Fluctuations and determinism of respiratory impedance in asthma and chronic obstructive pulmonary disease

Michael Muskulus,1 Annelies M. Slats,2 Peter J. Sterk,3 and Sjoerd Verduyn-Lunel1

1Mathematical Institute, Leiden University; 2Department of Pulmonology, Leiden University Medical Center, Leiden; and 3Department of Respiratory Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

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J Appl Physiol 109: 1582–1591, 2010. First published September 2, 2010; doi:10.1152/japplphysiol.01414.2009.—Asthma and COPD are chronic respiratory diseases that fluctuate widely with regard to clinical symptoms and airway obstruction, complicating treatment and prediction of exacerbations. Time series of respiratory impedance obtained by the forced oscillation technique are a convenient tool to study the respiratory system with high temporal resolution. In previous studies it was suggested that power-law-like fluctuations exist also in the healthy lung and that respiratory system impedance variability differs in asthma. In this study we elucidate such differences in a population of well-characterized subjects with asthma (n = 13, GINA 1+2), COPD (n = 12, GOLD I+II), and controls (n = 10) from time series at single frequency (12 min, f = 8 Hz). Maximum likelihood estimation did not rule out power-law behavior, accepting the null hypothesis in 17/35 cases (P > 0.05) and with significant differences in exponents for COPD (P < 0.03). Detrended fluctuation analysis exhibited scaling exponents close to 0.5, indicating few correlations, with no differences between groups (P > 0.14). In a second approach, we considered asthma and COPD as dynamic diseases, corresponding to changes of unknown parameters in a deterministic system. The similarity in shape between the combined probability distributions of normalized resistance and reactance was quantified by Wasserstein distances and reliably distinguished the two diseases (cross-validated predictive accuracy 0.80; sensitivity 0.83, specificity 0.77 for COPD). Wasserstein distances between 3 + 3 dimensional phase space reconstructions resulted in marginally better classification (accuracy 0.84, sensitivity 0.83, specificity 0.85). These latter findings suggest that the dynamics of respiratory impedance contain valuable information for the diagnosis and monitoring of patients with asthma and COPD, whereas the value of the stochastic approach is not clear presently.

Here we focus on signals obtained by the forced oscillation technique (FOT). Due to its relative ease, noninvasiveness, and good tolerance, FOT has become a valuable tool to investigate airway properties (38). A small pressure perturbation is superimposed on the inflowing air and the integrated response of the airways recorded. Assuming a linear response allows to estimate (input) respiratory system impedance (Zrs), a complex quantity whose real and imaginary parts are respiratory resistance (Rrs) and reactance (Xrs), such that Zrs = Rrs + jXrs (32). Commonly, only the magnitude (Rrs2 + Xrs2)1/2 is referred to as impedance Zrs, complemented by the phase angle arctan(Rrs/Xrs), and we also adopt this convention in the rest of the paper. Clinically, these quantities have proven useful to assess and study lung diseases (21), and this has been investigated in a plethora of studies. However, apart from a few exceptions, only the mean values of Zrs, averaged over a few breathing cycles, are used (28). It is the aim of the present study to investigate whether more involved analysis techniques allow to distinguish between asthma, COPD, or controls with increased accuracy, compared to just using mean Zrs.

For completeness, we mention that factors influencing Zrs include exercise, posture, and sympathetic tone (4). Within-breath measurements of Zrs show a marked biphasic pattern that is the result of volume and flow dependence (9, 55) with slightly distinct behavior for inspiratory and expiratory phases (39). This modulation is partially attributed for by interference with the larynx and glottis (51), but also hints at hysteresis, i.e., dependence on the volume history, in the respiratory system (59). On top of these, Zrs is influenced by ventilatory inhomogeneities (17), airway caliber (43), interactions between airways (61), and various artifacts, the most problematic being the upper airways shunt (5, 38).

