



Measuring central pulmonary pressures during exercise in COPD: how to cope with respiratory effects

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ABSTRACT Respiratory influences are major confounders when evaluating central haemodynamics during exercise. We studied four different methods to assess mean pulmonary artery pressure (mPAP) and pulmonary capillary wedge pressure (PCWP) in cases of respiratory swings.

Central haemodynamics were measured simultaneously with oesophageal pressure during exercise in 30 chronic obstructive pulmonary disease (COPD) patients. mPAP and PCWP were assessed at the end of expiration, averaged over the respiratory cycle and corrected for the right atrial pressure (RAP) waveform estimated intrathoracic pressure, and compared with the transmural pressures.

Bland–Altman analyses showed the best agreement of mPAP averaged over the respiratory cycle (bias (limits of agreement) 2.5 (-6.0–11.8) mmHg) and when corrected with the nadir of RAP (-3.6 (-11.2–3.9) mmHg). Measuring mPAP at the end of expiration (10.3 (0.5–20.3) mmHg) and mPAP corrected for the RAP swing (-9.3 (-19.8–2.1) mmHg) resulted in lower levels of agreement. The respiratory swings in mPAP and PCWP were similar ($r^2=0.82$, slope \pm SE 0.95 ± 0.1).

Central haemodynamics measured at the end of expiration leads to an overestimation of intravascular pressures in exercising COPD patients. Good measurement can be acquired even when oesophageal pressure is omitted, by averaging pressures over the respiratory cycle or using the RAP waveform to correct for intrathoracic pressure. Assessment of the pulmonary gradient is unaffected by respiratory swings.



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Measurement of intravascular pressures in exercising COPD patients requires correction for intrathoracic pressure <http://ow.ly/tVLLg>

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Introduction

Haemodynamic assessment remains the gold standard in the diagnosis of cardiovascular and pulmonary vascular disease. In an effort to detect early and potentially more treatable pulmonary vascular disease [1, 2], and heart failure with preserved ejection fraction [3], there has been renewed interest in the direct measurement of central pulmonary haemodynamics during exercise. Both heart and vessel abnormalities are frequently found in chronic obstructive pulmonary disease (COPD) [4, 5]. To minimise the effect of increased intrathoracic pressure changes on intravascular pressure measurements during right heart catheterisation at rest, it is recommended that pressures be analysed at the end of expiration [6]. During exercise in patients with COPD in particular, the increase in intrathoracic pressure during expiration can be a major confounder of the measurement of central pulmonary pressures.

COPD is characterised by a combination of derangements in respiratory mechanics, which alter intrathoracic pressure. At rest, increased lung compliance requires a larger lung volume to balance chest wall recoil. During exercise, increased compliance and resistance lead to ineffective and prolonged gas emptying on expiration. This causes inspiration to start before a full expiration has occurred, before the lung has returned to its relaxation volume. As a consequence, not only does the lung volume at the end of expiration rise dynamically (dynamic hyperinflation), the alveolar pressure at the end of expiration also becomes higher (intrinsic positive end-expiratory pressure (PEEP_i)). The consequence of this is that the respiratory muscles have to generate a more negative intrathoracic pressure during inspiration to overcome the presence of PEEP_i, and, especially, generate a large positive intrathoracic pressure during expiration. These pressures are exaggerated in exercise. When measuring haemodynamics during exercise in COPD, it is preferable to subtract oesophageal pressure (P_{oes}) in order to acquire the true intracavitary pressure, and thereby derive actual transmural pressure, which is critical in the detection of pulmonary vascular disease [7]. However, this is not practical in daily practice and, therefore, older studies reported the values of central pressures averaged over one or more respiratory cycles during exercise in COPD patients [8–10] and healthy subjects [11–13]. More recent studies abandoned this and reported end-expiratory measurements [14, 15], based on the recommendations for resting measurements under the assumption that they also hold during exercise. An alternative is to use the right atrial pressure (RAP) waveform, which is largely influenced by its surrounding pressure (which is intrathoracic pressure), to estimate intrathoracic pressure [16].

How to measure central pressures during exercise in cases of exaggerated intrathoracic pressure swings and the validity of using the RAP waveform to correct for intrathoracic pressure remain largely unknown. In this study, therefore, we evaluated the effect of intrathoracic pressure on the different central pressures in patients with COPD in order to find a method of adequately measuring pulmonary vascular pressures without measuring intrathoracic pressure in routine clinical practice. We hypothesised that measuring at the end of expiration leads to an overestimation of pulmonary vascular disease and that averaging over the respiratory cycle or correcting the pulmonary artery pressure (PAP) with an intrathoracic pressure results in better assessment of the intravascular pressure. Secondly, we hypothesise that the respiratory swings with exercise in PAP and wedge pressure are similar, so that the transpulmonary gradient can be assessed unaffected by respiratory swings.

Methods

Subjects

30 COPD patients were referred for the analysis of pulmonary hypertension. Patients were selected based on a moderate to very severe airway obstruction (forced expiratory volume in 1 s (FEV₁) <80% predicted) without significant reversibility (<12% or <200 mL change in FEV₁ value). Patients were on optimal medical therapy and had no acute exacerbation for ≥ 4 weeks. Pulmonary function testing was performed according to published guidelines [17, 18]. All tests were performed at the VU University Medical Center (Amsterdam, the Netherlands) and the VU University Medical Center ethics committee approved the study. Written informed consent was obtained from all patients.

