DOI: 10.1002/pul2.12348

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

Pulmonary vascular pressure respiratory swings in COPD and ILD candidates for lung transplantation: Large but different

Juan C. Grignola[1,2] | **Alvaro Calabuig**[3] | **Pedro Trujillo**[2,4] | **Carles Bravo**[5,6] | **Fernando Azpiroz**[7,8,9] | **Manuel López Messeguer**[5,6] | **Enric Domingo**[3,10]

[1]Departmento de Fisiopatología, Hospital de Clínicas, Facultad de Medicina, Universidad de la República, Montevideo, Uruguay

[2]Unidad de Hipertensión Pulmonar, Hospital Maciel, Ministerio de Salud Pública, Montevideo, Uruguay

[3]Department of Cardiology, Hospital Universitari Vall d'Hebron, Barcelona, Spain

[4]Departamento de Cardiología, Centro Cardiovascular Universitario, Hospital de Clínicas, Facultad de Medicina, Universidad de la República, Montevideo, Uruguay

[5]Departament of Pneumology, Hospital Universitari Vall d'Hebron, Barcelona, Spain

[6]CIBER de EnfermedadesRespiratorias, Instituto de Salud Carlos III, Madrid, Spain

[7]Digestive System Research Unit, Vall d'Hebron University Hospital, Barcelona, Spain

[8]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (Ciberehd), Barcelona, Spain

Abstract

We analyzed the effect of respiratory swings on interpreting intravascular pulmonary vascular pressures (PVPs) in chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) candidates for lung transplantation (LTx) and the role of the alterations in pulmonary function tests on the dynamic respiratory variations. Twenty-eight consecutive patients were included. All patients underwent a complete hemodynamic study (right atrial, mean pulmonary arterial, and pulmonary arterial occlusion pressures [RAP, mPAP, and PAOP]-) and pulmonary function testing (force vital capacity [FVC], forced expiratory volume in the first second [FEV1], and residual volume [RV]). A subgroup of 10 patients underwent simultaneous esophageal pressure (PES). All hemodynamic parameters and PES were collected during apnea after an unforced expiration (ee) and during spontaneous breathing averaging five respiratory cycles (mrc). The respiratory swing (osc) was estimated as the difference between maximum–minimum values of pressures during the respiratory cycle. Intravascular RAPee, mPAPee, and PAOPee were higher than mrc values ($p < 0.05$), leading to 11% of pulmonary hypertension (PH) misdiagnosis and 37% of postcapillary PH misclassification. PAOPosc of COPD was higher than ILD patients and RAPosc ($p < 0.05$). Only PAOPosc correlated with FVC, FEV1, and RV ($p < 0.05$). ILD PESmrc was lower than COPD ($p < 0.05$), and it was associated with a significantly higher transmural than intravascular RAPmrc, mPAPmrc,

Abbreviations: CO, cardiac output; COPD, chronic obstructive pulmonary disease; ee, end-expiratory pressure (pressure during apnea after unforced expiration); FEV1, forced expiratory volume in the first second; FVC, functional vital capacity; ILD, interstitial lung disease; LTx, lung transplantation; mPAP, mean pulmonary arterial pressure; mrc, mean respiratory cycle pressure (pressure averaged across five respiratory cycles); osc, respiratory swing pressure (difference between maximum–minimum pressure values during the respiratory cycle); PAOP, pulmonary arterial occlusion pressure; PES, esophageal pressure; PVP, pulmonary vascular pressure; RAP, right atrial pressure; RV, residual volume; tm, transmural pressure (difference between intravascular – PES values).

Juan C. Grignola and Alvaro Calabuig contributed equally to this study.

[9]Departmento de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain

[10]Departamento de Fisiología, Facultad de Medicina, Universitat Autonoma de Barcelona, Barcelona, Spain

Correspondence
Juan C. Grignola, Departamento de Fisiopatología, Hospital de Clínicas, Facultad de Medicina, Universidad de la República, Avda. Italia 2870, PC 11600 Montevideo, Uruguay.
Email: jgrig@fmed.edu.uy

Funding information
None

and PAOPmrc. PESmrc was significantly correlated with FVC. Transmural mPAPmrc and PAOPmrc readings determined around 20% of reclassification of the patients compared to ee measurements. Candidates for LTx showed large respiratory swings in PVP, which were correlated with pulmonary function alterations. mrc PVP would be more closely approximated to the true transmural PVP leading to PH reclassification. Adjusting PVP for PES should be considered in COPD and ILD candidates of LTx with severe alterations in pulmonary functional tests and suspicion of a PESmrc far from 0. PES respiratory swings could be different in ILD to COPD patients.

KEYWORDS
chronic lung disease, esophageal pressure, lung transplantation, pulmonary vascular pressure respiratory swing, transmural pulmonary vascular pressure

INTRODUCTION

Pulmonary vascular pressures (PVPs) are measured relative to the atmospheric pressure. However, the heart and pulmonary circulation are within the chest and are influenced by the transmission of the intrathoracic pressure generated by opposing elastic recoil of the lungs and chest wall. Intravascular PVP measured at end-expiration assumes that intrathoracic pressure is approximately equal to atmospheric pressure at functional residual capacity and, thus, measured pressures reflect the transmural PVPs.[1] Large respiratory variations of PVP are critical when interpreting pulmonary intravascular pressures in different clinical scenarios. End-expiratory intrathoracic pressure can be significantly greater than atmospheric pressure, and intravascular PVPs can overestimate true transmural ones. Mean intravascular PVPs across the respiratory cycle were proposed to overcome the impact of large respiratory swings on PVPs instead of using end-expiratory measurements.[1–3] However, this is correct if the time-averaged intrathoracic pressure is around 0.

Clinical conditions associated with increased intrathoracic pressure (obesity, airway obstruction and/or dynamic hyperinflation, chest wall deformities) may exaggerate the uncertainty of the PVP values with a pronounced respiratory swing of them.[1–4] Chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) patients are characterized by a combination of derangements in respiratory system mechanics (airway obstruction, dynamic hyperinflation, and low lung compliance) that could be associated with large but different dynamic respirophasic variations of intravascular PVPs.

The study analyzed the effect of the respiratory swing on the interpretation of pulmonary intravascular pressures in COPD and ILD candidates for lung transplantation (LTx) undergoing right heart catheterization (RHC) and the role of the alterations in pulmonary function tests on the dynamic respiratory variations. We hypothesized that pulmonary intravascular pressures could not represent accurate transmural PVPs in COPD and ILD candidates for LTx, leading to pulmonary hypertension (PH) misdiagnosis and misclassification.