Separation of Zrs into contributions from various airways and tissue components is possible by the use of mathematical compartment models (12). However, this necessitates the use

ASTHMA AND CHRONIC OBSTRUCTIVE pulmonary disease (COPD) are the two most common chronic respiratory diseases, affecting millions of people worldwide (19, 20). A characteristic of these diseases is their variability in clinical symptoms and in the degree of airway obstruction. Airway caliber is fluctuating with significant differences in exponents for COPD (P > 0.14). In a second approach, we considered asthma and COPD as dynamic diseases, corresponding to changes of unknown parameters in a deterministic system (14, 15). Interestingly, the variability in these PEF time series seems to correlate with predictability of airway obstruction, where increased airway instability occurs when correlations become weaker. Although the physiological origin of these long-range baseline correlations is mostly unknown, these findings highlight the importance of fluctuations in the respiratory system and suggest the existence of similar phenomena also on shorter time scales. Indeed, a well known example is provided by interbreath intervals that exhibit characteristic scaling exponents (13, 42, 53).

Address for reprint requests and other correspondence: Michael Muskulus, Dept. of Civil and Transport Engineering IVT-BAT, NTNU, Lerkendals bygget, 7491 Trondheim, Norway (e-mail: michael.muskulus@ntnu.no).
of complex excitation signals and estimation procedures and imposes limits on the temporal resolution, which is on the order of the inverse of the excitation frequency. Therefore, single frequency excitation signals are preferred to track Zrs in real time, and the role of deep inspirations and methacholine challenge has been studied thereby (29, 49, 55).

From the above we postulate that the temporal course of Zrs should contain valuable information that is differentially affected by respiratory diseases. In contrast to most studies that consider significance probabilities of differences on the group level, we estimate predictive accuracy when classifying individual subjects with regard to group membership. Employing cross-validated linear discriminant analysis (LDA) allows to quantify the amount of functionally differentiated information contained in the Zrs signals.

We present results obtained by two distinct approaches. In the first, Zrs time series are considered to arise from a stochastic process and we analyze their “noise” component (9) by distributional analysis of fluctuations, similar to the analysis of Que et al. (45). On the basis of recent recommendations, we employ state-of-the-art maximum likelihood estimation (8, 60). Furthermore, we employ detrended fluctuation analysis (DFA) (41) to quantify the extent to which Zrs signals are correlated in time and how self-similar these fluctuations appear; to our knowledge this method has not been applied to impedance measurements before.

In a second approach, the Zrs signal is considered to arise from a dynamic system. Thereby we will assume the respiratory system to contain a deterministic component. Moreover, we will make the assumption that the dynamic evolution of this deterministic component changes in distinct ways in Airways we will make the assumption that the dynamic evolution of this and other relevant diseases up to 2 wk prior to the study. None of the asthma or COPD patients had used inhaled or oral corticosteroids up to 3 mo prior to the study.

The healthy controls had no history of respiratory symptoms and were nonsmokers or ex-smokers with less than five pack years exposure. Baseline FEV<sub>1</sub> was >80% of predicted and PC<sub>20</sub> methacholine was >16 mg/ml. They showed no positive reaction to the skin prick test.

The baseline characteristics of the three groups have been listed previously (50). The Institutional Review Board for Human Studies approved the protocol, and the subjects gave their written informed consent before entering the study.

**Forced Oscillation Method**

A forced oscillation device (Woolcock Institute) with a fixed oscillation frequency of 8 Hz and an amplitude of ±1 cmH<sub>2</sub>O was used after calibration with tubes of known resistance. Subjects breathed through an antibacterial filter with a resistance of 0.2 cmH<sub>2</sub>O·l<sup>-1</sup>·s<sup>-1</sup> and respiratory flow was measured by a Fleisch pneumotachograph (diameter 50 mm, Vitalograph, Maids Moreton, UK). Differential pressure was measured by a ±2.5 cmH<sub>2</sub>O solid-state transducer (SurSense DCAL4; Honeywell Sensing and Control). A similar transducer with a higher range (±12.5 cmH<sub>2</sub>O) was used to measure mouth pressure (50). The pressure generator was connected by a 50-cm-long inertive tube.

