically precapillary subjects. There was no significant difference in age, sex, BMI, type of precapillary disease or comorbid medical conditions between the groups exhibiting end-expiratory PAWP ⩽15 mmHg or >15 mmHg (table 3). Cardiac output, mPAP, left atrial size and prevalence of echocardiographically abnormal right ventricle were also similar. Those with end-expiratory PAWP >15 mmHg had significantly lower PVR, greater RAP and greater respiratory variation in PAWP.

WHO group 1 and CTEPH

56 subjects with WHO group 1 PAH and/or CTEPH (one patient with congenital heart disease and surgically treated CTEPH fit into both groups) were analysed separately. Mean $PAWP_{mrc}$ was 9.0±3.0 mmHg, and end-expiratory PAWP was 12.1±3.9 mmHg. 13 (23.2%) subjects had end-expiratory PAWP >15 mmHg. BMI was greater in the subgroup with end-expiratory PAWP >15 mmHg; otherwise, there were no significant differences in demographics, comorbid conditions or echocardiography data (table 4). Again, significantly greater RAP and more respiratory variation in PAWP were reported in the group with end-expiratory PAWP >15 mmHg.

Respiratory variation in PAWP

For the full population, the mean difference between end-expiratory PAWP and $PAWP_{mrc}$ ($PAWP_{ee–mrc}$) was 3.3±1.9 mmHg, ranging to 13 mmHg (fig. 2a and c). Significant positive correlation was found between $PAWP_{ee–mrc}$ and BMI ($r=0.356$, $p<0.0001$). On univariate analysis, there was no significant relationship between $PAWP_{ee–mrc}$ and diagnoses of obstructive or restrictive lung disease or CHF. OSA was associated with greater $PAWP_{ee–mrc}$ and increased age with lower $PAWP_{ee–mrc}$. On multivariate analysis, a significant relationship was observed between $PAWP_{ee–mrc}$ and BMI ($p<0.0001$), while there was a trend towards increased $PAWP_{ee–mrc}$ in those with obstructive lung disease ($p=0.0548$).

TABLE 3 Characteristics of precapillary phenotype patients according to end-expiratory pulmonary artery wedge pressure (PAWP)

	End-expiratory PAWP		p-value
	⩽15 mmHg	>15 mmHg	
Subjects n	66	27	
Age years	59.3±14.8	59.4±14.1	0.98
Female %	54.6	59.3	0.68
BMI kg·m^{-2}	26.9 (23.5–32.2)	29.4 (25.2–33.3)	0.20
mPAP mmHg	34.5 (28–47)	33 (27–47)	0.74
PVR dyn·s·cm^{-5}	422 (298–658)	296 (203–630)	0.033
Cardiac output L·min^{-1}	4.67 (3.70–5.97)	5.33 (4.15–6.27)	0.40
RAP mmHg	5 (4–7)	8 (7–12)	<0.0001
End-expiratory PAWP mmHg	11 (9–13)	17 (16–18)	<0.0001
$PAWP_{mrc}$ mmHg	8 (6–10)	13 (12–14)	<0.0001
$PAWP_{ee-mrc}$ mmHg	3 (2–4)	5 (3–6)	0.0001
Abnormal right ventricle$^{\#}$ %	68.6	52.9	0.27
Left atrial diameter$^{\#}$ mm	33 (30–37)	34 (30–39)	0.32
Obstructive lung disease	27 (40.9)	12 (44.4)	0.75
Restrictive lung disease	22 (33.3)	7 (25.9)	0.48
WHO group 1 PAH	20 (30.3)	6 (22.2)	0.43
CTEPH	14 (21.2)	4 (14.8)	0.48
Obstructive sleep apnoea	8 (12.1)	5 (18.5)	0.42
Hypertension	29 (43.9)	13 (48.2)	0.71
Diabetes	12 (18.2)	6 (22.2)	0.65
Coronary artery disease	9 (13.6)	8 (29.6)	0.070

Data are presented as mean±SD, median (interquartile range) or n (%), unless otherwise stated. BMI: body mass index; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; $PAWP_{mrc}$: PAWP as mean across respiratory cycle; $PAWP_{ee-mrc}$: mean difference between end-expiratory PAWP and $PAWP_{mrc}$; WHO: World Health Organization; PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension. $^{\#}$: results only for those with echocardiogram data (n=35 and n=17 for end-expiratory PAWP ⩽15 and >15 mmHg, respectively).

