Quality control in respiratory oscillometry: reproducibility measures ignoring reactance?

Received: 6 Feb 2023
Accepted: 19 April 2023

To the Editor:

The growing increase in the use of oscillometry as an important adjunct to or a potential substitute for conventional pulmonary function tests (PFTs) has urged the standardisation of this technique, which was established for forced spirometry in 2005 [1] and updated in 2019 [2]. A key component of the standardisation of the PFTs is the establishment of upper limits of variability measures in the successive recordings within a trial. Whereas there are multiple criteria to be fulfilled in spirometry [1, 2], the within-trial reproducibility in oscillometry is consistently assessed by the coefficient of variation (CoV) of the lowest-frequency (4–7 Hz) values of respiratory resistance (R_{rs}) [3, 4]. Respiratory reactance (X_{rs}), the other component of respiratory impedance (Z_{rs}), has traditionally been ignored for this task. In fact, X_{rs} can be close to zero [5] and calculation of its CoV as the ratio of standard deviation (SD) and mean would result in unrealistic values [5] and proves a useless selection measure of reproducibility [6].

However, X_{rs} is arguably an equally important component of impedance, and its lowest-frequency values have been reported accordingly in all studies on Z_{rs}. While the values of X_{rs} at high frequencies may be of less clinical importance, resonance frequency (f_{res}) and the area of the X_{rs} *versus* frequency plot below f_{res} (AX) are widely used measures to characterise restrictive changes of the lungs and/or inhomogeneous behaviour of the pulmonary periphery [7, 8]. Indeed, importance of X_{rs} measures over that of R_{rs} has been emphasised by reports on the effects of disease severity [9] and expiratory flow limitation in COPD [10, 11], interstitial pulmonary fibrosis [12] and asthma [13]. Why is then X_{rs} ignored in the assessment of reproducibility in routine measurements of oscillometry?

In the present study, we investigated the within-trial variability of R_{rs} and X_{rs} at 5 Hz (R_5 and X_5, respectively), obtained with the same oscillometry device (tremoflo C-100, Thorasys Inc., Montreal, QC, Canada). The Z_{rs} data included in the analysis were collected from selected adult patient groups in the Pulmonary Function Laboratory, Toronto General Hospital, University Health Network (Toronto, ON, Canada; Site 1) between 1 January 2020 and 31 May 2022 and from all patients in a community respiratory practice clinic (Clinique pneumo Dandurand, Pointe-Claire, QC, Canada; Site 2) between 1 September 2021 and 31 May 2022. This study was approved by the University Health Network Research Ethics Board under protocols REB# 17-5373, 17-5652 and 19-5582 (Site 1) and the McGill University Health Centre Research Ethics Board MUHC-RI REB# 14-467-BMB (Site 2). Participants gave informed consent to participate in the study.

The main categories of the subjects from Site 1 were patients followed longitudinally post lung transplant (LTx), patients with interstitial lung disease (ILD), subjects measured before bone marrow transplant surgery (pBMT) and subjects with post COVID-19 infection (COVID). Subjects diagnosed with asthma, COPD and combined smaller groups of healthy subjects, patients suffering from various lung disorders and their overlaps (Varia) were from Site 2. The total number of subjects and trials was 2126 (male: 1041, female: 1085) and 5095, respectively (total measurement number: 17 295); the individual contributions of the subject groups are illustrated in the inset of figure 1a.

The SD values of R_5 (SD{R_5}) and X_5 (SD{X_5}) are compared in figure 1a. Note that the acceptance of Z_{rs} data was based on the criterion CoV{R_5} ⩽15% (before 31 October 2021) and ⩽10% (afterwards), while

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This study demonstrates the inadequacy of the current technical standards of oscillometry that are based on the within-trial reproducibility of the lowest-frequency R_{rs}, and suggests the use of a simple variability measure encompassing both R_{rs} and X_{rs} https://bit.ly/3AYRid6

Cite this article as: Hantos Z, Wu JKY, Dandurand RJ, *et al*. Quality control in respiratory oscillometry: reproducibility measures ignoring reactance? *ERJ Open Res* 2023; 9: 00070-2023 [DOI: 10.1183/23120541.00070-2023].