The pressure and flow signals were digitized at 400 Hz, and the resulting time series were transformed to the frequency-domain by a maximal overlap discrete Fourier transform that acts as a band-pass filter for the frequency 8 Hz (filter width 100 samples, i.e., a time window of 0.25 s). Time- and frequency-dependent complex respiratory impedance Z<sub>rs</sub> was then estimated, based on the hypothesis that random errors occur in both pressure and flow signals, by a total least squares (TLS) fit, which is equivalent to maximum likelihood estimation. Further details can be found in the online supplement of Slats et al. (50).

**Time Series and Artifact Removal**

Respiratory impedance was measured three times during 60 s of tidal breathing on four distinct days during the course of a few weeks, yielding 12 time series per subject. Before further analysis the signals were downsampled to 16 Hz, i.e., the Nyquist frequency for the applied pressure oscillation, to decrease the computational effort (this is admissible here where we were mainly interested in properties for larger time scales). Artifacts were removed automatically by a custom-written algorithm. Each respiratory cycle was considered individually and rejected if 1) negative resistance values occurred or the TLS estimation did not converge (indicative of artifacts) or 2) flow limitation occurred. The latter was detected if the difference in mean Xrs for inspiratory and expiratory phases was >3 cmH<sub>2</sub>O·l<sup>-1</sup>·s<sup>-1</sup> or if the difference in peak Xrs for inspiratory and expiratory phases exceeded 8 cmH<sub>2</sub>O·l<sup>-1</sup>·s<sup>-1</sup> (10; with slightly adjusted threshold values). These events occurred infrequently and only a few percent of breathing cycles were thereby rejected.

**Analysis**

**Statistical properties.** In addition to mean and standard deviation (SD) over time, the time series were characterized by two functions of higher moments. Excess kurtosis, defined as the fourth central moment divided by the square of the variance minus 3, was used as a measure of peakedness of the distributions, and skewness, defined as the third central moment divided by the third power of SD, was used as a measure of asymmetry of the distributions. Distributions of parameters are shown in box and whisker plots for each group separately (with labels A: asthma, C: COPD, N: controls), that also show significance probabilities of differences in mean (unpaired two-sample nonparametric Wilcoxon tests) for all pairwise contrasts.
and additionally between controls and a “diseased” group D that comprises both asthmatics and COPD patients. Statistical significance was tested at the $P = 0.05$ level.

**Power-law analysis.** Fluctuations of $Z_{rs}$ were defined by

$$Z_{\text{var}}(i) = \left[ Z_{rs}(i) - \text{mean}(Z_{rs}) \right]^2,$$

(1)

as in Que et al. (45). The probability density $f(x)$ of $Z_{\text{var}}$ follows a power-law if it is proportional to $x^{\alpha}$, with an exponent $\alpha \leq -1$. Thereby, it is assumed that power-law behavior is only present for values $x \geq x_{\text{min}}$ for a finite threshold $x_{\text{min}} > 0$. The probability density of the two-parameter power-law distribution is then

$$f(x) = -(\alpha + 1)x_{\text{min}}^{(\alpha + 1)}x^\alpha,$$

(2)

which is also known as the Pareto distribution. The value of $\alpha$ is determined by its maximum likelihood estimate (60). The threshold $x_{\text{min}}$ is estimated by optimizing the goodness-of-fit of the estimated power-law with the empirical distribution of the data, quantified by the Kolmogorov-Smirnov statistic $D$ (8). To avoid spurious minima for very short tails, only values of $x_{\text{min}}$ were considered such that at least 200 values of $Z_{\text{var}}$ remained in the tail. Figure 1 shows an example of the estimation procedure. To compare with results obtained in Que et al. (45), we also extrapolate the probability distribution for unit fluctuations, i.e., consider $\log_{10} f(1) = \log_{10} ((-\alpha - 1) + (\alpha + 1) \log_{10} x_{\text{min}})$.