TABLE 4 Characteristics of World Health Organization group 1 and chronic thromboembolic pulmonary hypertension patients according to end-expiratory pulmonary artery wedge pressure (PAWP)

	End-expiratory PAWP		p-value
	⩽15 mmHg	>15 mmHg	
Subjects n	43	13	
Age years	56.1±15.5	58.9±10.3	0.54
Female %	65.1	69.2	0.78
BMI kg·m^{-2}	27.4 (23.5–30.9)	31.8 (27.6–35.9)	0.015
mPAP mmHg	41 (34–49)	47 (39–62)	0.099
PVR dyn·s·cm^{-5}	520 (361–846)	706 (396–1089)	0.36
Cardiac output L·min^{-1}	4.84 (4.05–6.55)	4.85 (4.15–5.40)	0.69
RAP mmHg	6 (5–9)	10 (8–12)	0.0028
End-expiratory PAWP mmHg	11 (9–12)	17 (16–18)	<0.0001
PAWP$_{mrc}$ mmHg	8 (6–9)	13 (12–15)	<0.0001
PAWP$_{ee\text{-}mrc}$ mmHg	3 (2–3)	5 (4–6)	0.0007
Abnormal right ventricle# %	70.8	77.8	0.69
Left atrial diameter# mm	33 (30–37)	38 (34–39)	0.097
Obstructive sleep apnoea	5 (11.6)	4 (30.8)	0.10
Hypertension	14 (32.6)	5 (38.5)	0.69
Diabetes	5 (11.6)	3 (23.1)	0.30
Coronary artery disease	5 (11.6)	3 (23.1)	0.30

Data are presented as mean±SD, median (interquartile range) or n (%), unless otherwise stated. BMI: body mass index; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; PAWP$_{mrc}$: PAWP as mean across respiratory cycle; PAWP$_{ee\text{-}mrc}$: mean difference between end-expiratory PAWP and PAWP$_{mrc}$. #: results only for those with echocardiogram data (n=24 and n=9 for end-expiratory PAWP ⩽15 and >15 mmHg, respectively).

Respiratory variation in LVEDP

75 (22.8%) patients had assessment of LVEDP at the time of right heart catheterisation; of these, 30 catheterisations saved tracings at an appropriate scale for evaluation of LVEDP. The mean difference between end-expiratory LVEDP and LVEDP$_{mrc}$ (LVEDP$_{ee–mrc}$) was 4.1±3.0 mmHg, ranging to 16 mmHg (fig. 2b and c). There was a very strong correlation between PAWP$_{ee–mrc}$ and LVEDP$_{ee–mrc}$ (r=0.859, p<0.0001). Respiratory variation in LVEDP was, on average, 0.5 mmHg (95% CI -0.1–1.1) greater than PAWP$_{ee–mrc}$ (fig. 3).

Discussion

In this study, end-expiratory PAWP had poor sensitivity for identifying patients with precapillary pulmonary hypertension, as defined by clinical history. In an attempt to classify patients as having precapillary pulmonary hypertension using more than just PAWP, we defined clinical phenotypes that were then compared with PAWP, both as a respiratory cycle mean and at end expiration. Among patients with precapillary disease who had no evidence, clinically or by echocardiogram, of left heart dysfunction, elevation in end-expiration PAWP was common (29%). Strict use of end-expiratory PAWP would have led to misclassification of this group as having pulmonary venous hypertension. These patients did not appear to be different to comparable patients with strictly normal end-expiratory PAWP, with similarities in demographics, medical history, echocardiogram findings and most catheterisation haemodynamics. However, right atrial pressure was significantly higher in the group with elevated end-expiratory PAWP, and there was also greater respirophasic variation in PAWP in these patients.