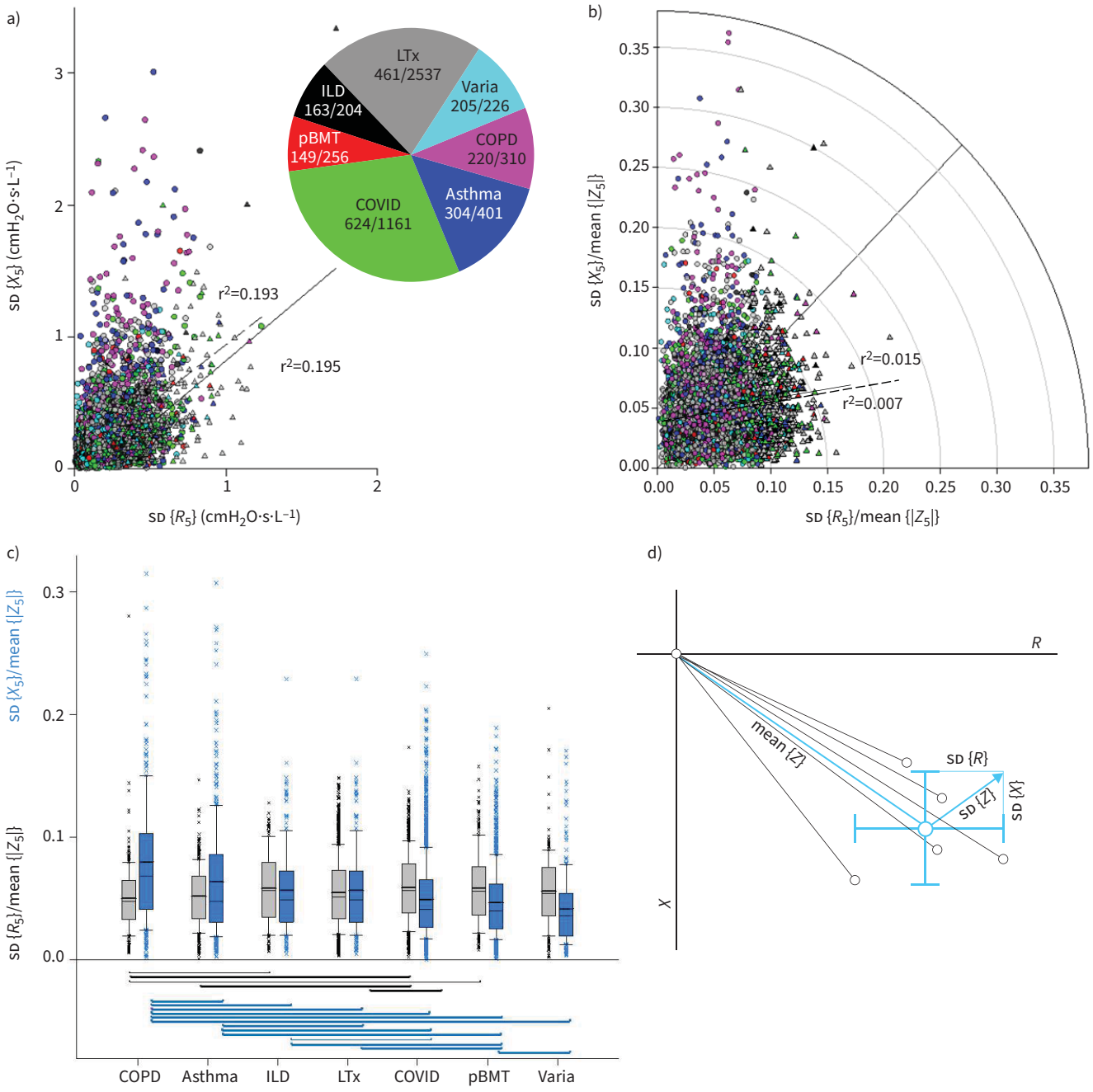

FIGURE 1 a) Relationship between standard deviations (SD) of resistance and reactance at 5 Hz (R_5 and X_5, respectively) for all trials in subject groups studied (see text for specifications). Inset: colour codes with the subject/trial numbers in each group. Solid and broken lines, respectively, indicate the regressions for data with ⩽10% coefficient of variation in R_5 (circles) and for all data including that with >10% (triangles). b) Relationship between SD data (defined above) normalised by the mean values of impedance magnitude $|Z_5|$. Note the excess trials above the line of identity in each band of normalised SD ranges. c) Box plots of normalised SD data of R_5 (grey) and X_5 (blue) showing the 25th and 75th percentiles with the median (thin lines) and the mean (thick lines). Whiskers correspond to the 10th and 90th percentiles; crosses indicate the outliers. Results of Dunn's pairwise multiple comparison test are shown with thick lines ($p<0.001$) and thin lines ($p<0.05$). d) Schematic explanation of the coefficient of variation of impedance data (Z), plotted in the resistance (R)–reactance (X) plane. Individual Z data measured in a trial are represented by black open circles. Blue symbol and lines with caps, respectively, illustrate the mean Z and the SD values of R and X determining the SD of Z (arrow). LTx: post lung transplant; pBMT: before bone marrow transplant surgery; ILD: interstitial lung disease.

no limit was imposed on the X_{rs} measures. This explains, at least in part, the appearance of large SD$\{X_5\}$ data associated with low SD$\{R_5\}$ values. Despite this bias, the SD values correlate, although modestly, both for the whole sample and the subset with CoV$\{R_5\}$ ⩽10%. This limit was imposed *a posteriori* for the

sake of uniformity and also because a number of trials had "escaped" the software or operator controls and exceeded the CoV$\{R_5\}$ limits of 10% in 632 trials of the total 5095. For all trials considered, the Mann–Whitney rank sum test showed that SD$\{R_5\}$ was higher than SD$\{X_5\}$ with median (interquartile range) values of 0.053 (0.035–0.074) *versus* 0.043 (0.027–0.068), p<0.001, likely reflecting the dominance of the mixed phenotype (Varia, LTx and COVID) groups. In contrast, an opposite relationship was found for the COPD group (0.048 (0.033–0.065) *versus* 0.069 (0.042–0.1038), p<0.001), and non-significant differences were observed for the asthma and ILD groups.