To test whether the power-law hypothesis is a viable description of the data, we employed the permutation test of Clauset et al. (8). A number of synthetic dataset were generated with similar distributional properties as the original data. The power-law estimation was repeated independently for each of these and the fraction of values of the Kolmogorov-Smirnov statistic $D$ that were larger than the value of the observed data forms the significance probability ($P$ value) of this test. For a conservative test, if $P < 0.05$ the null hypothesis of power-law behavior was rejected, otherwise power-law behavior was accepted to be a valid model of the experimental data. We employed this test with 100 Monte Carlo datasets for each $Z_{\text{var}}$ time series, but did not correct for multiple comparisons ($n = 35$). Note that accepting the null hypothesis does not prove the existence of power-law behavior, but the compatibility of this model, i.e., that there is no significant evidence against the power-law hypothesis.

As an alternative to the power-law behavior we fitted two- and three-parameter log-normal distributions (47) to both the tail and the complete set of $Z_{\text{var}}$ values and considered the three-parameter truncated power-law distribution (1) that introduces an additional upper bound $x_{\text{max}}$ and allows for general exponents $\alpha < 0$. The significance of an improvement in fitting the data was assessed by the asymptotic likelihood ratio test.

**Detrended fluctuation analysis.** Individual time series of $Z_{rs}$ were submitted to DFA (41) to assess self-similar behavior. Thereby, the deviations of the $X(i) = Z_{\text{var}}(i)$ time series from the mean were first integrated,

$$Y(i) = \sum_{j=1}^{i} \left[ X(j) - \bar{X} \right].$$

(3)

The profile $Y(i)$ was then divided into $N_s = \text{int}(N/s)$ nonoverlapping segments of length $s$. Since the length $N$ of the time series is usually not a multiple of the scale $s$, a short part at the end of the profile may remain. In order not to disregard this part of the series, the procedure was repeated starting from the opposite end, leading to a total of $2N_s$ segments (24). For each such segment either a linear (DFA1) or a quadratic (DFA2) trend was estimated by least-squares regression and subtracted from the data. The squares of the residuals were integrated and divided by the length to yield the mean-square error $F^2(j,s)$ of the $jth$ segment at scale $s$. The second-order fluctuation function is given by the total root-mean square (RMS) error,

$$F(s) = \left( \frac{1}{2N_s} \sum_{j=1}^{2N_s} F^2(j,s) \right)^{1/2}.$$

(4)

Scaling behavior of $F(s)$ was assessed in a double logarithmic plot for a variety of scales. The smallest scale considered was $s = 8$ samples. The scale was successively increased by a factor of $\sqrt{2}$ until $s$ was at most half of the length of the time series. Scaling behavior results in a line in the double logarithmic plot of $F(s)$ against $s$, which was estimated by weighted linear regression. Weights

![Fig. 1. Power-law behavior in the distribution of $Z_{rs}$ fluctuations (Zvar, Eq. 1). A: time series of $Z_{\text{var}}$; the broken lines indicate the 12 distinct measurements. B: estimated of the probability density of $Z_{\text{var}}$ (dotted line). The 3-parameter log-normal distribution (solid line) fits the data best, the power-law distribution (broken line) fits the tail somewhat better but is not a good model for small values of $Z_{\text{var}}$. C: estimated power-law exponent $\alpha$ (right coordinate axis) and Kolmogorov-Smirnov statistic $D$ (left coordinate axis). The optimal value of the threshold $x_{\text{min}}$ is located at the minimum of $D$ (broken vertical line). D: estimate of the probability density of $Z_{\text{var}}$ for the tail with $x \geq x_{\text{max}}$ (dotted line). The (truncated) power-law distribution (dotted line) fits the tail best, but the (three-parameter) log-normal distribution (solid line) is comparable.](http://jap.physiology.org/doi/abs/10.1152/jappl.00490.2010)
proportional to the inverse of scale were used to account for the fact that the larger scales are estimated from less segments, with increased variance. The occurrence of two separate scaling regimes (crossover phenomenon) was tested by assuming each scale individually as a change point and separately fitting lines to $F(x)$ for both scales smaller and for scales larger. If the introduction of a change point led to an increase in total RMS error of more than a factor 5, the existence of a crossover phenomenon was assumed. Figure 5A shows an example.