METHODS

COPD and ILD adult consecutive candidates for LTx who undergo RHC for suspected PH were included between November 2016 and October 2017. The study was conducted with the approval of the Hospital Universitari Vall d'Hebron Institutional Review Board. Informed consent was obtained from all patients.

Data analysis

RHC was done at rest, in the supine position, after 12 h of fasting and breathing room air. A 7.5-Fr pulmonary artery catheter (Edwards Lifesciences) was advanced to the pulmonary artery from a brachial or femoral vein, and a 5 F end-hole catheter was inserted into a radial artery. Catheters were connected to fluid-filled transducers and zeroed at the atmospheric pressure. The zero-reference level for recording was at the mid-thoracic level.[2] We obtained intravascular right atrial pressure (RAP), systolic, diastolic, and mean pulmonary arterial pressure (mPAP), and pulmonary arterial occlusion pressure (PAOP). The following conditions were taken to ensure the accuracy of the PAOP measurement: the correct PAOP position (confirmed via appearance on

fluoroscopy), the characteristic "a" and "v" waveforms, and the saturation of 94% or greater. Cardiac output (CO) was measured by the thermodilution method (average three determinations that fell within <10% difference) and indexed to body surface area to calculate the cardiac index. Pulmonary vascular resistance (PVR) was calculated as (mPAP − PAOP)/CO). PH diagnosis and classification were based on the 2022 European Society of Cardiology/European Respiratory Society guidelines.[3]

A subgroup of patients underwent simultaneous RHC and esophageal pressure (PES) to assess the transmural PVPs. We obtained PES as a surrogate of intrathoracic pressure.[5] A manometric catheter (Latitude® Esophageal Motility Catheter; Unisensor AG; model GIM600E) (2.7 mm outside diameter) with four microballoons at 5 cm intervals was introduced through the nose and placed with two recording sites above (esophageal) and two below (intragastric) the gastroesophageal junction. The microballoons were filled with air and were connected to calibrated transducers (manometric calibration system, GIM6100/GIM6130), avoiding the need for the occlusion test.[6] PES was continuously monitored.

All hemodynamic parameters and PES were collected in two conditions: during apnea after an unforced expiration (ee); and spontaneous normal breathing averaging five respiratory cycles (mrc) (Figure 1). Transmural PVPs were assessed in both conditions. The respiratory swing was estimated as the difference between maximum–minimum RAP, PAOP, mPAP, and PES values during the respiratory cycle (osc).

Pulmonary function testing consisted of spirometry (functional vital capacity [FVC], forced expiratory volume in the first second [FEV1], and residual volume [RV]) and single-breath CO diffusion capacity (DLCO). Pulmonary function variables were expressed as the percent predicted, indicated by % following the variable.

Statistical analysis

Continuous data were expressed as the mean ± standard error of the mean. We determined the normal distribution of the data by the Shapiro–Wilk test. Comparison of ILD and COPD subjects, end-expiratory and mean respiratory cycle, and intravascular and transmural were performed with independent sample *t* tests and paired *t* tests as appropriate. The strength and direction of the association between continuous variables were measured with Spearman's rank correlation coefficient (r_S). A Spearman coefficient value of >0.7 was considered strong, a value of 0.4–0.69 was considered moderate, and a value of <0.4 was considered poor.[7] A p value (two-tailed) of <0.05 was considered significant. Statistical analyses were performed with SPSS (Version 21.0 for Windows; SPSS Inc.).

RESULTS

Twenty-eight consecutive patients were included, 14 COPD and 14 ILD. Table 1 shows patient demographics, pulmonary functional tests, and intravascular hemodynamic data. COPD showed higher airflow limitation and hyperinflation of the lungs than in ILD subjects ($p < 0.05$).

End-expiratory, mean respiratory cycle, and respiratory swing of intravascular pressures

Intravascular RAPee, mPAPee, and PAOPee were higher than mrc values ($p < 0.05$) (Table 1 and Figure 2). Nineteen subjects (68%) showed mPAPee of >20 mmHg (17 with PVR > 2 Wu, and 2 with PVR ≤2 Wu—unclassifiable), and seven corresponded to postcapillary PH (37%). Seventeen patients (61%) showed mPAPmrc of >20 mmHg (all with RVP > 2 Wu), and none were postcapillary PH (0%). PAOPee and mPAPee correlated with PAOPmrc (r_S =0.81; $p = 0.0001$) and mPAPmrc ($r_S = 0.87$; $p = 0.0001$), respectively. The mean PAOP and mPAP difference between end-expiratory and mean respiratory cycle values was 3.4 ± 0.6 and 1.8 ± 0.6 mmHg, respectively, which were similar to the corresponding y-intercept of the correlations between ee and mrc values of PAOP and RAP (3.45 and 1.5 mmHg, respectively).

We obtained large respiratory swings of both, PAOP and RAP. While RAPosc was similar in both groups, PAOP swings of COPD subjects were higher than those of ILD patients ($p < 0.05$). COPD subjects showed less pronounced RAP respiratory swing compared with PAOPosc ($p < 0.05$) (Table 1).

Esophageal and transmural pressures

PES was simultaneously monitored in 10 (36%) patients (5/14 COPD and 5/14 ILD). Table 2 shows patients' demographics, pulmonary functional tests, intravascular hemodynamics, and PES data.

PESee values were positive, similar in COPD and ILD, and significantly higher than PESmrc. However, ILD PESmrc was lower ($p < 0.05$) than COPD at the expense of a higher negative inspiratory swing in PES