Preparation of subjects

A balloon-tipped, flow-directed, triple-lumen 7.5-F Swan–Ganz catheter (Baxter Healthcare Corporation, Irvine, CA, USA) was inserted under local anaesthesia into the jugular vein. The ports of the catheter were positioned in the right atrium, right ventricle and pulmonary artery. A radial artery catheter was inserted at either the right or left wrist under sterile conditions and following local anaesthesia. A standard oesophageal balloon catheter (Microtek Medical BV, Zutphen, the Netherlands) was inserted transnasally with the use of lidocaine gel (2%). The balloon tip was first positioned 45 cm from the nares and the balloon was emptied by performing a Valsalva manoeuvre [19]. After this, 5 mL air was injected into the balloon followed by the withdrawal of 4 mL, to partially inflate the balloon. The pressure signal was checked and, in case of cardiac artefacts, the position of the balloon catheter was slightly adjusted in the proximal direction.

Patients were placed on an electromagnetically braked cycle ergometer (Ergoline GmbH, Bitz, Germany), in the semisupine position. The zero reference for the pressure transducers was 5 cm below the middle of the sternum. All catheters were connected to a PowerLab data acquisition system (ADInstruments, Dunedin, New Zealand) in order to record and digitalise pressures from the right atrium, right ventricle and pulmonary artery simultaneously with P_{oes} .

Protocol

The protocol consisted of 3 min of rest after which workload was increased every 3 min until exhaustion. Oxygen consumption ($V'O_2$) was measured continuously using a metabolic cart (Vmax 229; Viasys Healthcare, Yorba Linda, CA, USA). Patients were asked to signal just prior to exhaustion in case the last workload could not be fulfilled for 3 min, to complete the data collection at maximal exercise. During the last 30 s of every workload, pulmonary capillary wedge pressure (PCWP) was acquired, and mixed venous and arterial blood samples were drawn. Cardiac output was calculated using the direct Fick method from arterial and mixed venous oxygen saturation and $V'O_2$. Pulmonary vascular resistance (PVR) was calculated as (mean PAP (mPAP) – PCWP)/cardiac output.

Post-processing of pressure waveforms

The recorded pressure tracings were visually checked and 30 s of good-quality pressure waveforms were selected near the end of each workload in addition to the part with the PCWP tracing. At each workload, we selected the PAP tracing as close as possible to the PCWP tracing to minimise changes in flow and intrathoracic pressure between the two measurements. Each selected timeframe was analysed using an in-house programme for Matlab (MathWorks, Natick, MA, USA) using two different methods. We automatically acquired systolic, mean (mPAP) and diastolic PAP together with the transmural values of mPAP (mPAP_{tm}) and PCWP (PCWP_{tm}) by subtracting P_{oes} in a beat-to-beat manner. All values were acquired and averaged over a period of 10–20 inspiratory and 10–20 expiratory heartbeats. This way, we acquired robust inspiratory and expiratory values separately as well as the swings (expiratory–inspiratory values) (fig. 1).

We then corrected expiratory mPAP and PCWP for the increased P_{oes} in four different ways, and compared them with mPAP_{tm} and PCWP, which we considered the gold standard. 1) End-expiratory: mPAP and PCWP measured at the moment of the last heartbeat during expiration without any further correction (mPAP_{end-exp} and PCWP_{end-exp}). 2) Averaged over the full respiratory cycle: mPAP and PCWP averaged over three full respiratory cycles including inspiratory and expiratory heartbeats (mPAP_{averaged} and PCWP_{averaged}). 3) Corrected for nadir RAP (RAP_{nadir}): mPAP and PCWP at expiration corrected for the nadir in the RAP waveform during the same period of expiration. This assumes that during the relaxation period RAP falls to the pressure surrounding the right atrium and, therefore, is useful in estimating and correction for P_{oes} [16] (mPAP_{RAP_{nadir}} and PCWP_{RAP_{nadir}}). Figure 2 shows the determination of RAP_{nadir}. 4) Corrected for RAP swing: mPAP and PCWP at expiration corrected for the swing in RAP from inspiration to expiration during the same breathing cycle. This assumes that the swing in RAP is useful in estimating and correction for P_{oes} mPAP_{RAP_{swing}} and PCWP_{RAP_{swing}}. See figure 2 for the determination of the RAP swing.

Statistical methods

Demographic, pulmonary function and haemodynamic data are presented as mean \pm SD. Differences in the slope and absolute values at rest and exercise before and after correction were tested using a two-way ANOVA. The accuracy of the four different methods of measurements of mPAP and PCWP was evaluated by Bland–Altman analyses with mPAP_{tm} and PCWP_{tm} as the gold standards. Relationships were analysed by linear regression. Differences between respiratory swings at different pressures were tested using a two-tailed t-test. $p < 0.05$ was considered significant. Analyses were performed using GraphPad Prism 5.0 (GraphPad, La Jolla, CA, USA).