It is likely that the mechanism for "false" elevation in end-expiratory PAWP seen in our cohort relates to intrathoracic pressure swings throughout the respiratory cycle. During catheterisation, use of end-expiratory PAWP assumes that intrathoracic pressure is approximately equal to atmospheric pressure at end-exhalation and, thus, measured PAWP reflects a transmural left ventricular filling pressure. In the setting of mechanical ventilation [14, 15], obesity [16], or chronic obstructive pulmonary disease (COPD) [17–21], end-expiratory intrathoracic pressure can be significantly greater than atmospheric pressure. In these scenarios, use of end-expiratory PAWP overestimates true transmural PAWP (as well as RAP). BOERRIGTER *et al.* [20] recently reached similar conclusions in exercising COPD patients. PAWP averaged over the respiratory cycle provided a more accurate estimate of transmural PAWP, as determined using simultaneous oesophageal pressure measurements [20].

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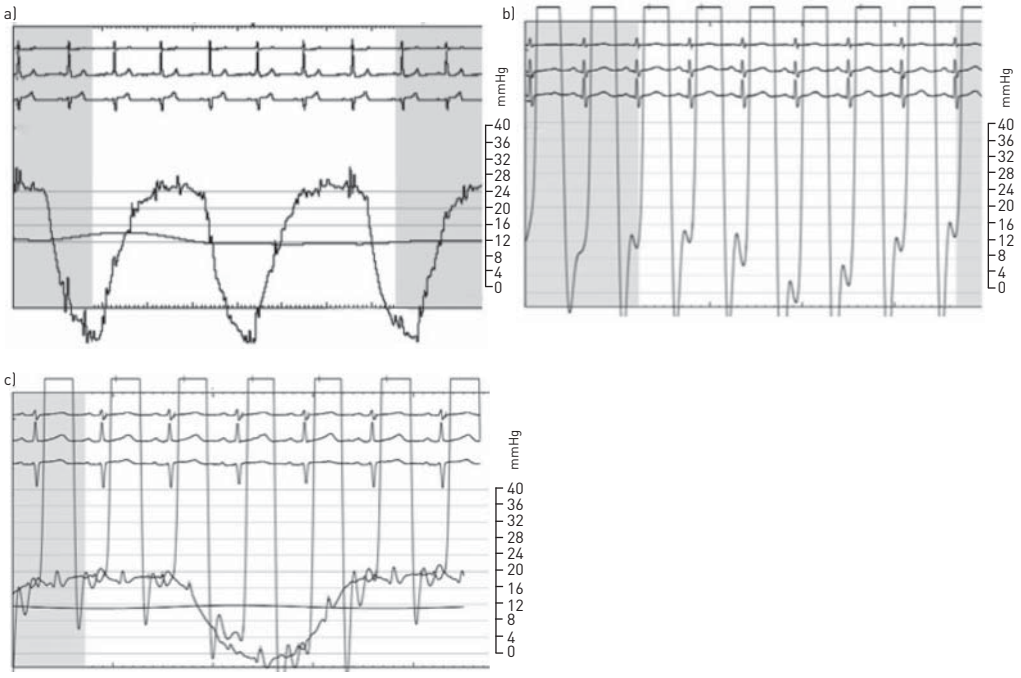

FIGURE 2 a) Pulmonary artery wedge pressure tracing from one subject demonstrating extreme respirophasic variation in wedge pressure, with >10 mmHg difference between end-expiratory and respiratory mean measurements. b) Left ventricular pressure tracing from a second subject demonstrating large respirophasic variation in left ventricular end-diastolic pressure. c) Simultaneous wedge pressure and left ventricular pressure tracings from a third subject, illustrating overlapping respirophasic variation.

