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ORIGINAL RESEARCH

Relationships between respiratory and airway resistances and activity-related dyspnea in patients with chronic obstructive pulmonary disease

Bruno Mahut[1,2]
Aurore Caumont-Prim[3,4]
Laurent Plantier[1,5]
Karine Gillet-Juvin[1,6]
Etienne Callens[1]
Olivier Sanchez[5,6]
Brigitte Chevalier-Bidaud[3]
Plamen Bokov[1]
Christophe Delclaux[1,5,7]

[1]Assistance Publique – Hôpitaux de Paris (AP-HP), Hôpital Européen Georges Pompidou, Service de Physiologie – Clinique de la Dyspnée, F-75015 Paris, France; [2]Cabinet La Berma, 4 avenue de la Providence; F-92160 Antony, France; [3]AP-HP, Hôpital Européen Georges Pompidou, Unité d'Épidémiologie et de Recherche Clinique, F-75015 Paris, France; [4]INSERM, Centre d'Investigation Épidémiologique 4, F-75015 Paris, France; [5]Université Paris Descartes, Sorbonne Paris Cité, Faculté de Médecine, F-75015 Paris, France; [6]AP-HP, Hôpital Européen Georges Pompidou, Service de Pneumologie; F-75015 Paris, France; [7]CIC 9201 Plurithématique, Hôpital Européen Georges Pompidou, F-75015 Paris, France

Correspondence: Christophe Delclaux
Physiologie Respiratoire – Clinique de la Dyspnée, Hôpital Européen Georges Pompidou, 20, rue Leblanc; 75015 Paris, France
Tel +33 1 56 09 34 88
Email christophe.delclaux@egp.aphp.fr

Background: The aims of the study were: (1) to compare numerical parameters of specific airway resistance (total, $sRaw_{tot}$, effective, $sRaw_{eff}$ and at 0.5 L · s^{-1}, $sRaw_{0.5}$) and indices obtained from the forced oscillation technique (FOT: resistance extrapolated at 0 Hz [$Rrs_{0\,Hz}$], mean resistance [Rrs_{mean}], and resistance/frequency slope [Rrs_{slope}]) and (2) to assess their relationships with dyspnea in chronic obstructive pulmonary disease (COPD).

Methods: A specific statistical approach, principal component analysis that also allows graphic representation of all correlations between functional parameters was used. A total of 108 patients (mean ± SD age: 65 ± 9 years, 31 women; GOLD stages: I, 14; II, 47; III, 39 and IV, 8) underwent spirometry, body plethysmography, FOT, and Medical Research Council (MRC) scale assessments.

Results: Principal component analysis determined that the functional parameters were described by three independent dimensions (airway caliber, lung volumes and their combination, specific resistance) and that resistance parameters of the two techniques were not equivalent, obviously. Correlative analyses further showed that Raw_{tot} and Raw_{eff} (and their specific resistances) can be considered as equivalent and correlated with indices that are considered to explore peripheral airways (residual volume (RV), RV/ total lung capacity (TLC), Rrs_{slope}), while Rrs_{mean} and $Raw_{0.5}$ explored more central airways. Only specific resistances taking into account the specific resistance loop area ($sRaw_{tot}$ and $sRaw_{eff}$) and Rrs_{slope} were statistically linked to dyspnea.

Conclusion: Parameters obtained from both body plethysmography and FOT can explore peripheral airways, and some of these parameters ($sRaw_{tot}$, $sRaw_{eff}$, and Rrs_{slope}) are linked to activity-related dyspnea in moderate to severe COPD patients.

Keywords: body plethysmography, forced oscillation technique, principal component analysis

Introduction

DuBois and colleagues developed different ways of assessing airway obstruction in the late 1950s, namely airway resistance obtained from body plethysmography and respiratory system resistance from FOT.[1,2] The former method seems neglected and is absent from the most recent international recommendations on pulmonary function testing, while the latter has regained interest and was the subject of recommendations by the European Respiratory Society (ERS) in 2003.[3]

The American Thoracic Society (ATS)/ERS Task Force stated that "airflow resistance is rarely used to identify airflow obstruction in clinical practice. It is more sensitive for detecting narrowing of extrathoracic or large central intrathoracic airways than of more peripheral intrathoracic airways,"[4] which may justify its disuse.