Results

Study population

14 males and 16 females with a mean \pm SD age of 64 ± 9 years and a body mass index of 27 ± 6 kg·m⁻² were included in this study. Pulmonary function and haemodynamic measurements are summarised in table 1. All patients were former or current smokers (mean \pm SD 37 ± 18 pack-years), and had been diagnosed with emphysema based on pulmonary function and computed tomography of the chest. The severity of the airflow limitation was moderate in 16 patients, severe in 11 patients and very severe in three patients, according to the Global Initiative for Chronic Obstructive Lung Disease criteria. Nine patients were

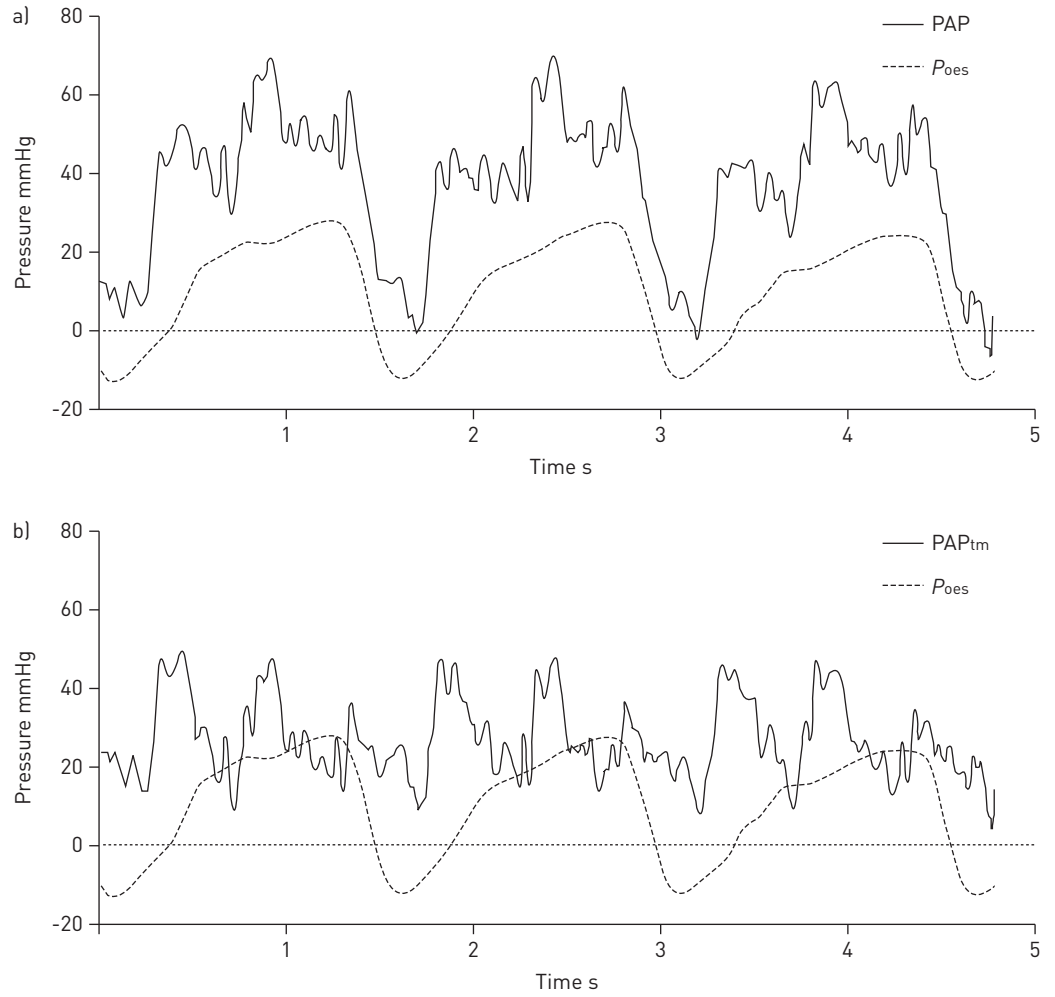


FIGURE 1 Example of pulmonary artery pressure (PAP) a) before and b) after (transmurial PAP (PAP_{tm})) continuous correction for oesophageal pressure (P_{oes}) at maximal exercise in a patient with severe chronic obstructive pulmonary disease (forced expiratory volume in 1 s $\leq 30\%$ predicted).