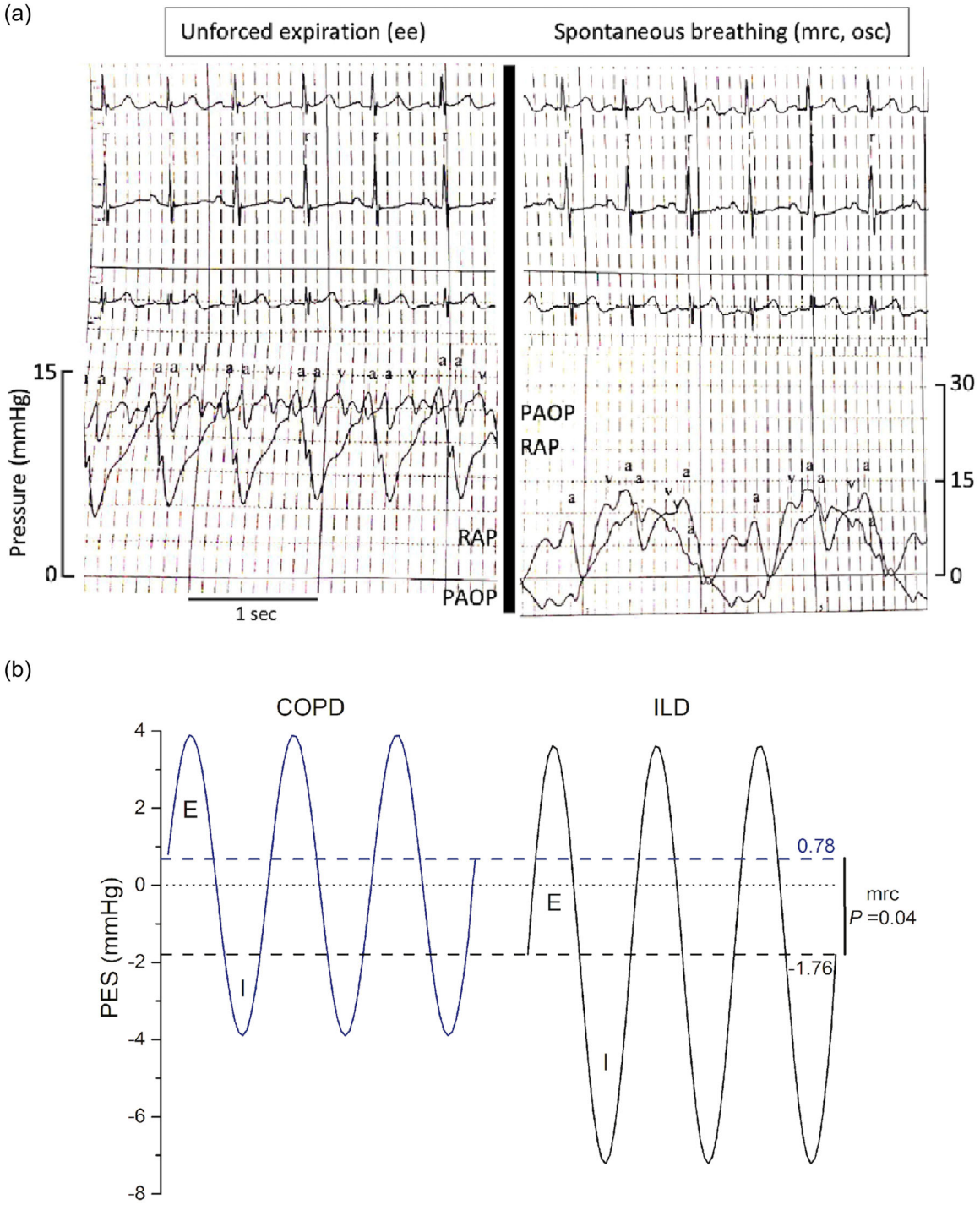

FIGURE 1 (a) Representative recordings of right atrial (RAP) and pulmonary arterial occlusion (PAOP) pressures during an ILD patient's unforced expiration and spontaneous breathing. (b) Graphical representation of mean values of esophageal pressure (PES) in COPD and ILD patients (I: mean inspiratory PES; E: mean expiratory PES). COPD, chronic obstructive pulmonary disease; ee, end-expiratory pressure; ILD, interstitial lung disease; mrc, mean respiratory cycle; osc, respiratory swing pressure.

(Table 2). PESosc was similar to PAOP respiratory swing and higher than RAPosc ($p < 0.05$). However, it was not correlated with either of the two.

ILD subjects showed significantly higher transmural than intravascular mPAPmrc (26.0 ± 5.2 vs. 24.2 ± 5.4 mmHg), RAPmrc (4.6 ± 1.6 vs. 2.8 ± 1.2 mmHg), and PAOPmrc (7.8 ± 1.6 vs. 6.0 ± 1.8 mmHg). By contrast, transmural than intravascular mPAPmrc and PAOPmrc in COPD subjects did not show significant differences (Figure 3). One patient (10%) had to be reclassified to PH.

TABLE 1 Patient demographics, pulmonary function tests, and intravascular hemodynamic data of the whole cohort.

	All ($n = 28$)	ILD ($n = 14$)	COPD ($n = 14$)
Age, years	60 ± 1	62 ± 2	59 ± 2
Sex, Female/Male	10/18	5/9	5/9
BMI, kg/m^2	24.9 ± 0.7	24.7 ± 0.9	25.1 ± 1.2
BSA, m^2	1.76 ± 0.05	1.71 ± 0.05	1.8 ± 0.07
Pulmonary function tests			
FVC, % predicted	48 ± 2	48 ± 3	48 ± 3
FEV1, % predicted	41 ± 3	54 ± 4	29 ± 3*
DLCO, % predicted	29 ± 3	31 ± 4	28 ± 4
RV, % predicted	133 ± 16	52 ± 2	215 ± 12*
Hemodynamics			
CI, L/min/m^2	2.6 ± 0.1	2.9 ± 0.2	2.4 ± 0.1
SVI, mL/m^2	35 ± 2	38 ± 3	32 ± 2
PVR, Wu	3.6 ± 0.5	4.2 ± 0.9	3.0 ± 0.4
mPAPmrc, mmHg	24 ± 2	26 ± 2	22 ± 2
PAOPmrc, mmHg	8.1 ± 0.7	7.2 ± 1.2	9.1 ± 0.6
RAPmrc, mmHg	5.9 ± 0.8	5.2 ± 1.1	6.6 ± 1.2
mPAPee, mmHg	26 ± 2#	27 ± 2	24 ± 2#
PAOPee, mmHg	11.6 ± 0.9#	11.0 ± 1.5#	12.0 ± 1.1#
RAPee, mmHg	7.9 ± 0.8#	6.9 ± 1.0#	8.9 ± 1.2#
PAOPosc, mmHg	12.8 ± 1.0°	10.1 ± 1.0	15.4 ± 1.6*°
RAPosc, mmHg	9.9 ± 0.9	9.6 ± 1.3	10.1 ± 1.4

Note: Mean ± SEM.

Abbreviations: BMI, body mass index; BSA, body surface area; CI, cardiac index; COPD, chronic obstructive pulmonary disease; DLCO, CO diffusing capacity; ee, end-expiratory; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; ILD, interstitial lung disease; mPAP, mean pulmonary arterial pressure; mrc, mean respiratory cycle; osc, respiratory swing; PAOP, pulmonary arterial occlusion pressure; PES, esophageal pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RV, residual volume. SVI, stroke volume index.

*$p < 0.05$ ILD versus COPD.