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Nevertheless, there are several lines of evidence indicating that airway resistance obtained from body plethysmography is less proximal than often stated. For instance, we have established that in asthmatic children, $sRaw_{0.5}$ and $Raw_{0.5}$ (airway resistance at a flow of 0 ± 0.5 L/s) more closely correlated with forced expiratory flow $(FEF)_{50\%}$ than with forced expiratory volume $(FEV)_1$, both conceptually and empirically.[5] We have also shown that in COPD patients, the best correlate of Raw (inspiratory Raw_{tot}) was the lumen area of the sixth bronchial generation on the CT scan, which is not quite proximal.[6] Based on these assumptions, the clinical usefulness of airway resistance measurement in COPD patients deserves to be investigated together with the determination of which numerical parameters should be chosen.

Indeed, the different numerical parameters that can be calculated from the specific resistance loop further complicate matters. The content of the sRaw loop is often quite complex and is not a simple narrow linear oval loop, especially in COPD patients. Consequently, different investigators have utilized different portions of the loop to approximate a representative value for the entire cycle. The total specific resistance ($sRaw_{tot}$), effective specific resistance ($sRaw_{eff}$), and the specific resistance at 0.5 L $\cdot$ s^{-1} ($sRaw_{0.5}$) have been well established, which further allows the calculation of Raw_{tot}, Raw_{eff}, and $Raw_{0.5}$, respectively.[1,7–10] As stated by Dab and Alexander in their initial description of specific resistance measurement, sRaw "is a volume-corrected resistance which better describes an individual's pulmonary function than the use of either Raw or Thoracic Gas Volume alone."[11] Nevertheless, the comparison of sRaw and Raw numerical parameters in COPD patients is still lacking, to the best of our knowledge.

The resistive component of respiratory impedance, Rrs, includes proximal and distal airways, lung tissue, and chest wall resistance.[3] In healthy subjects, Rrs is almost independent of oscillation frequency and mainly assesses airway resistance. In distal airway obstruction, Rrs is highest at low oscillation frequencies and falls with increasing frequency. As a consequence, it has been stated that FOT includes functional assessment of peripheral airways, which may explain the regain of interest in it.[3] Overall, the analysis of the relationships between all functional parameters obtained from spirometry, body plethysmography, and FOT in COPD patients would help to better define their functional redundancy and their respective contribution to activity-related dyspnea. Therefore, our first objective was to compare the different parameters characterizing resistance obtained from both whole-body plethysmography and FOT in COPD patients, while the second objective was to assess their clinical usefulness using correlative analyses with activity-related dyspnea. Since multiple parameters are obtained from pulmonary function tests, the first objective was achieved using a specific statistical approach, principal component analysis that also allows graphic representation of all correlations, allowing visualization of their similarities and differences.

Patients and methods

This was a cross-sectional study in which informed consent was obtained and ethical approval was received from an Institutional Review Board Committee (CPP IDF IV, n° 1391593 v0). These results constitute an ancillary study of a project designed for dyspnea assessment in patients with altered ventilatory capacity (DYSPNEE1 study, manuscript submitted). Only data from COPD patients (smoking history >15 pack-years and post-bronchodilator FEV_1/forced vital capacity (FVC) < 70%)[12] who underwent respiratory system impedance (Oscilink; Datalink-MSR, Rungis, France), spirometry, and body plethysmography measurements (MasterScreenBody, Jaeger, CareFusion, San Diego, CA) according to ATS/ERS recommendations,[3,13–15] while receiving their regular COPD treatment, were included in the present analyses. Patients were not included if they had (1) other unstable medical conditions that could cause or contribute to breathlessness (ie, metabolic, cardiovascular, or other respiratory diseases), (2) pulmonary hypertension (systolic pulmonary artery pressure >35 mmHg at rest on echocardiography), or (3) a severe psychiatric condition.