**Wasserstein distances.** The time series were alternatively assumed to be projections of a dynamic system, considering $R_{ts}$ and $X_{rs}$ as two dynamic variables. In the simplest case the two-dimensional scatterplot of $R_{ts}$ vs. $X_{rs}$ captures the dynamic range of the impedance over the course of time. To allow for comparisons of distinct systems and to put the two parameters on equal standing, we normalized their marginal distributions independently to zero mean and unit variance and considered the resulting two-dimensional joint probability distributions (Fig. 2).

To quantify differences between two such empirical probability distributions we employed quadratic Wasserstein distances (35, 36). Assume $X(i)$ and $Y(i)$ $\{i=1, \ldots, N\}$ to be two vector-valued time series (here with normalized $R_{ts}$ and $X_{rs}$ as its two components) of the same length $N$. In this case the quadratic Wasserstein distance between $X$ and $Y$ reduces to the optimal transportation problem

$$W_2(X, Y) = \min_{\sigma} \left\{ \sum_{i=1}^{N} \|X(i) - Y(\sigma(i))\|^2 \right\}^{1/2}$$

over all permutations $\sigma$ of the set $\{1, 2, \ldots, N\}$. The value $W_2(X,Y)$ can be interpreted as the average work (in terms of distance) needed to transform one distribution into the other after optimally matching sample points. This convex optimization problem was solved numerically by a network simplex algorithm (30).

The embedding dimension $m$ should be large enough to unfold the dynamics properly and was here estimated by the method of false nearest neighbors (FNN) (26). If the distance between a point $X_{m}(i)$ and its nearest neighbor $X_{m}(k)$ increases by a factor of more than 10 when increasing the embedding dimension $m$, then $X_{m}(k)$ is classified as a (relative) false neighbor. The optimal embedding dimension was assessed as the value of $m$ where the fraction of FNN dropped below the 1 percent threshold.

Combining two m-dimensional delay vector series for $R_{ts}$ and $X_{rs}$ into a 2m dimensional vector-valued time series $X_{m}$ we again employed the Wasserstein distances (see above) in 2m dimensions to robustly quantify differences in the shape of their impedance dynamics for each pair of subjects. This approach was pioneered by Moeckel and Murray (34).

**Multidimensional scaling.** Measuring distances between phase space distributions for each pair of subjects ($n = 35$) leads to an $n$-by-$n$ matrix of distances $D_{ij} = W_2(X_i, X_j)$. To analyze these statistically it is advantageous to represent these distances by points in an Euclidean space $R^k$, which is achieved by metric multidimensional scaling (MDS) (3). The coordinates of points in the space $R^k$ are ordered according to their contribution to the variance of the distances and can often be assigned functional meaning or lead to the formulation of hypotheses about it (35). This dimension reduction method introduces misrepresentation errors, which were quantified by stress-per-point; for the $i$th point with $k$ coordinates $x_i$ the stress-per-point is the average of $(|x_{i} - x_{j}| - D_{ij})^2$ over all points $j \neq i$.