#$p < 0.05$ ee versus mrc.

°$p < 0.05$ PAOPosc versus RAPosc in each group.

Transmural PAOP and mPAP at end-expiration (PAOPtm-ee and mPAPtm-ee) and over the respiratory cycle (PAOPtm-mrc and mPAPtm-mrc) did not show significant differences and were correlated ($r_S = 0.71$; $p = 0.02$ and $r_S = 0.84$; $p = 0.002$, respectively). However, 20% was misdiagnosed (3 mPAPtm-ee to 5 mPAPtm-mrc >20 mmHg patients) and misclassified (2 PAOPtm-ee to 0 PAOPtm-mrc > 15 mmHg patients).

Impact of lung functional alterations on PVP swings and esophageal pressures

PAOP respiratory swings were significantly correlated with all pulmonary function variables (Figure 4). On the contrary, only PESmrc (intrathoracic pressure "offset") was significantly correlated with FVC (Figure 5).

Table 3 shows the values of the PESosc and PESmrc according to the median of the lung function variables. PESmrc was significantly different depending on the value of FVC and RV above and below the median.

DISCUSSION

We confirmed the presence of large PAOP and RAP respiratory swings at rest in a cohort of COPD and ILD candidates for LTx. We noted that the end-expiration reading of intravascular mPAP, PAOP, and RAP overestimated the averaging over respiratory cycle values,

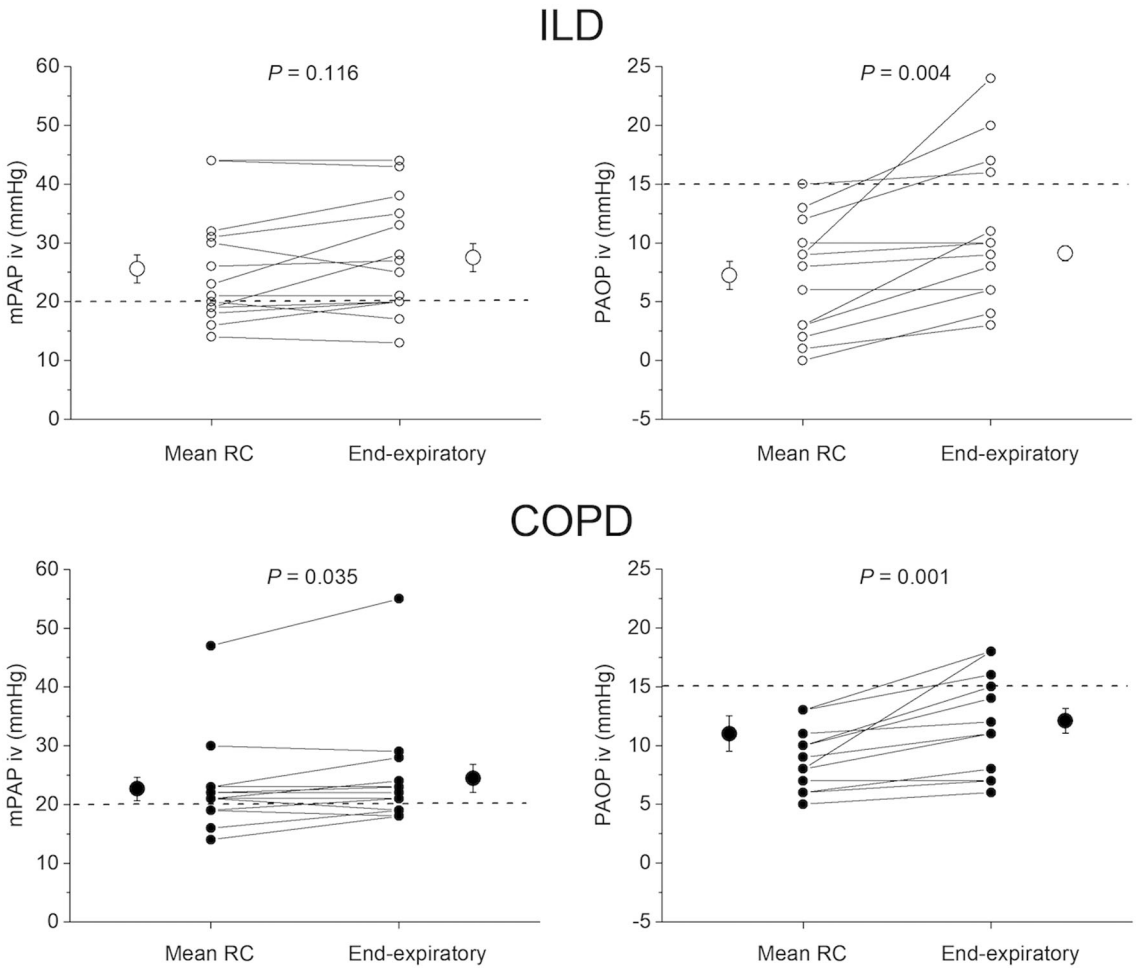

FIGURE 2 Intravascular end-expiratory and mean respiratory cycle (mean RC) of mean pulmonary arterial pressure (mPAP) and pulmonary arterial occlusion pressure (PAOP) in COPD and ILD patients. COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease.

leading to about 11% of patients no longer having PH (misdiagnosis) and a 37% decrease in patients with postcapillary PH (misclassification). Accordingly, Jawad et al. reported that the diagnosis of postcapillary PH decreased from 74% to 37% in overweight patients.[8] More recently, Khirfan et al. reclassified about 20% of obese patients, reducing the percentage of postcapillary PH from 60% to 47%.[4]

Intrathoracic pressure, as estimated by pleural pressure measured by PES, is approximately −1 to 2 mmHg at end-expiration and further decreases by 2 mmHg during normal inspiration, leading to a small respiratory swing in healthy resting subjects.[2] Both patient groups presented larger PES respiratory swings (~10 mmHg) but lower PES respiratory swings than obese patients (~15 and 20 mmHg in the sitting and supine positions, respectively).[4] Previously published data reported similar absolute values of COPD PES respiratory swings.[9,10] The lowest values of RAP respiratory swings suggest that changes in intrathoracic pressure during the respiratory cycle are not fully transmitted to the right heart. Besides, the absence of correlations of the respiratory swings between PAOP, RAP, and PES illustrates the complexity of transmitting intrathoracic pressure to the PVPs in these severe pathological pulmonary conditions. Although PAOP respiratory swings were similar to PESosc and significantly higher than RAP respiratory swings, they were the only ones correlated with FVC, FEV1, and RV.