Dyspnea during daily activities was assessed using the Medical Research Council (MRC) Scale.[16]

The different indices characterizing sRaw were:[9,10] $sRaw_{tot}$ (parameter line connecting the flow points at maximum change in plethysmographic volume (pressure)), $sRaw_{0.5}$ (parameter line connecting the points where the flow reaches a fixed value of 0.5 L/s), and $sRaw_{eff}$ (calculated from multiple points throughout the breathing cycle: the integration method).[3] From the FOT technique, the following indices were obtained: the average resistance between 4 and 30 Hz (Rrs_{mean}, kPa $\cdot$ s^{-1} $\cdot$ L^{-1}), the intercept ($Rrs_{0\,Hz}$, resistance extrapolated to 0 Hz: obtained by linear regression analysis over the 4 to 16 Hz frequency range), the resistance/frequency slope (Rrs_{slope}, between 4 and 16 Hz: null to negative values), and the compliance of the respiratory system (Cp, mL $\cdot$ hPa^{-1} using model fitting on the reactance data). All these parameters have previously been described extensively

and were standardized as percentages of predicted normal values.[3,4,17–19]

Statistical analyses

Since multiple parameters were obtained from pulmonary function tests, we first reduced the number of parameters to fewer relevant dimensions based on a statistical approach, namely principal component analysis (PCA). To obtain reliable results, we determined that the minimum number of subjects providing usable data for the analysis should be five times the number of variables being analyzed (n = 20).[20] This transformation is defined in such a way that the first principal component has a variance as high as possible and each succeeding component in turn has the highest variance possible under the constraint that it is orthogonal to (uncorrelated with) the preceding components. PCA is the simplest of the true eigenvector-based multivariate analyses. Its operation is often thought of as revealing the internal structure of the data in a way that best explains the variance in the data (see the legend of Figure 2 for additional explanation). We used the "cumulative percentage of variance accounted for" as the criterion for solving the problem with the number of components and retained enough components so that the cumulative percentage of variance accounted for at least ~70% (this was further confirmed via a Cattell scree plot: Figure 1). Correlative analyses between the MRC score and pulmonary function parameters used the Pearson coefficient.

A P value <0.05 was considered significant. The statistical software SAS (release 9.2; SAS Institute Inc, Cary, NC, USA) was used for all analyses.

Results
Patients

A total of 108 patients were enrolled into the study. The clinical and functional characteristics of the patients are described in Table 1. The initial sample size of the COPD group was 128, but four had lung volume measurement using helium dilution and FOT measures were lacking for 16 additional patients.

Relationships between functional indices
Principal component analysis

The PCA allowed the description of all functional parameters according to the three axes responsible for 79.3% of total inertia. Figure 2 displays the functional indices in three different planes that help explain their respective relationships. The upper and middle panels show that axis 1 (responsible for the main part of inertia ~variance) is well described by specific resistances (mixed parameter: airway obstruction and volume, analogous to viscosity according to its unit). Axis 2 is probably related to lung volumes; among static volumes, TLC is closer to the axis than functional residual capacity
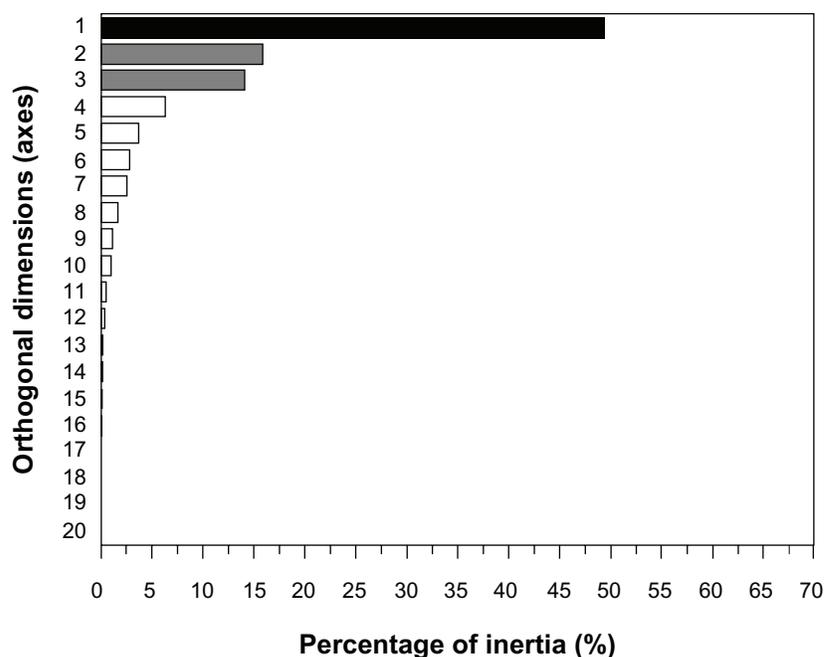