**Discriminant analysis.** To assess the predictive value of observed differences between groups of subjects, we employed linear discriminant analysis (LDA) as implemented in the statistical software R (56). A linear discriminant function is obtained that projects each of the $k$ data items (from c distinct groups) onto $r$ numerical scores, where $r = \text{min}(c - 1, k)$, corresponding to the optimal linear separation between the classes. The latter is given by a linear combination that maximizes a generalized signal-to-noise ratio, leading to $r$ canonical variates that identify a vector subspace containing the variability across the c classes. From the $r$ scores data items are classified according to the nearest group centroid, measured in terms of Mahalanobis distance. These centroids are estimated from the sample covariance matrix, and LDA makes the assumption that there are no differences between the group covariances. Here we will use LDA on the k MDS coordinates (derived from the Wasserstein distances), an idea that goes back to Anderson and Robinson (2).

Results are given in terms of total accuracy, i.e., the fraction of correctly identified group memberships, and for binary classifications additionally in terms of sensitivity and specificity relative to the diagnosis of a positive condition (mostly COPD in the following) against a negative (mostly asthma). Let TP denote the number of true

![Fig. 2. Wasserstein distances of mixed resistance (Rts) and reactance (Xrs) time series. A: trajectory of Rts/Xrs in a 1+1 dimensional embedding for a subject with asthma, normalized to zero mean and unit variance for each component separately. To improve visualization, stippled lines instead of individual sample points are shown. B: analogous trajectory for a subject with COPD. The Wasserstein distance quantifies the work needed to transform one of these embeddings into the other, and thereby robustly quantifies differences in shape. For this example, the mean Wasserstein distance was 0.412 ± 0.029 SE (bootstrapped 25 times from 512 sample points each).](http://jap.physiology.org/), A: , B: }

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positives, FP the number of false positives, and TN, FN analogously for the negatives. Then

\[
sensitivity = TPR = TP / (TP + FN),
\]

\[
specificity = 1 - FPR = TN / (FP + TN),
\]

where TPR is the true positive rate and FPR the false positive rate. For such binary classifications receiver-operator characteristics can be given that elucidate the relationship between FPR and TPR, depending on the decision boundary.

**Cross-validation and worst-case classifier.** All classification methods suffer from the fact that resubstitution accuracy, i.e., predictive accuracy of the data used to derive a classifier, invariably improves as the prediction model becomes more complex. Eventually the prediction model can distinguish data items by irrelevant chance differences, i.e., by using the noise in measurements to classify. To control for such overfitting we employed leave-one-out cross validation. When using LDA on coordinates derived by MDS of Wasserstein distances, it is then necessary to estimate the MDS coordinates of a time series in the MDS space defined by the remaining \( n-1 \) time series. This is achieved by estimating the fallible scalar products by a nonlinear optimization procedure (54) and is the reason why we consider metric MDS here instead of nonmetric generalizations (3).

All classification accuracies should be judged in the light of the null accuracy, achieved by randomly “guessing” class membership, of 1/3 (0.33) and 2) the worst-case classification accuracies, classifying all subjects as belonging to the largest group, which were 13/35 (0.37) (all 3 groups) and 13/25 = 0.52 (asthma vs. COPD).

**Multiple response permutation procedures.** Apart from being used for classification, the Wasserstein distances were assessed in terms of how significant was the separation between classes. This was achieved by a multiple response permutation procedure (MRPP) (33). The test statistic \( \delta \) is the overall weighted mean of within-group means of all pairwise distances. It is first calculated under the known true group assignment and then by randomly permuting the group labels. The number of values of \( \delta \) obtained under the permutation distribution that are larger than the original \( \delta \) defines the significance probability \( P \) value of this test. All MRPP tests were run with \( 10^5 \) randomly generated permutations.

Additionally, the chance-corrected within-group agreement

\[
A = 1 - \delta / E[\delta]
\]

was determined, where \( E[\delta] \) is the average of \( \delta \) over the permutations. This quantifies the proportion of the distances explained by group structure and is analogous to a coefficient of determination.