It is essential to differentiate the respirophasic changes of intrathoracic pressure (PESosc) from the time-averaged value over the respiratory cycle (PESmrc). Whenever negative inspiratory and positive expiratory intrathoracic pressures cancel each other out (time-averaged PES-PESmrc- ~0 mmHg), averaging intravascular PVP tracings throughout the respiratory cycle would be relatively accurate in assessing true transmural vascular pressure beyond the value of the respiratory changes. Our COPD

TABLE 2 Patient demographics, pulmonary function tests, intravascular hemodynamic, and esophageal pressure data.

	All ($n = 10$)	ILD ($n = 5$)	COPD ($n = 5$)
Age, years	63 ± 2	64 ± 3	59 ± 2
Sex, Female/Male°	2/8	1/4	1/4
BMI, kg/m^2	25 ± 1	26 ± 2	24 ± 2
BSA, m^2	1.78 ± 0.07	1.77 ± 0.08	1.79 ± 0.11
Pulmonary function tests			
FVC, % predicted	52 ± 3	46 ± 2	59 ± 5*
FEV1, % predicted	39 ± 4	48 ± 3	30 ± 5*
DLCO, % predicted	24 ± 4	20 ± 6	30 ± 4
RV, % predicted	145 ± 33	52 ± 3	238 ± 23*
Hemodynamics			
CI, L/min/m^2	2.6 ± 0.2	2.8 ± 0.4	2.3 ± 0.1
SVI, mL/m^2	36 ± 2	37 ± 3	34 ± 3
PVR, Wu	3.3 ± 0.9	4.2 ± 1.8	2.5 ± 0.5
mPAPmrc, mmHg	22 ± 3	24 ± 5	20 ± 2
PAOPmrc, mmHg	7.9 ± 1.2	6.0 ± 1.8	9.8 ± 1.1*
RAPmrc, mmHg	5.5 ± 1.2	2.8 ± 1.2	8.2 ± 1.2*
mPAPee, mmHg	24 ± 3#	26 ± 5	22 ± 2
PAOPee, mmHg	11.9 ± 1.9#	11.2 ± 3.6	12.6 ± 1.8#
RAPee, mmHg	8.3 ± 1.3#	5.6 ± 1.8#	11.0 ± 0.9#
PAOPosc, mmHg	10.3 ± 1.2°	9.0 ± 1.6°	11.6 ± 1.8°
RAPosc, mmHg	6.2 ± 1.5	5.6 ± 2.1	6.8 ± 2.4
Esophageal pressures			
PESmrc, mmHg	−0.49 ± 0.7	−1.76 ± 0.8	0.78 ± 0.7*
PESee, mmHg	3.3 ± 0.6#	3.6 ± 0.9#	3.0 ± 1.0#
PESosc, mmHg	9.6 ± 0.9°	10.9 ± 1.7°	8.3 ± 0.6
PESI, mmHg	−5.8 ± 1.1	−7.4 ± 1.8	−4.3 ± 0.9
PESE, mmHg	3.8 ± 0.3	3.6 ± 0.1	4.0 ± 0.6

Note: Mean ± SEM.

Abbreviations: BMI, body mass index; BSA, body surface area; CI, cardiac index; COPD, chronic obstructive pulmonary disease; DLCO, CO diffusing capacity; E, maximum expiratory pressure; ee, end-expiratory; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; I, maximum inspiratory pressure; ILD, interstitial lung disease; mPAP, mean pulmonary arterial pressure; mrc, mean respiratory cycle; osc, respiratory swing; PAOP, pulmonary arterial occlusion pressure; PES, esophageal pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RV, residual volume. SVI, stroke volume index.

*$p < 0.05$ ILD versus COPD.

#$p < 0.05$ ee versus mrc.

°$p < 0.05$ swing pressure versus RAPosc in each group.

subjects presented a time-averaged PES that was slightly positive. Therefore, as Rice et al. have already proposed, pleural pressure correction for PVP would not be needed.[11] Accordingly, intravascular did not differ from tm pulmonary pressures over the respiratory cycle (Figure 3). More recently, Boerrigter et al. showed that both mPAP and PAOP averaged over the respiratory cycle are representative measures of intravascular pressure in a cohort of less ill COPD patients at rest and exercise.[10] By contrast, ILD patients' large respiratory swing occurs at the expense of the inspiratory phase, driving a negative time-averaged PES. Hence, intravascular PVP underestimated tm