Figure 1 Percentage of inertia explained by the orthogonal axes obtained by principal component analysis.
Note: The first axis is responsible for roughly half the inertia and there was a clear decrease in the explained inertia after the first three axes (Cattell scree plot).
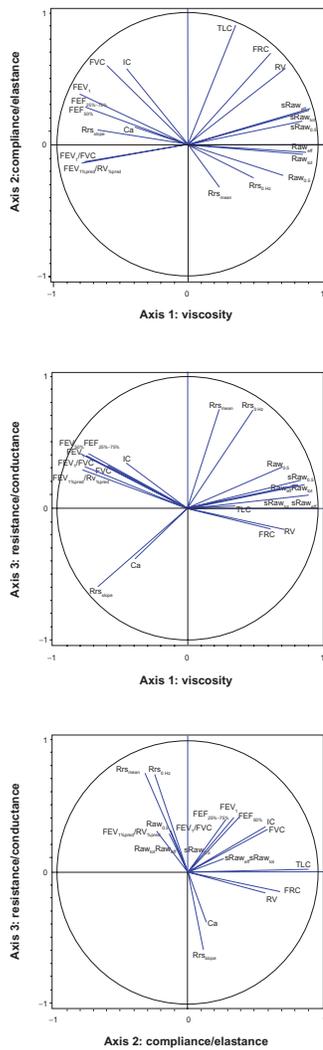
Figure 2 Correlation circles in two-dimensional maps.

Notes: The correlation circles show a projection of the initial variables in the factor space. Three planes are described according to the orthogonal dimensions determined by the PCA analysis. In a plane, when two variables are far from the center, then we can infer the following: if they are close to each other, they are significantly positively correlated (r close to 1); if they are orthogonal, they are not correlated (r close to 0); and if they are on opposite sides of the center, they are significantly negatively correlated (r close to −1). When the variables are close to the center, this means that some information is carried on other axes and that any interpretation would be hazardous.

Upper panel: representation of correlation circle in the first plane determined by axes 1 and 2. Middle panel: second plane determined by axes 1 and 3. Lower panel: third plane determined by axes 2 and 3. Since TLC was close to axis 2 (upper and lower panel), we may infer that this axis mainly represents lung volume. As volume is linked to compliance, one may hypothesize that positive values of the axis are linked to compliance while negative values are linked to elastance. The eigenvectors of FOT indices ($Rrs_{0\,Hz}$ and Rrs_{mean}) are the closest to the third axis (positive values), which may mainly represent resistance of the respiratory system, while negative values on this axis could be linked to respiratory system conductance. Finally, the positive values of the first axis (main inertia) are described well by the specific airway resistance values ($sRaw_{tot}$ and $sRaw_{eff}$) that have a viscosity unit (kPa · s).

Abbreviations: Rrs, resistance of the respiratory system (mean over 4–30 Hz; 0 Hz, resistance extrapolated to 0 Hz; slope, resistance/frequency slope); Ca, capacitance of the respiratory system obtained by FOT (~compliance); Raw, airway resistance (tot [total], eff [effective], 0.5 [at 0.5 L/s]) and their specific resistances (sRaw); TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; FEV1, forced expiratory flow at 1 s; FEF25%–75%, forced expiratory flow between 25% and 75% of vital capacity; FEF50%, forced expiratory flow at 50% vital capacity; FVC, forced vital capacity; IC, inspiratory capacity.