**RESULTS**

**Statistical Results and Predictive Accuracies**

The mean values of Zrs, Rts, and Xrs are shown in Fig. 3. There were significant differences between COPD patients and asthmatics \( P = 0.035 \) or healthy controls \( P = 0.014 \) in mean Zrs, but not between asthmatics and controls \( P = 0.61 \). This increase in mean Zrs was reflected in significant decreases in Xrs for the COPD group \( P = 0.0055 / P = 0.0016 \) and to a lesser degree in increases in Rrs \( P = 0.053 / P = 0.014 \). Although some of these differences were highly significant (e.g., mean Xrs for COPD vs. controls), classification of COPD vs. controls by LDA of mean Xrs only achieved an accuracy of 0.77 and accuracies of 0.73 for both mean Rrs and Zrs. Discrimination between asthma and COPD was possible with accuracies of 0.72 (mean Xrs) and 0.64 (mean Rts or Zrs).

Mean lnZrs and lnZrsSD were considered for completeness [to compare with the results of (11, 44)] and differed significantly between asthma and COPD \( P = 0.046 / P = 0.030 \) and led to similar classification (lnZrs) or slightly worse (lnZrsSD) classification results. No significant differences between asthmatics and controls were detected \( P = 0.49 / P = 0.70 \), consistent with the findings of (11), but COPD showed marginal increases in lnZrs \( P = 0.017 \), but not in lnZrs variability \( P = 0.081 \). Regarding higher moments, there were significant differences in kurtosis (peakedness) and skewness (asymmetry) of Zrs between COPD and the other groups \( A: P = 0.0037 / P = 0.040; N: P = 0.043 / P = 0.025 \). These allowed for an accuracy of 0.68 (kurtosis) and 0.64 (skewness) when distinguishing asthma from COPD.

**Software used.** All data analysis was performed in the statistical computing environment R (46) using the MASS package (56), the fractal package (W. Constantine and D. Percival, unpublished), the vegan package (J Oksanen, R Kindt, P Legendre, B O’Hara and MIH Steven, unpublished), and the ROCR package (48). Note that the implementation of DFA in fractal is faulty and was replaced by a custom-written algorithm that can be obtained from the authors on request. The two matrices of Wasserstein distances (one shown in Fig. 6A) are available as data supplements in the online journal.

![Fig. 3. Statistical summary of impedance data. Significance probabilities are indicated in the boxplots. Groups are labeled (A, asthma; C, COPD; N, healthy controls). A: mean values of respiratory impedance Zrs; B: resistance Rts; C: reactance Xrs. Higher moments of Zrs: kurtosis (D) and skewness (E). As a measure of variability, lnZrsSD (F).](http://jap.physiology.org/Downloaded from 10.22032/247N10317M303179732173)
Power-Law Analysis

Estimated power-law exponents and thresholds are shown in Fig. 4 for the Zvar fluctuations. There were significant differences in exponents between COPD and asthma or controls ($P = 0.018$/$P = 0.023$), with slightly smaller exponents $\alpha$ in COPD, indicating that relatively larger fluctuations in COPD occur less often than in asthmatics or healthy controls. The threshold $x_{\min}$ was significantly higher in COPD than for the other groups ($P < 0.008$). The latter could be explained by a slightly larger variability in COPD (see Fig. 3F) and resulted in classification accuracies of 0.72 (asthma/COPD) and 0.73 (COPD/controls). The logarithm of the extrapolated probability density at $Zvar = 1.0$ (cmH2O·l⁻¹·s²) showed a significant increase for COPD with respect to the other groups ($P < 0.002$; Fig. 4D), and this indeed resulted in classification accuracies of 0.80 (against asthma) and 0.82 (against controls), whereas classification of asthma vs. controls was more or less random with an accuracy of 0.57, in contrast to the earlier findings of Que et al. (45).

The null hypothesis of power-law behavior was accepted for 17/35 subjects, distributed almost evenly among the three groups (Fig. 4C). Fitting a three- or two-parameter log-normal distribution to the same data in the tail of the Zvar distribution resulted in a comparable fit, with an insignificant likelihood ratio in all cases. The truncated power-law distribution generally resulted in the best fit of the tail data, but also with an insignificant increase in likelihood. It can be concluded that both log-normal and power-law distributions are plausible models for the tails (see Fig. 1B).