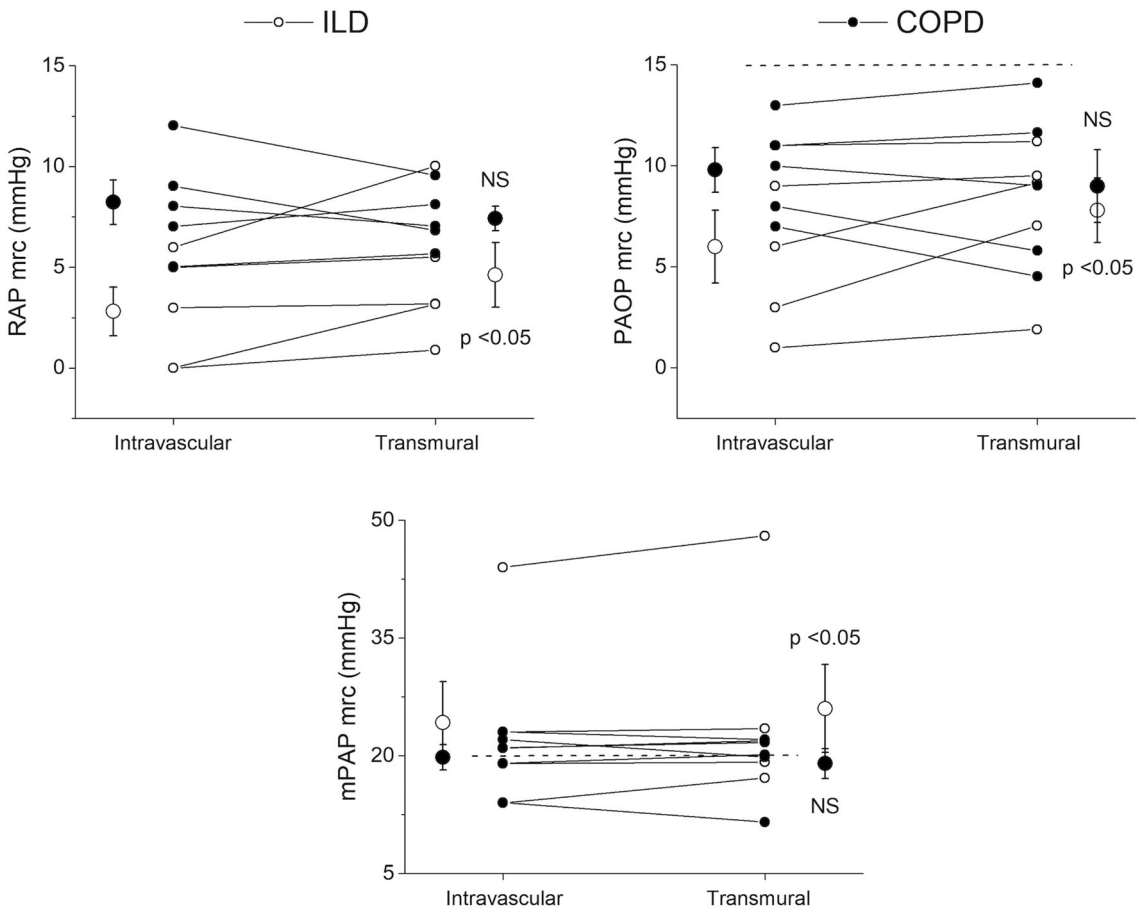

FIGURE 3 Intravascular and transmural mean respiratory cycle (mrc) of right atrial pressure (RAP), pulmonary arterial occlusion pressure (PAOP), and mean pulmonary arterial pressure (mPAP) in COPD and ILD patients. COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; NS, not significant.

pressure values. Therefore, tm PVPs were significantly higher than intravascular pressure over the respiratory cycle (Figure 3). This fact could partially explain the higher PA stiffness in ILD subjects and could associated with worse survival.[12–14]

In the subgroup of patients with PES estimation, tm mPAP, and PAOP averaged across the respiratory cycle determined around 20% of reclassification of the patients, both in diagnosis (30%–50% PH) and in the phenotype (20% to 0% postcapillary PH). Accordingly, in obese patients, the correction of PVPs respiratory changes by concomitant measurement of PES decreased the percentage of patients with PH (from 100% to 77%) and with postcapillary PH (from 47% to only 8%).[4]

It is well known that in COPD patients, respiratory pressure swings increase proportionally to increased airflow obstruction, further amplified by dynamic hyperinflation and by active expiratory muscle contraction during exercise.[1,3,4,6,7] This would explain the significant correlations between PAOP respiratory swings and FVC, FEV1, and RV. On the contrary, it is striking that the PESosc did not correlate with the different pulmonary function variables. A more rigid lung could determine an increased inspiratory effort in ILD patients, resulting in a larger inspiratory negative PES swing, which could be proportional to the predicted FVC. Therefore, the lower the % predicted FVC the lower PESmrc ($p < 0.05$). Besides, PESmrc showed a significantly different behavior according to the median of the lung function variables. All patients with FVC values ≤50% of predicted value and RV values ≤105% of predicted value showed subatmospheric and significantly lower PESmrc than patients with FVC > 50 and RV > 105% of predicted value.

Finally, in agreement with Boerrigter et al., we confirmed that pulse PAP decreases during expiration in spontaneously breathing COPD patients. Pulse PAP decreased at about 17% ($p < 0.05$) during expiration associated with a RAPtm of 6.0 ± 0.9 mmHg.[15]

Study limitations. Our cohort is small, but it highlights the importance of correctly interpreting the measurement of PVPs in the presence of large respiratory pressure swings in a new group of patients.

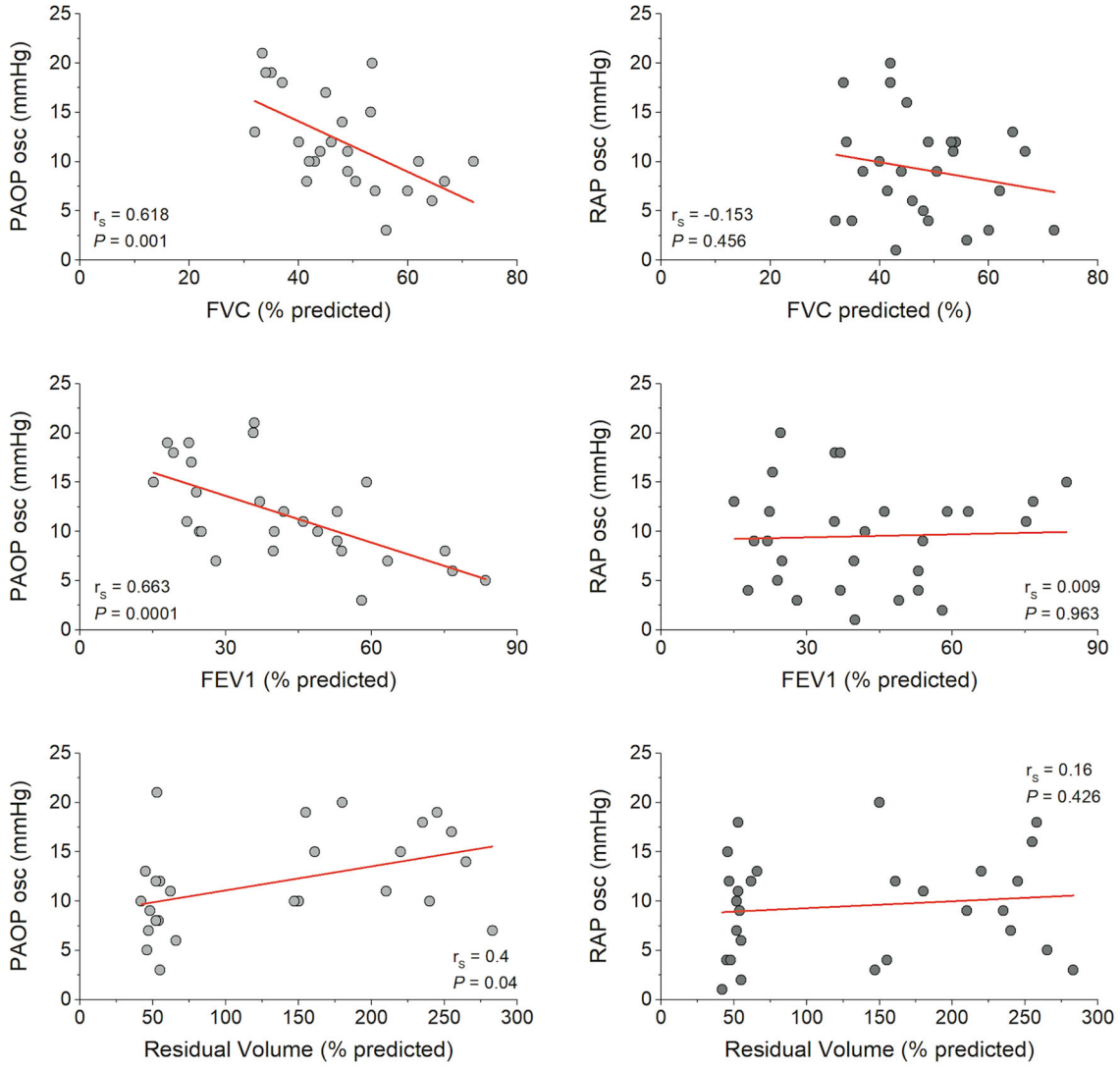

FIGURE 4 Correlation between respiratory changes of PAOP (PAOPosc) and RAP (RAPosc) and percentage of predicted forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and residual volume.