Table 1 Clinical and functional characteristics of the COPD patients

Characteristic	COPD
Mean ± SD or n (%)	N = 108
Age, years	65 ± 9
Sex ratio, F/M	31/77
Weight, kg	70 ± 14
Height, m	1.71 ± 0.08
BMI, kg · m^{-2}	23.9 ± 4.0
Current smokers	44 (41%)
Ex-smokers	64 (59%)
Cigarettes, pack-years	52.5 ± 25.9
GOLD classes: I, II, III, IV	14/47/39/8
Scores:	
MRC I/II/III/IV/V, n	34/37/23/8/6
Pulmonary function tests	
Spirometry, slow vital capacity	
FEV_1, L	1.58 ± 0.63
FEV_1, % predicted	56 ± 20
FVC, L	2.79 ± 0.77
FVC, % predicted	79 ± 19
$FEF_{25\%-75\%}$, L · s^{-1}	0.75 ± 0.48
$FEF_{25\%-75\%}$, % predicted	24 ± 13
IC, L	2.17 ± 0.65
IC, % predicted	74 ± 19
Lung volume measurements	
Plethysmography	
TLC, L	6.95 ± 1.41
TLC, % predicted	111 ± 19
FRC, L	4.78 ± 1.30
FRC, % predicted	144 ± 36
RV, L	3.84 ± 1.26
RV, % predicted	165 ± 51
RV/TLC	0.55 ± 0.11
$Raw_{0.5}$, kPa · s · L^{-1}	0.28 ± 0.12
$sRaw_{0.5}$, kPa · s	1.49 ± 0.81
Raw_{tot}, kPa · s · L^{-1}	0.48 ± 0.22
$sRaw_{tot}$, kPa · s	2.66 ± 1.63
Raw_{eff}, kPa · s · L^{-1}	0.42 ± 0.19
$sRaw_{eff}$, kPa · s	2.31 ± 1.40
$FEV_{1\%pred}/RV_{\%pred}$	0.39 ± 0.24
Forced oscillation technique	
$Rrs_{0\,Hz}$, kPa · s · L^{-1}	0.52 ± 0.20
$Rrs_{0\,Hz}$, % predicted	208 ± 80
Rrs_{mean}, kPa · s · L^{-1}	0.33 ± 0.10
Rrs_{mean}, % predicted	197 ± 76
Rrs_{slope}, kPa · s^2 · L^{-1}	−0.0145 ± 0.0093
Rrs_{slope}, % predicted	3954 ± 36637
Compliance, mL · hPa^{-1}	17.84 ± 24.82
Compliance, % predicted	83.13 ± 124.76

Abbreviations: F/M, female/male; BMI, body mass index; MRC, Medical Research Council dyspnea scale; Rrs, resistance of the respiratory system (mean over 4–30 Hz; 0 Hz, resistance extrapolated to 0 Hz; slope, resistance/frequency slope) and their specific resistances (sRaw); Raw, airway resistance (tot [total], eff [effective], 0.5 [at 0.5 L/s]); TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; FEV1, forced expiratory flow at 1 s; FEF25%–75%, forced expiratory flow between 25% and 75% of vital capacity; FEF50%, forced expiratory flow at 50% vital capacity; FVC, forced vital capacity; IC, inspiratory capacity.

(FRC) and RV due to increasing contribution of obstruction to these latter volumes. This axis may be related to compliance/elastance of the respiratory system. Finally, axis 3 is mainly related to airway caliber: increased resistance for positive values and hyperinflation for negative values, which is related to the resistance/conductance of the respiratory system. $FEV_{1\%pred}/RV_{\%pred}$ was also computed because this new index may theoretically describe both airflow limitation and hyperinflation.

Figure 2 emphasizes the pathophysiological indication of the indices obtained from FOT in COPD; compliance is weakly described by the three axes that have been chosen. The Rrs_{slope} (negative values) is in the opposite direction to Raw and is better described by the first axis, while Rrs_{mean} and $Rrs_{0\,Hz}$ are parameters of airway obstruction that are influenced by a decrease in lung volume (possibly due to airway closure).