In many of our subjects with elevated end-expiratory PAWP and RAP, we hypothesised that these high pressures reflect elevated end-expiratory intrathoracic pressure with normal transmural right and left atrial pressures. As additional support of this, we noted that those with elevated end-expiratory PAWP demonstrated significantly more respiratory variation in PAWP than those with lower end-expiratory PAWP. Interpretation of this finding is limited by selection bias, *i.e.* a subject with end-expiratory PAWP of 20 mmHg must have a $PAWP_{ee\text{-}mrc}$ difference of at least 5 mmHg to be included. However, this larger respiratory variation may be a surrogate for positive end-expiratory intrathoracic pressure, which must be overcome before establishment of inspiratory airflow.

We further analysed the distribution of respirophasic wedge pressure variation within a diverse population of subjects undergoing catheterisation. While normal respiratory cycle–ventricular filling interactions are complex [22, 23], the most significant factor influencing respirophasic wedge pressure variation appears to be intrathoracic pressure variation. Previous work in COPD has supported a close relationship between variable intrathoracic pressure and measured wedge pressures [19–21, 24, 25]. For example, RICE *et al.* [19] demonstrated very tight correlation (slope 1.04, r=0.98) between changes in oesophageal and wedge pressures during respiration in COPD patients. One would anticipate COPD and other conditions associated with spontaneous positive end-expiratory intrathoracic pressure show greater $PAWP_{ee\text{-}mrc}$. In our study, a nonsignificant trend towards increased $PAWP_{ee\text{-}mrc}$ in those with obstructive disease was reported; the study was probably underpowered to detect a significant difference in this group.

The magnitude of phasic PAWP change was strongly correlated with BMI. Obesity has been repeatedly associated with positive end-expiratory intrathoracic pressure during spontaneous breathing, particularly in the supine position [16, 26, 27]. Among our WHO group 1 PAH and/or CTEPH subjects, those in the high end-expiratory PAWP group had higher BMI. Similarly, recent analysis of the REVEAL (Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management) registry found higher prevalence of obesity in those with higher PAWP [28].

As positive end-expiratory intrathoracic pressure impacts all catheterisation pressure measurements, those with higher end-expiratory PAWP should also have higher measured (though not transmural) mPAP. Interestingly, in the REVEAL study mPAP and RAP were both greater in patients with higher levels of PAWP [28]. In our analysis of WHO group 1 and CTEPH patients, a trend towards increased mPAP was seen in the group with end-expiratory PAWP >15 mmHg. It should be noted that mPAP measurements