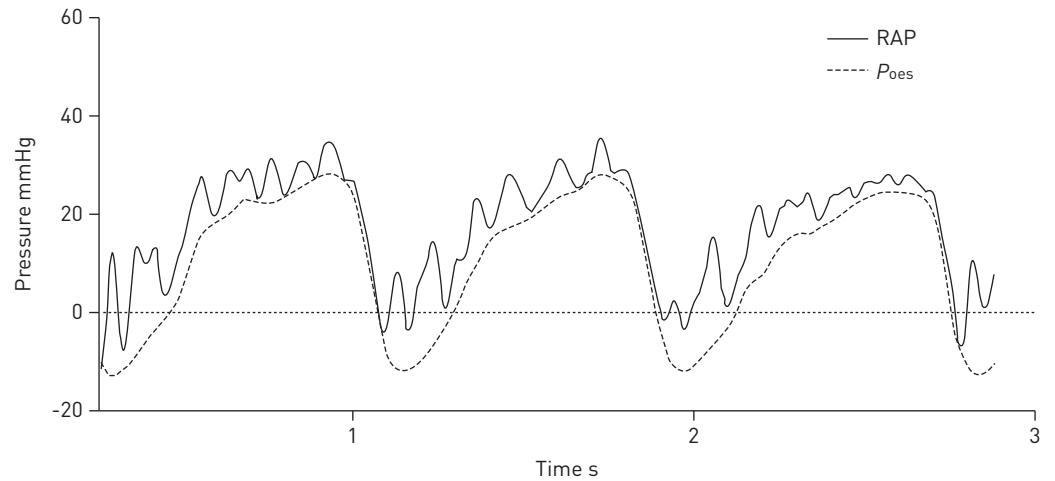


FIGURE 2 Example of determinations of right atrial pressure (RAP). The simultaneous measurement of RAP and oesophageal pressure (P_{oes}) are shown at maximal exercise in the same patient as shown in figure 1. Nadir RAP is the lowest point in RAP during expiration, which represents RAP during relaxation. Note that RAP falls towards P_{oes} during relaxation. RAP swing was determined as the difference between inspiratory RAP and expiratory RAP.

TABLE 1 Pulmonary function and haemodynamic characteristics

FEV₁	
L	1.58 ± 0.62
% pred	56 ± 18
FEV₁/VC %	46 ± 18
VC	
L	3.46 ± 1.09
% pred	98 ± 22
TLC	
L	6.54 ± 1.20
% pred	109 ± 17
FRC	
L	4.19 ± 1.02
% pred	136 ± 34
Cardiac index L·min⁻¹·m⁻²	3.3 ± 0.9
Heart rate beats·min⁻¹	80 ± 17
P_{aO₂} mmHg	65 ± 15
P_{aCO₂} mmHg	39 ± 9

Data are presented as mean ± SD. FEV₁: forced expiratory volume in 1 s; % pred: % predicted; VC: vital capacity; TLC: total lung capacity; FRC: functional residual capacity; P_{aO₂}: arterial oxygen tension; P_{aCO₂}: arterial carbon dioxide tension.

hypoxaemic (arterial oxygen tension <60 mmHg) at rest while breathing room air and four patients had arterial carbon dioxide tension >45 mmHg.

Pressures during exercise with and without correction for intrathoracic pressure

Maximal exercise was at a workload of 48 ± 31 W with a V̇O₂ of 922 ± 379 mL. A mean ± SD cardiac output of 10.9 ± 3.8 L·min⁻¹ was reached with a heart rate of 118 ± 19 beats·min⁻¹. The central haemodynamic pressures are summarised in table 2. The large swings in P_{oes} were transduced into all central pressure, on average responsible for a difference between inspiratory values and expiratory values of ~20 mmHg. The expiratory P_{oes} at maximal exercise ranged from +3 mmHg to +25 mmHg (fig. 3). The mean ± SD slope decreased from 6.4 ± 3.7 mmHg·L⁻¹ to 4.4 ± 3.2 mmHg·L⁻¹ (p < 0.001) after correction for intrathoracic pressure. Seven patients had a mPAP/cardiac output slope >3 mmHg before correction, which decreased to <3 mmHg after correction for intrathoracic pressure. 19 out of the 22 patients who had a PCWP recording had a PCWP >20 mmHg with exercise without correction for intrathoracic pressure. Seven patients had a PCWP_{tm} >20 mmHg; in three of them PCWP_{tm} was 20–25 mmHg.

mPAP measurement and potential correction methods

mPAP_{tm} and PCWP_{tm} at maximal exercise were 47 ± 15 mmHg and 17 ± 8 mmHg, respectively. The average mPAP values at maximal exercise of each of the four methods were mPAP_{end-exp} 59 ± 14 mmHg, mPAP_{averaged} 50 ± 14 mmHg, mPAP_{RAP_{nadir}} 44 ± 15 mmHg and mPAP_{RAP_{swing}} 38 ± 15 mmHg. The average PCWP values at maximal exercise of each of the four methods were PCWP_{end-exp} 27 ± 9 mmHg, PCWP_{averaged} 20 ± 8 mmHg, PCWP_{RAP_{nadir}} 15 ± 7 mmHg and PCWP_{RAP_{swing}} 11 ± 8 mmHg. Bland–Altman

TABLE 2 Central pressure over the respiratory cycle at rest and during exercise

	Rest			Exercise		
	Expiration	Inspiration	Swing	Expiration	Inspiration	Swing
P_{oes} mmHg	3 ± 2	-7 ± 1	10 ± 3	12 ± 6	-11 ± 2	22 ± 6
sPAP mmHg	53 ± 20	45 ± 19	8 ± 6	87 ± 24	64 ± 21	22 ± 11
mPAP mmHg	33 ± 12	28 ± 11	6 ± 6	59 ± 14	40 ± 13	19 ± 8
dPAP mmHg	23 ± 9	15 ± 7	8 ± 5	40 ± 11	23 ± 11	19 ± 11
PCWP mmHg	11 ± 4	2 ± 4	9 ± 4	26 ± 8	5 ± 9	21 ± 6
mRAP mmHg	6 ± 2	-2 ± 3	7 ± 4	16 ± 6	-4 ± -4	20 ± 6

Data are presented as mean ± SD. P_{oes}: oesophageal pressure; s: systolic; PAP: pulmonary artery pressure; m: mean; d: diastolic; PCWP: pulmonary capillary wedge pressure; RAP: right atrial pressure.