Correlations between the functional parameters
Airway resistance
In our patients, Raw_{eff} and Raw_{tot} (and their specific resistances) can be regarded as equivalent (Pearson correlation coefficient, r = 0.96, $P < 0.0001$, and r = 0.98, $P < 0.0001$, respectively). Among the other functional indices (except resistances), the best correlates to Raw_{tot} were FEV_1 and RV/TLC (r = −0.63 and r = −0.62, respectively; both P values < 0.0001), while the best correlates to $sRaw_{tot}$ were RV and FEV_1/FVC (r = 0.75 and r = −0.66, respectively; both P values < 0.0001).

Respiratory system resistance
All the functional indices (except other indices obtained from FOT measurement) weakly correlated with Rrs_{mean} and $Rrs_{0\,Hz}$ (r values < 0.50). The best correlates of the slope of the respiratory system resistance were Raw_{tot}, Raw_{eff}, $sRaw_{tot}$, and $sRaw_{eff}$ (all r values ~ −0.60, all P values <0.0001).

Relationships with activity-related dyspnea (MRC score)
All parameters that statistically correlated with the MRC score had a similar degree of explained variance (for instance, FEV_1: r = −0.23 [−0.40; −0.04], $P = 0.025$). Among the resistance measurements, the only indices that significantly correlated with the MRC score were $sRaw_{tot}$ and $sRaw_{eff}$ (r = 0.24 [0.05; 0.41], $P = 0.012$ and r = 0.23 [0.04; 0.40], $P = 0.017$, respectively). The only parameter obtained from the FOT measurement that significantly correlated with the MRC score was Rrs_{slope} (r = −0.25 [−0.42; −0.06], $P = 0.010$).

Discussion
The main result of this study is that all parameters characterizing resistance obtained from both whole-body plethysmography and FOT in COPD patients were not equivalent. The PCA analysis allows the visualization of their relationships. Our results demonstrated that Raw_{tot} and Raw_{eff} (and their specific resistances) can be considered as equivalent and correlated with indices that are considered to explore peripheral airways (RV, RV/TLC, Rrs_{slope}), while Rrs_{mean} (and possibly $Raw_{0.5}$) explored more central airways. We further showed that only specific resistances ($sRaw_{tot}$ and $sRaw_{eff}$) and Rrs_{slope} were statistically linked to activity-related dyspnea in COPD patients.

Methodological issues
First, the choice of the statistical analysis needs justification. When dealing with multiple parameters that are in essence correlated, it is difficult to obtain an overall view of their similarities and differences. PCA allows this overall view, since it creates from all the parameters the independent dimensions that need further "physiological interpretation": the three axes in our study, which may represent specific resistance, volume, and airway caliber. Each parameter is then characterized by a vector and its location in each plane may characterize its functional meaning. Correlative analyses between parameters are provided to further illustrate the strength of the relationships, and two parameters can be considered as equivalent when the Pearson correlation coefficient is >0.85.

As stated by the ERS task force, since the first FOT measurements,[2] numerous variants of the FOT have been developed in terms of measurement configuration, oscillation frequencies and evaluation principles.[3] It has to be stated that some of the calculated parameters as $Rrs_{0\,Hz}$, Rrs_{slope} and Cp are still under debate.[3] Nevertheless, in adult patients with intrapulmonary airway obstruction, Rrs increases at the lower frequencies (characterized by $Rrs_{0\,Hz}$, resistance extrapolated to 0 Hz) and decreases when frequency increases (characterized by the resistance/frequency slope, Rrs_{slope}).

Relationships between resistance parameters
The choice of the most clinically useful measure of airway resistance varies in different countries. Most North American clinicians use $Raw_{0.5}$ (the parameter initially described by DuBois and colleagues),[1] which primarily reflects the resistance in the larger central airway. Nevertheless, based on theoretical grounds, physical meaning can be attributed only to Raw_{eff}, which corresponds to a linear resistor accounting

for the dissipation of the nonlinear and time variant airway system,[7] whereas the empirical measure $Raw_{0.5}$ approximates the lowest resistance. The sRaw loop is not a simple narrow linear oval loop, especially in COPD patients. The area of the loop (taken into account in Raw_{eff} measurement)[7] is related to the flow-resistive work of breathing, which may explain its correlation with activity-related dyspnea.