The effect of emphysema on the respiratory-phasic variations of PVP was not estimated.[16] We used PES as a surrogate for the measurement of intrathoracic pressure. The degree to which PES reflects the regional intrathoracic pressure is uncertain. Although respiratory swings of PVP almost exclusively reflect PES changes, we cannot discard the associated changes in venous return and left ventricular afterload affecting mPAP.[17] Although PES values in a supine obese subject are higher than in a sitting position, the difference in lean patients has less relevance.[4] The 10 patients chosen to measure PES were not randomized and corresponded to the last ones recruited, which could lead to selection bias. They were used as a "proof-of-concept" for analyzing true tm PVPs. The predicted FVC was more preserved in the COPD patients with PES than without PES ($57 \pm 5\%$ vs. $43 \pm 3\%$, $p < 0.05$), and RAPosc of the ILD patients with PES was higher than without PES ($11.7 \pm 1.3\%$ vs. 5.8 ± 2.2 mmHg, $p < 0.05$). Although digital esophageal pressure corrections are ideal for both the respiratory cycle variations and its 'offset', obtaining the end-expiratory and mean respiratory cycle values of PES would help adjust the PVPs. Our findings suggest that using tm PVPs over the respiratory cycle instead of end-expiratory values may reflect true distending vascular pressure more accurately.[8] Finally, we cannot discard the presence of "occult" postcapillary PH by using some dynamic maneuver protocols during RHC.

In summary, we add another clinical group where the measurement and interpretation of PVPs can lead to errors because of large respiratory cycle variations. COPD

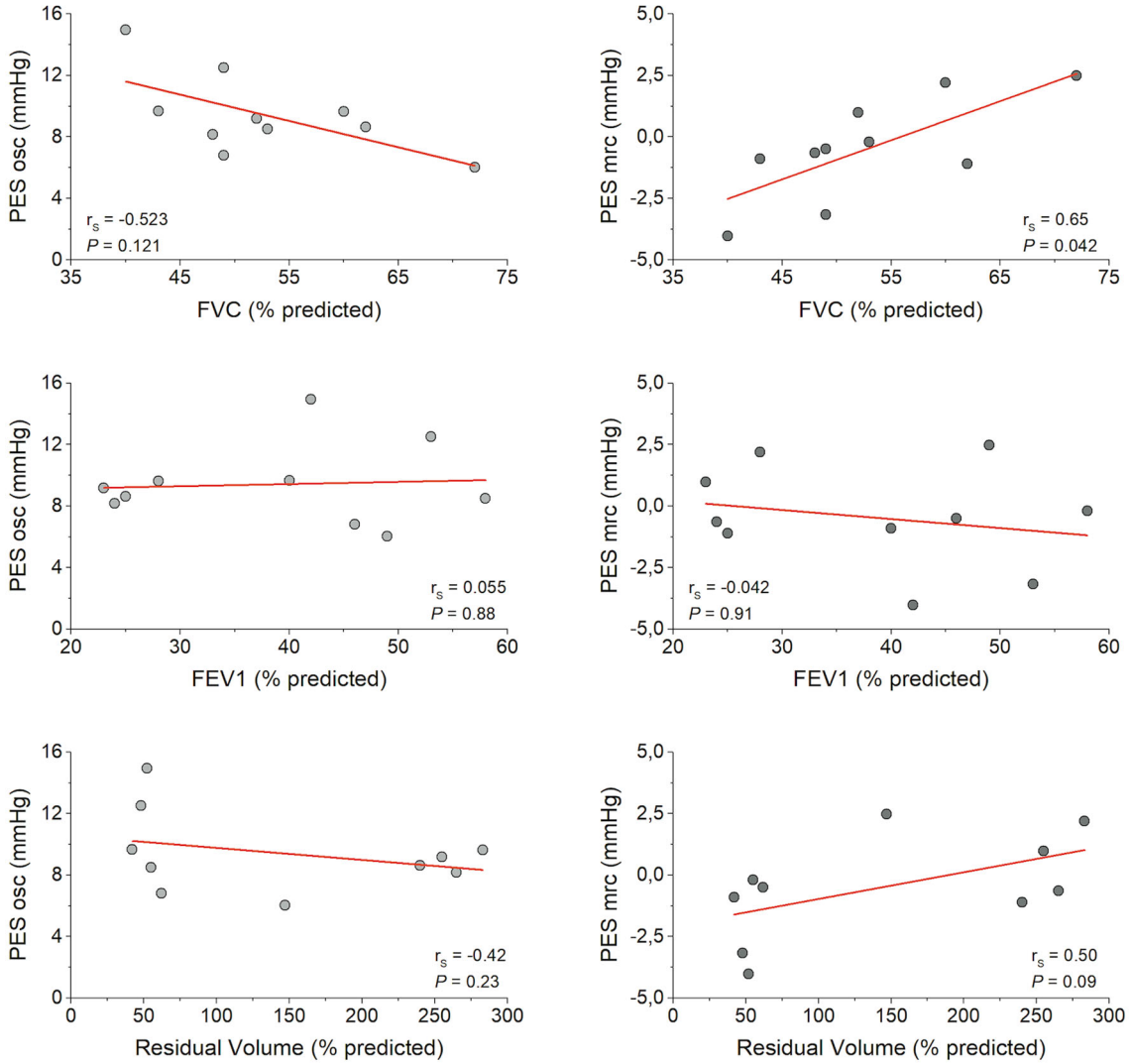

FIGURE 5 Correlation between the mean respiratory cycle PES (PESmrc) and the respiratory PES swing (PESosc) and the percentage of predicted forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and residual volume.

TABLE 3 Esophageal pressure according to the median values of the pulmonary function variables.

