Quality control in respiratory oscillometry: reproducibility measures ignoring reactance?

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 $CoV(R_5) \leq 15\%$ (before 31 October 2021) and $\leq 10\%$ (afterwards), while...
no limit was imposed on the $X_5$ 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 $CoV\{R_5\} \leq 10\%$. This limit was imposed \textit{a posteriori} for the

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure1.png}
\caption{(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 $\leq 10\%$ 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 ($Z_5$), plotted in the resistance ($R$)–reactance ($X$) plane. Individual $Z_5$ data measured in a trial are represented by black open circles. Blue symbol and lines with caps, respectively, illustrate the mean $Z_5$ 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.}
\end{figure}
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 $R_5 \leq |Z_5|$. 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 $R_5$ and $X_5$ 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 $sd(R_5)/\text{mean}(|Z_5|)$ 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 $X_5$ 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 $R_5$, alone was initiated in an analytical study by Tiernkorn et al. [6], testing primary and derived $Z_5$ measures as reproducibility measures. Our approach focuses on the most variable lowest-frequency estimates but encompasses the complex $Z_5$ 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 $sd(Z_5)\equiv \sqrt{sd(R_5)^2+sd(X_5)^2}$, as illustrated schematically in figure 1d. By normalisation of $|sd(Z_5)|$ by $\text{mean}(|Z_5|)$ 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 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 $Z_5$ 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].

Zoltán Hantos 1, Joyce K.Y. Wu 2, Ronald J. Dandurand 3,4 and Chung-Wai Chow 5

1Department of Anaesthesiology, Semmelweis University, Budapest, Hungary. 2Pulmonary Function Laboratory, Toronto General Hospital, University Health Network, Toronto, ON, Canada. 3Lakeshore General Hospital, Pointe-Claire, QC, Canada. 4Oscillometry Unit of the Centre for Innovative Medicine and Meakins-Christie Labs, McGill University Health Centre, and McGill University, Montreal, QC, Canada. 5Division of Respiratory, Toronto General Hospital, University Health Network, Toronto, ON, Canada.

Corresponding author: Zoltán Hantos (hantos.zoltan@szte.hu)

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