Our study demonstrates that among the numerical parameters obtained from sRaw measurements, either the $sRaw_{tot}$ or $sRaw_{eff}$ can be used interchangeably. These two parameters are the only ones that significantly correlate with activity-related dyspnea. To the best of our knowledge, this study is the first demonstration that specific resistance is one of the better descriptors of lung function due to its dual nature, including resistance and volume components that may be related to the viscoelastic behavior of the lung (kPa.s is a dynamic viscosity unit). In COPD patients with nonhomogeneous small airway partial obstruction, the sRaw loop area increases, especially during expiratory flow. Such alinearity represents expiratory flow limitation and/or dynamic airway compression, the former being clearly linked to activity-related dyspnea in COPD patients,[21] which may explain our results.

We further observed that $Rrs_{0 Hz}$ and Rrs_{mean} were not closely associated with Raw indices, except $Raw_{0.5}$, which suggests that these measures assess more central airways. The Rrs_{slope}, which has been suggested to assess more peripheral airways,[17] was quite closely linked to Raw_{tot}, suggesting that airway resistance in COPD is not as proximal as often stated[4] and that is in agreement with ex vivo measurements.[22] It has been reported that FOT may provide useful clinical information in COPD patients[23] beyond that available from commonly used pulmonary function tests.[17] Surprisingly, few investigators have assessed the degree of correlation between Rrs and Raw (with the exception of the assessment of bronchodilator response). The first assessment of patients with obstructive lung diseases using both techniques was made by Fisher, DuBois and Hyde.[2] They showed that airway resistance represents approximately 60% of respiratory resistance, which also incorporates tissue resistance,[2] possibly explaining the absence of a close relationship between $Raw_{0.5}$ and Rrs.

Limitations

From our results, we cannot determine formally which index better assesses peripheral airways in the absence of a gold standard. Furthermore, since the majority of patients had overt airflow limitation, our study was not designed to evaluate the sensitivity of the indices for early disease. It should be noted that we described the reactive component

of respiratory impedance only by the compliance describing the ability of the respiratory tract to store capacitive energy, primarily present in the lung periphery. One may hypothesize that within-breath tracking of respiratory impedance may give additional information.[24]

Assessment of activity-related dyspnea

Finally, our study showed that specific resistance and spirometry indices similarly but weakly explained activity-related dyspnea, as assessed by the MRC score. The MRC score is a crude assessment of activity-related dyspnea, but it is the most widely used dyspnea score.[25] Since dyspnea of COPD patients results from both altered ventilatory capacity (assessed by resistance or spirometry) and ventilatory demand (increased wasted ventilation for instance),[26–28] the weak relationship between dyspnea and the indices of airway obstruction was not unexpected.

In conclusion, parameters obtained from both body plethysmography and forced oscillation technique can explore peripheral airways, and some of these parameters ($sRaw_{tot}$, $sRaw_{eff}$ and Rrs_{slope}) are linked to activity-related dyspnea in moderate to severe COPD patients.

Authors' contributions

The listed authors made substantial contributions to conception and design (ACP, BM, PB, CD), acquisition of data (LP, KGJ, EC, BCB, OS), or analysis (ACP) and interpretation of data (all authors). The listed authors made substantial contributions to drafting the article (BM, ACP, PB, CD), revising it critically for important intellectual content (LP, KGJ, EC, BCB, OS), and final approval of the version to be published (all authors).

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Disclosures

BM declares no competing interests. ACP declares no competing interests. LP declares no competing interests. KGJ declares no competing interests. EC declares no competing interests. OS declares no competing interests. BCB declares no competing interests. PB declares no competing interests. CD declares no competing interests.