	FVC (% predicted)		FEV1 (% predicted)		RV (% predicted)	
	≤50	>50	≤41	>41	≤105	>105
PESmrc, mmHg	−1.85 ± 0.7	0.87 ± 0.7*	0.11 ± 0.6	−1.1 ± 1.1	−1.76 ± 0.8	0.78 ± 0.7*
PESosc, mmHg	10.4 ± 1.5	8.4 ± 0.6	9.1 ± 0.3	9.8 ± 1.7	10.5 ± 1.4	8.3 ± 0.6

Note: Mean ± SEM.

Abbreviations: FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; mrc, mean respiratory cycle; osc, respiratory swing; PES, esophageal pressure; RV, residual volume.

*$p < 0.05$ ≤ median value versus > median value of each pulmonary function variable.

and ILD candidates for LTx showed large respiratory swings in PVP (especially PAOP) correlated with pulmonary function alterations. End-expiratory reading of PVPs spuriously increases mPAP, PAOP, and RAP estimations, leading to PH reclassification. Averaging PVPs throughout respiratory cycles would be more closely approximated to the true tm PVPs. Adjusting PVPs for PES should be considered in COPD and ILD candidates of LTx with severe alterations in pulmonary functional tests and suspicion of a PESmrc far from 0 to avoid PH misdiagnosis and misclassification. PES respiratory swings could be different in ILD to COPD patients.

AUTHOR CONTRIBUTIONS

All authors fulfill the criteria for authorship. Juan C. Grignola and Alvaro Calabuig participated in the study's design, analyzed the data, and wrote the manuscript. Pedro Trujillo analyzed the data and wrote the manuscript. Carles Bravo and Manuel López Messeguer were responsible for patient selection and clinical follow-up. Fernando Azpiroz conducted the esophageal measurements. Enric Domingo conceived and conducted the study, participated in its design, analyzed the data, and wrote the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

Preliminary data of this study were presented in part at the European Society of Cardiology Congress in Barcelona, Spain. *Eur Heart J.* 2022; 43(Suppl_2):1878. doi:10.1093/eurheartj/ehac544.1878. Juan C Grignola is a member of Programa para el Desarrollo de las Ciencias Básicas (PEDECIBA) and Sistema Nacional de Investigadores-Agencia Nacional de Investigación e Innovación (SNI-ANII). The authors have no funding to report.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

We confirm that this study has approval from the research ethics committee, institutional review board, and informed consent from all study participants.

ORCID

Juan C. Grignola https://orcid.org/0000-0003-1748-7217

REFERENCES

1. LeVarge BL, Pomerantsev E, Channick RN. Reliance on end-expiratory wedge pressure leads to misclassification of pulmonary hypertension. Eur Respir J. 2014;44:425–34.
2. Kovacs G, Avian A, Pienn M, Naeije R, Olschewski H. Reading pulmonary vascular pressure tracings. how to handle the problems of zero leveling and respiratory swings. Am J Respir Crit Care Med. 2014;190:252–7.
3. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, Ferreira DS, Ghofrani HA, Giannakoulas G, Kiely DG, Mayer E, Meszaros G, Nagavci B, Olsson KM, Pepke-Zaba J, Quint JK, Rådegran G, Simonneau G, Sitbon O, Tonia T, Toshner M, Vachiery JL, Vonk Noordegraaf A, Delcroix M, Rosenkranz S. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Eur Heart J. 2022;43(43):3618–731.
4. Khirfan G, Melillo CA, Al Abdi S, Lane JE, Dweik RA, Chatburn RL, Hatipoğlu U, Tonelli AR. Impact of esophageal pressure measurement on pulmonary hypertension diagnosis in patients with obesity. Chest. 2022;162:684–92.
5. Cherniack RM, Farhi LE, Armstrong BW, Proctor DF. A comparison of esophageal and intrapleural pressure in man. J Appl Physiol. 1955;8:203–11.
6. Pham T, Telias I, Beitler JR. Esophageal manometry. Respir Care. 2020;65:772–92.
7. Schober P, Boer C, Schwarte LA. Correlation coefficients: appropriate use and interpretation. Anesth Analg. 2018;126:1763–8.
8. Jawad A, Tonelli AR, Chatburn RL, Wang X, Hatipoğlu U. Impact of intrathoracic pressure in the assessment of pulmonary hypertension in overweight patients. Ann Am Thorac Soc. 2017;14:1861–3.
9. Naeije R, Boerrigter BG. Pulmonary hypertension at exercise in COPD: does it matter? Eur Respir J. 2013;41:1002–4.
10. Boerrigter BG, Waxman AB, Westerhof N, Vonk-Noordegraaf A, Systrom DM. Measuring central pulmonary pressures during exercise in COPD: how to cope with respiratory effects. Eur Respir J. 2014;43:1316–25.
11. Rice DL, Awe RJ, Gaasch WH, Alexander JK, Jenkins DE. Wedge pressure measurement in obstructive pulmonary disease. Chest. 1974;66:628–32.
12. Domingo E, Grignola JC, Aguilar R, Messeguer ML, Roman A. Pulmonary arterial wall disease in COPD and interstitial lung diseases candidates for lung transplantation. Respir Res. 2017;18:85.
13. Hayes D, Black SM, Tobias JD, Kirkby S, Mansour HM, Whitson BA. Influence of pulmonary hypertension on patients with idiopathic pulmonary fibrosis awaiting lung transplantation. Ann Thorac Surg. 2016;101:246–52.
14. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest. 2006;129:746–52.
15. Boerrigter B, Trip P, Bogaard HJ, Groepenhoff H, Oosterveer F, Westerhof N, Vonk Noordegraaf A. Right atrial pressure affects the interaction between lung mechanics and right ventricular function in spontaneously breathing COPD patients. PloS one. 2012;7:e30208.
16. Scharf SM, Iqbal M, Keller C, Criner G, Lee S, Fessler HE. Hemodynamic characterization of patients with severe emphysema. Am J Respir Crit Care Med. 2002;166:314–22.
17. Kovacs G, Naeije R, Olschewski H. Reply: reading of pulmonary artery pressure tracings: the best compromise of accuracy and clinical pertinence. Am J Respir Crit Care Med. 2014;190:1198–9.

How to cite this article: Grignola JC, Calabuig A, Trujillo P, Bravo C, Azpiroz F, Messeguer ML, Domingo E. Pulmonary vascular pressure respiratory swings in COPD and ILD candidates for lung transplantation: Large but different. Pulm Circ. 2024;14:e12348. https://doi.org/10.1002/pul2.12348