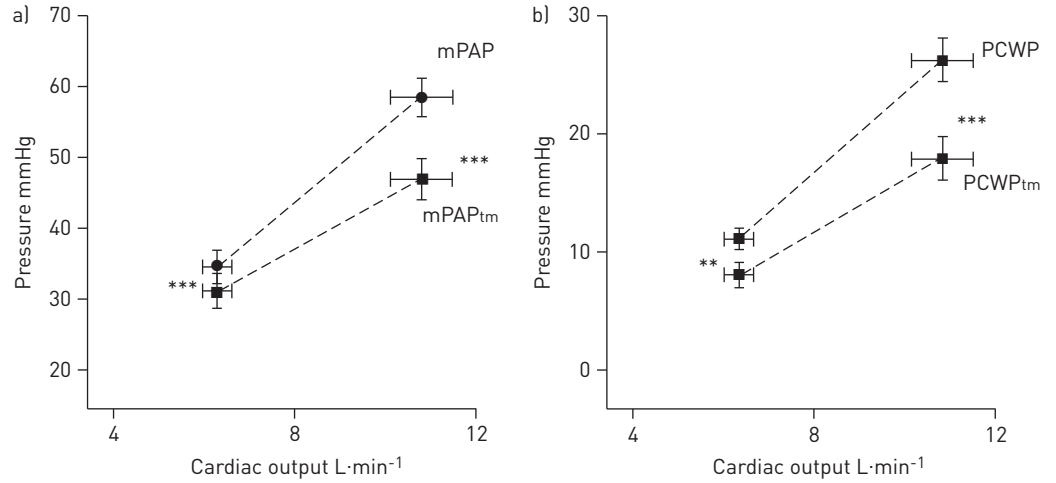


FIGURE 3 Average pressure flow relations before and after correction for oesophageal pressure (P_{oes}). a) Mean pulmonary artery pressure (mPAP) and transmural mPAP (mPAP_{tm}) (calculated as mPAP - P_{oes}); b) pulmonary capillary wedge pressure (PCWP) and transmural PCWP (PCWP_{tm}) (calculated as PCWP - P_{oes}). **: $p < 0.01$; ***: $p < 0.001$.