This is reflected by the plot of SD$\{X_5\}$ *versus* SD$\{R_5\}$ data, both normalised by the mean magnitude of Z_5 ($|Z_5|$), in figure 1b, with the notion that the use of $|Z_5|$ instead of R_5 as the normalisation factor reduces the variability, since $R_5 \leqslant |Z_5|$. Although the data set is biased because the upper limits imposed either originally or retrospectively on CoV$\{R_5\}$ have an unknown effect on SD$\{X_5\}$, it is obvious that the latter may substantially exceed SD$\{X_5\}$. The correlation between the normalised SD values was even weaker than that of the absolute SD values; this is convincing evidence that the determinants of the variabilities of R_{rs} and X_{rs} are largely independent.

Kruskal–Wallis one-way ANOVA on ranks with Dunn's pairwise multiple comparison test was performed to compare the variabilities of R_5 and X_5 between the subject groups (figure 1c). The SD$\{R_5\}$/mean$\{|Z_5|\}$ data are fairly balanced between the groups; interestingly, the values are lowest in COPD. The corresponding X_5 data exhibit largest variabilities for the COPD patients (p<0.001 *versus* all other groups) and the asthma subjects (p<0.001 *versus* groups of LTx, COVID and pBMT). These results are at variance with the findings in a recent study [14] where the values of CoV$\{R_5\}$ were the highest in the COPD group, followed by the asthmatic and the healthy subjects; this discrepancy is most likely due to different degrees of obstruction and the relatively small group sizes (n=15 each) in the latter study. We hypothesise that SD$\{R_5\}$ may have a significant component due to upper airway nonlinearities (orifice effects in the laryngeal region) that can be more related to the changes in breathing pattern than the distal resistance values in the different subject groups. In contrast, SD$\{X_5\}$ may be enhanced in COPD and asthma as a result of the decreased mean X_{rs} due to both inhomogeneity [7, 9, 11] and dynamic flow limitation [10, 11] in the small airways which, in addition, are sensitive to the actual lung volume and thus unstable. Our results suggest that the variability of X_5 captures the inhomogeneity and instability of the peripheral lung in obstructive diseases and needs to be incorporated in both short-term and follow-up reproducibility measures.

Changing the paradigm from the reproducibility criteria based on the lowest-frequency R_{rs} alone was initiated in an analytical study by THERKORN *et al.* [6], testing primary and derived Z_{rs} measures as reproducibility measures. Our approach focuses on the most variable lowest-frequency estimates but encompasses the complex Z_{rs} data. Indeed, in addition to monitoring both SD$\{R_5\}$ and SD$\{X_5\}$ to infer to the sources of variability, a single measure of SD$\{Z_5\}$ can be constructed as $|\text{SD}\{Z_5\}| = \sqrt{(\text{SD}\{R_5\}^2 + \text{SD}\{X_5\}^2)}$, as illustrated schematically in figure 1d. By normalisation of $|\text{SD}\{Z_5\}|$ by mean$\{|Z_5|\}$ an indicator of CoV$\{|Z_5|\}$ is obtained; the effects of the variabilities in R_5 and X_5 are thus combined. For this CoV an upper limit has to be established in the quality control similarly to that declared in the recommendations [3, 4]. Whether the CoV of 10% should remain as the practical limit for Z_5 or more permissive thresholds [5] are indicated is beyond the scope of this study; however, at any threshold, identification of measurements with high SD$\{X_5\}$ values will improve the quality control of oscillometry in obstructive diseases in particular. Finally, while the Z_{rs} data analysed in the present study were collected with the same oscillometry equipment, we think that the reproducibility considerations apply to the other commercial devices even if they are different in frequency content, measurement accuracy and signal processing algorithms [3, 15].

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Provenance: Submitted article, peer reviewed.

Conflict of interest: Z. Hantos reports support from the Hungarian Scientific Research Fund (grant K 128701) and the European Respiratory Society (Clinical Research Collaboration award CRC-2013-02_INCIRCLE), and consultation fees from THORASYS Thoracic Medical Systems Inc. J.K.Y. Wu reports support from the Lung Health Foundation and honoraria from THORASYS. R.J. Dandurand reports support from Boehringer Ingelheim and the European Respiratory Society, and honoraria from THORASYS and Boehringer Ingelheim. C-W. Chow reports support from the Canadian Institutes for Health Research, Natural Sciences and Engineering Research Council, the Lung Health Foundation, and the Pettit Block-term grants, and receipt of equipment to the institution from THORASYS.

Support statement: Funding is reported from the European Respiratory Society (CRC-2013-02_INCIRCLE) and the Hungarian Scientific Research Fund (K 128701). Funding information for this article has been deposited with the Crossref Funder Registry.

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