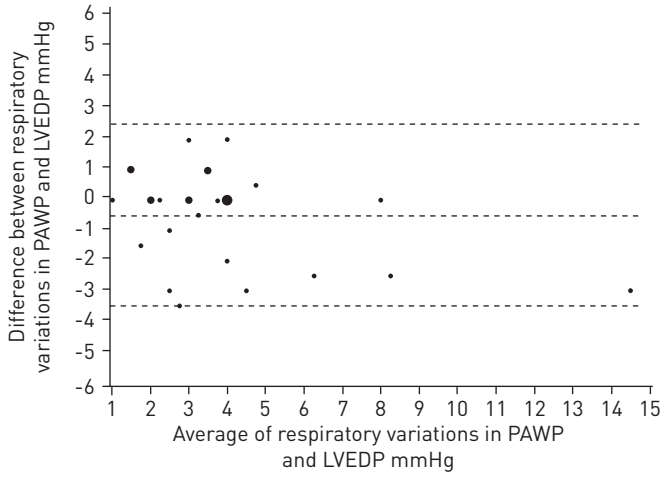

FIGURE 3 Bland–Altman plot of difference between $PAWP_{ee\text{-}mrc}$ and $LVEDP_{ee\text{-}mrc}$ *versus* average of respiratory variation in $PAWP_{ee\text{-}mrc}$ and $LVEDP_{ee\text{-}mrc}$. A positive value on the y-axis indicates subjects for whom respiratory variation in pulmonary artery wedge pressure was greater than respiratory variation in left ventricular end-diastolic pressure. Larger circles represent identical observations in multiple patients. Mean difference: -0.5 mmHg (95% CI -1.1–0.1); limits of agreement: -3.5–2.5. $PAWP_{ee\text{-}mrc}$: mean difference between end-expiratory pulmonary artery wedge pressure (PAWP) and PAWP as respiratory mean; $LVEDP_{ee\text{-}mrc}$: mean difference between left ventricular end-diastolic pressure (LVEDP) and LVEDP as respiratory mean.

were obtained from catheterisation reports, and thus were not necessarily end-expiratory values. If our hypothesis holds true we would anticipate end-expiratory mPAP to be even greater in those with end-expiratory PAWP >15 mmHg, further exaggerating this difference between groups.

Although reflective of a small sample (n=30) of subjects, we additionally demonstrated respirophasic change in LVEDP, which correlated well with respirophasic variability in PAWP. The relationship between absolute values of LVEDP and PAWP has been previously described, with closer correlations found in studies in which the respiratory phase of PAWP and LVEDP is specifically observed and uniformly recorded [10, 29], compared to studies in which tracings were not individually reviewed and/or were not necessarily measured in the same phase of respiration [13, 30]. Routine measurement of LVEDP, in addition to adding procedural risk, is subject to the same debates regarding respiratory variability as PAWP.

Clinical decisions made using data obtained by nonstandardised methodology can have substantial consequence. As recently analysed by KOVACS *et al.* [31], the choice of zero reference level has very clinically significant effects on interpretation of PAWP, altering the diagnosis in up to 31% of patients. Similarly, the practical question of where, within the respiratory cycle, to measure PAWP carries great importance and is worthy of further discussion and investigation. Strict use of $PAWP_{mrc}$ can underdiagnose pulmonary venous hypertension; we also argue that use of end-expiratory PAWP underdiagnoses PAH. Inaccurate interpretation of PAWP has the potential to lead to inappropriate use of PAH therapies (both overuse and underuse). While published inclusion criteria for most randomised clinical trials in PAH specified PAWP <15 mmHg or ⩽15 mmHg, none specified where in the respiratory cycle this value was measured [32–40]. Interestingly, in major PAH registries and trials that report baseline PAWP, means ranged between 7.5 mmHg and 10 mmHg [32, 35, 37–45], matching more closely with our WHO group 1 $PAWP_{mrc}$ (9.1±3.3) in comparison to end-expiratory PAWP (12.3±4.2). We hypothesise that many or all of these studies utilised $PAWP_{mrc}$ and, had end-expiratory PAWP been used instead, some of these subjects would have been, possibly inappropriately, excluded from the trials.

The limitations of this study are important to discuss. Our study occurred at a single centre, thus, wedge pressure reporting practices at our institution may not mirror other centres. Our methods of designating phenotypes, while similar to those commonly used in practice, were not specifically validated. Phenotype designation required chart documentation of pertinent diagnoses; as these were not universally performed, radiological and pulmonary function studies were not routinely reviewed for verification. While our total study population was large (n=329), our phenotyping strategies decreased evaluated numbers to smaller groups. Our power to detect meaningful differences between precapillary subjects with high *versus* low end-expiratory PAWP, for example, may be insufficient. The REVEAL analysis detected differences in several medical comorbidities between those with high and low PAWP [28]. We were probably underpowered to detect such differences.

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We conclude that patients with precapillary pulmonary hypertension may be mislabelled as having pulmonary venous hypertension if end-expiratory wedge pressure is always utilised, especially in the setting of obesity or obstructive lung disease. The addition of clinical phenotyping can enhance interpretation of these often complex haemodynamic measurements.

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