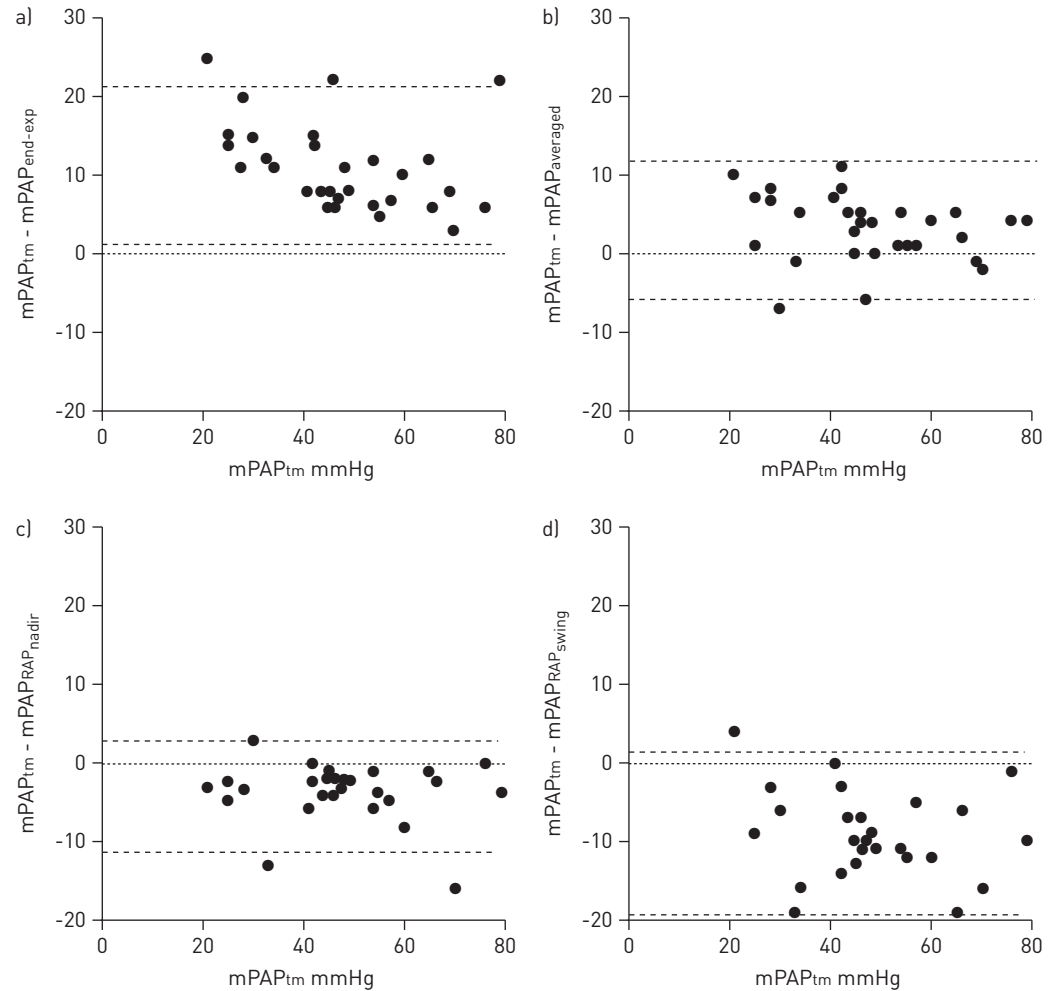


FIGURE 4 Bland–Altman analyses of the difference between mean pulmonary artery pressure (mPAP) and transmural mPAP (mPAP_{tm}) plotted *versus* the mPAP_{tm}. a) mPAP measured at the end of expiration (mPAP_{end-exp}); b) mPAP averaged over the respiratory cycle (mPAP_{averaged}); c) mPAP corrected for the lowest point of right atrial pressure (RAP) during expiration (mPAP_{RAPnadir}); and d) mPAP corrected with the swing in RAP (mPAP_{RAPswing}). Dotted lines represent the 95% limits of agreement.

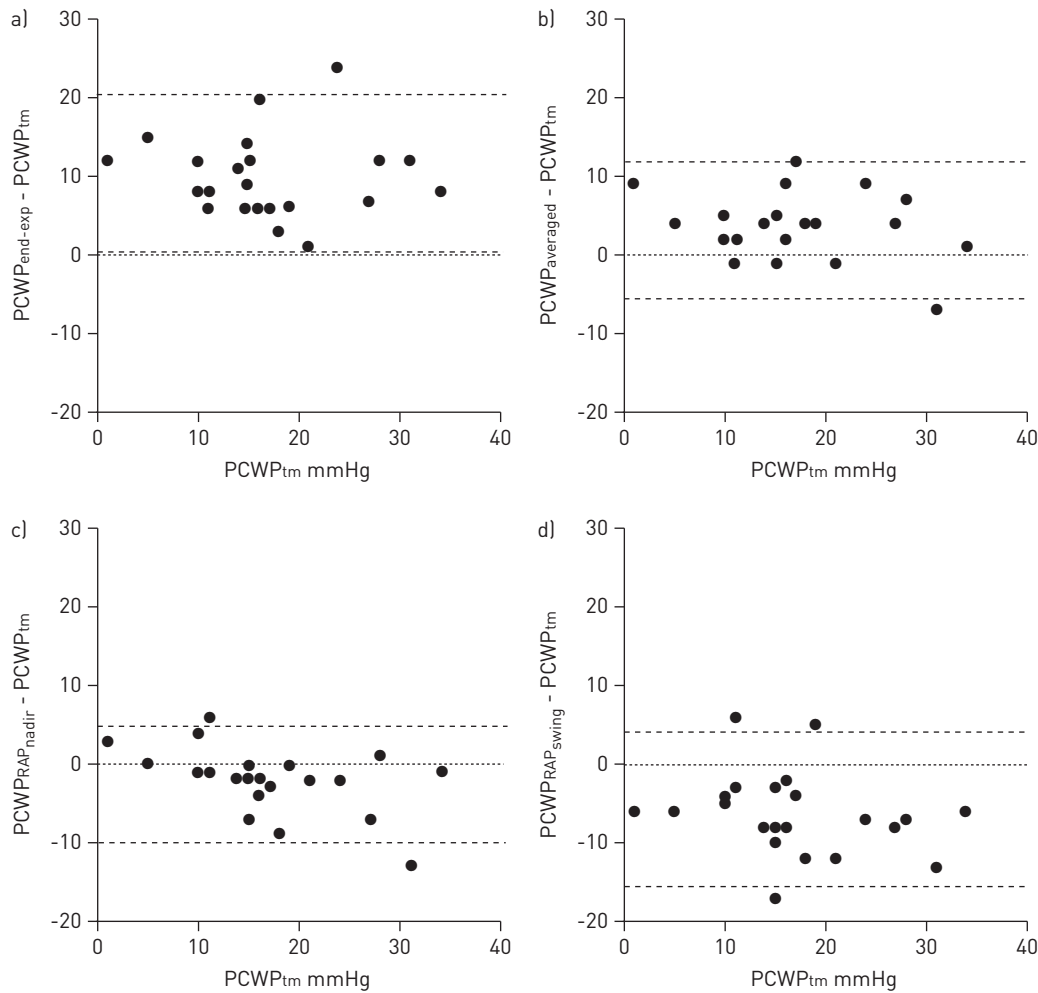


FIGURE 5 Bland–Altman analyses of the difference between pulmonary capillary wedge pressure (PCWP) and transmural pulmonary capillary wedge pressure (PCWP_{tm}) plotted *versus* the PCWP_{tm}. a) PCWP measured at the end of expiration (PCWP_{end-exp}); b) PCWP averaged over the respiratory cycle (PCWP_{averaged}); c) PCWP corrected with the lowest point of RAP during expiration (PCWPRAP_{nadir}); and d) PCWP corrected with the swing in RAP (PCWPRAP_{swing}). Dotted lines represent the 95% limits of agreements.

plots of the four methods of mPAP and PCWP measurements during exercise are shown in figures 4 and 5, respectively, and summarised in table 3.