References

1. DuBois AB, Botelho SY, Comroe JH Jr. A new method for measuring airway resistance in man using a body plethysmograph: values in normal subjects and in patients with respiratory disease. *J Clin Invest.* 1956;35(3):327–335.
2. Fisher AB, DuBois AB, Hyde RW. Evaluation of the forced oscillation technique for the determination of resistance to breathing. *J Clin Invest.* 1968;47(9):2045–2057.
3. Oostveen E, MacLeod D, Lorino H, et al. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. *Eur Respir J.* 2003;22(6):1026–1041.
4. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J.* 2005;26(5):948–968.
5. Mahut B, Trinquart L, Bokov P, et al. Relationships between specific airway resistance and forced expiratory flows in asthmatic children. *PLoS One.* 2009;4(4):e5270.
6. Bokov P, Mauroy B, Revel MP, et al. Lumen areas and homothety factor influence airway resistance in COPD. *Respir Physiol Neurobiol.* 2010;173(1):1–10.
7. Jaeger MJ, Otis AB. Measurement of airway resistance with a volume displacement body plethysmograph. *J Appl Physiol.* 1964;19(4):813–820.
8. Matthys H, Orth U. Comparative measurements of airway resistance. *Respiration.* 1975;32(2):121–134.
9. Bisgaard H, Nielsen KG. Plethysmographic measurements of specific airway resistance in young children. *Chest.* 2005;128(1):355–362.
10. Kirkby J, Stanojevic S, Welsh L, et al. Reference equations for specific airway resistance in children: the asthma UK initiative. *Eur Respir J.* 2010;36(3):622–629.
11. Dab I, Alexander F. A simplified approach to the measurement of specific airway resistance. *Pediatr Res.* 1976;10(12):998–999.
12. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med.* 2007;176(6):532–555.
13. Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. *Eur Respir J.* 2005;26(1):153–161.
14. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J.* 2005;26(2):319–338.
15. Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. *Eur Respir J.* 2005;26(3):511–522.
16. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax.* 1999;54(7):581–586.
17. Brochard L, Pelle G, de Palmas J, et al. Density and frequency dependence of resistance in early airway obstruction. *Am Rev Respir Dis.* 1987;135(3):579–584.
18. Chinet T, Pelle G, Macquin-Mavier I, Lorino H, Harf A. Comparison of the dose-response curves obtained by forced oscillation and plethysmography during carbachol inhalation. *Eur Respir J.* 1988;1(7):600–605.
19. Zerah F, Lorino AM, Lorino H, Harf A, Macquin-Mavier I. Forced oscillation technique vs spirometry to assess bronchodilatation in patients with asthma and COPD. *Chest.* 1995;108(1):41–47.
20. Mahut B, Peyrard S, Delclaux C. Exhaled nitric oxide and clinical phenotypes of childhood asthma. *Respir Res.* 2011;12:65.
21. Eltayara L, Becklake MR, Volta CA, Milic-Emili J. Relationship between chronic dyspnea and expiratory flow limitation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1996;154(6):1726–1734.
22. Hogg JC, Macklem PT, Thurlbeck WM. Site and nature of airway obstruction in chronic obstructive lung disease. *N Engl J Med.* 1968;278(25):1355–1360.
23. Haruna A, Oga T, Muro S, et al. Relationship between peripheral airway function and patient-reported outcomes in COPD: a cross-sectional study. *BMC Pulm Med.* 2010;10:10.
24. Dellaca RL, Duffy N, Pompilio PP, et al. Expiratory flow limitation detected by forced oscillation and negative expiratory pressure. *Eur Respir J.* 2007;29(2):363–374.
25. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med.* 2004;350(10):1005–1012.
26. Giuntini C, Camiciottoli G, Maluccio NM, Mariani L, Lavorini F, Pistolesi M. Chronic effort dyspnea explained by lung function tests and by HRCT and CRX radiographic patterns in COPD: a post-hoc analysis in 51 patients. *COPD.* 2007;4(3):169–176.
27. O'Donnell DE, Webb KA. Breathlessness in patients with severe chronic airflow limitation. Physiologic correlations. *Chest.* 1992;102(3):824–831.
28. Sahebjami H, Sathianpitayakul E. Influence of body weight on the severity of dyspnea in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2000;161(3 Pt 1):886–890.