Effect of intrathoracic pressure swings on PCWP, mPAP and RAP

See table 2 for a summary of the pressure fluctuations. Figure 6 illustrates the relationship between the swing in mPAP (mPAP_{swing}) and PCWP (PCWP_{swing}). The mPAP_{swing} and PCWP_{swing} did not differ (mean difference 0.9 mmHg, p=0.35). There was a strict relationship between RAP_{swing} and PCWP_{swing} (r²=0.9, p<0.001), with a slope of 1.02, and no significant difference between RAP_{swing} and PCWP_{swing} (mean difference 0.7 mmHg, p=0.28).

Discussion

Errors due to respiratory variation are a major concern when interpreting central vascular pressures during exercise, especially in patients with airflow limitation. The aim of this study was to evaluate the potential error introduced in mPAP by measuring at the end of expiration only and to evaluate potential correction methods. We found that: 1) a significant error is introduced when mPAP and PCWP are measured at the end of expiration in exercising COPD patients, due to increases in expiratory intrathoracic pressure; 2) averaging mPAP and PCWP over the respiratory cycle are better estimates of mPAP_{tm} and PCWP_{tm}; 3) the right atrial waveform can be used to correct for intrathoracic pressure in patients without right heart failure; 4) the transpulmonary pressure gradient (mPAP - PCWP) and, thus, PVR, is unaffected by swings in intrathoracic pressure. To better understand individual patients, pulmonary haemodynamics and

TABLE 3 Summary of Bland–Altman analyses performed

	Subjects n	r ²	Bias mmHg	95% limits of agreement mmHg
mPAP _{end-exp}	30	0.86	10.3 ± 5.9	0.5–20.3
mPAP _{averaged}	30	0.92	2.5 ± 4.4	-6.0–11.8
mPAPRAP _{nadir}	30	0.94	-3.6 ± 3.8	-11.2–3.9
mPAPRAP _{swing}	30	0.86	-9.3 ± 5.9	-19.8–2.1
PCWP _{end-exp}	22	0.69	9.9 ± 5.3	-0.5–20.3
PCWP _{averaged}	22	0.75	3.2 ± 4.4	-5.3–11.8
PCWPRAP _{nadir}	22	0.73	-2.0 ± 4.2	-2.0–4.2
PCWPRAP _{swing}	22	0.64	-6.3 ± 5.3	-16.6–4.0

Data are presented as mean ± SD, unless otherwise stated. mPAP: mean pulmonary artery pressure; mPAP_{end-exp}: mPAP measured at the end of expiration; mPAP_{averaged}: mPAP averaged over the respiratory cycle; mPAPRAP_{nadir}: mPAP corrected with the lowest point of right atrial pressure (RAP); mPAPRAP_{swing}: mPAP corrected with the swing in RAP; PCWP: pulmonary capillary wedge pressure; PCWP_{end-exp}: PCWP measured at end-expiration; PCWP_{averaged}: PCWP averaged over the respiratory cycle; PCWPRAP_{nadir}: PCWP corrected for the lowest point of RAP; PCWPRAP_{swing}: PCWP corrected for the swing in RAP.

mechanics should be reported (averaged over several cycles) at the end of expiration, the end of inspiration and averaged over the respiratory cycle raw and corrected for RAP_{nadir} in routine clinical practice.

Our findings support the use of mPAP and PCWP averaged over two or three respiratory cycles in order to acquire more accurate assessment of the mPAP_{tm} and PCWP_{tm} during exercise in COPD patients. The patients in the present study showed a wide range of expiratory *Poes* at exercise, reaching as much as 25 mmHg, which is consistent with previous studies on pulmonary mechanics [20, 21]. In these studies, as well as in the present study, the positive excursion of *Poes* during expiration is at least as large as the negative excursion during inspiration. It is, therefore, not surprising that mPAP averaged over the respiratory cycle is a more realistic measure of intravascular pressure. Although more accurate than mPAP_{end-exp}, mPAP_{averaged} was still a slight overestimation, which can be explained by the increased expiratory time. In COPD patients, expiratory time during exercise is longer than inspiratory time [22]. As a consequence, mPAP_{averaged} is more influenced by the “high” expiratory mPAP than by the “low” inspiratory mPAP.

The usefulness of the RAP waveform to estimate the pressure surrounding the heart was shown by TYBERG *et al.* [16]. This method assumes that pressure in the very compliant right atrium is predominantly dependent on pressure surrounding the heart (pericardial pressure or, in this case, intrathoracic pressure), rather than by right atrial volume. We showed that this method was useful during exercise in COPD patients, as long as RAP_{nadir} during expiration was used. This is explained by the fact that during the right atrial contraction, a dissociation between RAP and intrathoracic pressure is created. Therefore, only the pressure of an empty and relaxing right atrium is useful to estimate intrathoracic pressure. We found a small bias with mPAP_{tm} and PCWP_{tm} when RAP_{nadir} was used to correct expiratory mPAP and PCWP, with a very reasonable 95% limits of agreement. The small overcorrection in all patients is because it is

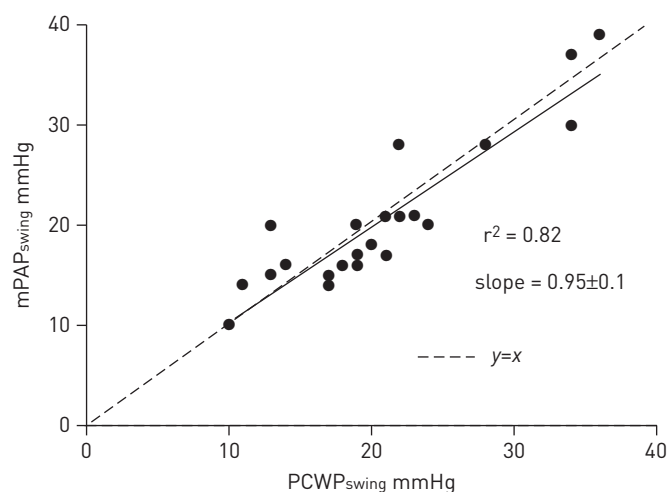


FIGURE 6 The relationship between the swing in mean pulmonary artery pressure (mPAP_{swing}) and the swing in pulmonary capillary wedge pressure (PCWP_{swing}).

unlikely that RAP_{nadir} can be lower than intrathoracic pressure at the same moment. This method may not be useful in patients with more pronounced right heart failure, as this causes RAP to rise, even during relaxation. Despite the average mPAP at rest in our cohort of COPD patients being higher than normally reported in COPD [15, 23], only two patients showed a RAP_{nadir} higher than intrathoracic pressure during exercise. We previously showed that some patients with COPD have impaired venous return due to the high expiratory intrathoracic pressure, which brings RAP_{nadir} even closer to intrathoracic pressure. Furthermore, we showed that RAP_{swing} to estimate expiratory intrathoracic pressure was not useful in our patients. As during inspiration, RAP can reach significant negative values, the total swing is larger than the positive excursion of intrathoracic pressure with expiration. Correction of mPAP with RAP_{swing} therefore leads to an underestimation of $mPAP_{tm}$.

Lastly, we showed that the swings in mPAP, PCWP and RAP were similar. This has several convenient implications. The consequence of an identical effect of intrathoracic pressure swing on mPAP and PCWP is that the difference between the two, the transpulmonary pressure gradient, is unaffected by the swing in intrathoracic pressure. This only holds when both the mPAP and PCWP are recorded at the same time point in the respiratory cycle. So, although individually, mPAP and PCWP are overestimations of intravascular pressure, the $mPAP_{end-exp}$ and $PCWP_{end-exp}$ combined lead to the correct transpulmonary pressure gradient or PVR (transpulmonary gradient/cardiac output). It underscores the importance of PVR as part of the suggested definition of exercise induced pulmonary arterial hypertension [2], as it prevents patients being diagnosed simply because of an increased intrathoracic pressure. The similar rise in mPAP and PCWP from inspiration to expiration is consistent with the high intrathoracic pressure *per se* not contributing to right ventricular afterload, which is in agreement with previous literature on the effect of positive end expiratory pressure on right ventricular afterload [24, 25].

The similar effect of intrathoracic pressure swings in RAP and PCWP also has a potential implication in evaluating exercise haemodynamics. The increase in PCWP calculated as a ratio to the increase in RAP, as previously suggested [26], is unaffected by intrathoracic pressure swings. This ratio might therefore be of potential help in the difficult situation of a high PCWP with exercise in the presence of intrathoracic pressure swings, a situation that is common in COPD patients. This would be especially helpful in diagnosing exercise-induced heart failure with preserved ejection fraction [3].

The patients in the present study had at least moderate airflow limitation, probably a worst-case scenario for the influence of intrathoracic pressure on central pressure measurements. We can only speculate to what extent our findings can be extrapolated to patients with less severe airflow limitation or the normal elderly population. The positive expiratory intrathoracic pressure in COPD is mainly due to the use of expiratory muscles, which is not well related to the airflow limitation, and the pattern of expiratory muscle recruitment differs between patients [27]. In the healthy population, the use of expiratory muscles can lead to substantial positive intrathoracic pressure as well, albeit only at maximal exercise [28]. Pulmonary vascular pressure, therefore, should be averaged over two to three respiratory cycles, not only in COPD [7, 8, 29], but also healthy subjects [11–13]. Whether $mPAP_{averaged}$ is a more accurate estimate of the intravascular pressure at maximal exercise in this population remains unknown, and depends on the amplitude and the length of the inspiratory and expiratory excursions in intrathoracic pressure. What is clear is that respiratory variation in central haemodynamic pressures during maximal exercise is not only present in severe COPD.

Limitations of this study warrant discussion. The average mPAP at rest in our cohort of COPD patients is higher than normally reported in COPD due to a referral bias, as our hospital is a pulmonary hypertension centre. Therefore, no conclusion should be drawn with regards to the incidence and severity of pulmonary hypertension at rest or during exercise in COPD from this study. We felt it was justified to use mPAP and PCWP after subtracting P_{oes} as a gold standard, although small errors might be present in the measurement of P_{oes} . This was the only method in which intrathoracic pressure was taken into account when evaluating mPAP and PCWP, and therefore the best way to answer our question.

In conclusion, the present study shows that substantial errors are introduced in the interpretation of the absolute values of mPAP and PCWP during exercise in COPD when read only at the end of expiration. In order to acquire more accurate values, averaging over the respiratory cycle or correction with the estimated intrathoracic pressure from the RAP waveform should be performed. The transpulmonary gradient is unaffected by the respiratory swings when its components are measured at the same time point in the respiratory cycle.

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