Detrended Fluctuation Analysis

Although DFA is to a certain extent robust against the removal of segments (7, 31), it is advisable to analyze only contiguous data. In contrast to the previous section we therefore employed DFA on individual 1-min measurements only, with ~800–900 data points each. The quasi-periodic nature of the breathing cycle introduces spurious residuals due to the detrending for scales that are smaller than the average breathing period (e.g., 37). In particular, the scaling exponents obtained from DFA1 and DFA2, respectively, differ largely. Above this period, the scaling behavior changes (Fig. 5A) and results for DFA1 and DFA2 mostly agree. We chose the values of the more robust DFA1 for the larger scales and averaged this for all 12 measurements of each subject.

There were no significant differences in scaling exponents between groups ($P > 0.14$), compare Fig. 5B, although it seems that scaling behavior might be closer to the value 0.5 of Brownian motion for COPD than for asthma and controls.

Distance-Based Analysis

The Wasserstein distances for the 1+1 dimensional joint probability distributions of $Rts$ and $Xrs$ (both normalized independently) allowed to distinguish asthma and COPD with above chance accuracies. The eigenvalue distribution indicated that the distances can be represented reasonably well in $k=2$ dimensions (explaining a fraction 0.65 of their variance) with an intermediate misrepresentation error (a fraction of 0.10 of the average distance) more or less uniformly distributed among the points. The group structure in this functional space was significantly clustered ($P = 0.002$), but a within-group agreement $A=0.06$ suggests that only ~6% of the variance among distances is explained by group structure. Including more reconstruction dimensions, the cross-validated classification accuracies decreased. LDA in two MDS dimensions classified with accuracy 0.51 in the full contrast and with accuracy 0.76 between asthma/COPD. The best asthma/COPD classification was achieved in just one dimension, leading to an accuracy of 0.80, sensitivity 0.83, and specificity 0.77.

Fig. 4. Estimated power-law behavior. Exponent (A) and onset threshold (B) in a group-wise comparison (A, asthma; C, COPD; N, healthy controls). Significance probabilities are indicated. C: evidence for power-law behavior by permutation test (100 bootstraps; see text for details) and estimated intercept (D) to compare with the findings of Que et al. (45). The null hypothesis of power-law behavior is not rejected (0.05 level, broken line) for 17 of 35 cases, indicating compatibility with the power-law hypothesis.
Assuming the $R_{rs}$ and $X_{rs}$ time series to result from an underlying dynamic system, the proper time lag for delay vector reconstruction was assessed by the decorrelation time of the autocorrelation functions, with mean values of $14 \pm 13$ SD and $12 \pm 9$ SD, respectively. Due to the high variability, and since stochastic contributions to the signal might bias these estimates to larger values, the median values of 10 (for $R_{rs}$ and $X_{rs}$ alike) were chosen, corresponding to 0.625 s as characteristic time scale of the impedance dynamics, i.e., about one-fourth of a breathing cycle. Assessment of FNN suggested an embedding dimension of three to four (FNN $R_{rs}$: relative $3.8 \pm 0.6$ SD, $X_{rs}$: relative $3.9 \pm 0.7$ SD) and $m=3$ was chosen, as balancing the influence of noise seemed more important than improved resolution of the dynamics.

As in the 1+1 dimensional case, we quantified differences between the 3+3 dimensional delay vector distributions of $R_{rs}$ (3 delay coordinates) and $X_{rs}$ (the other 3 coordinates), normalizing the two to zero mean and unit variance independently. Results are shown in Fig. 6. The eigenvector distribution (Fig. 6C) suggests that although two dimensions captured most of the variance of the distances (a fraction of 0.48), quite a few more are needed to represent the distances faithfully. Indeed, for a two-dimensional MDS reconstruction the misrepresentation error was relatively large (Fig. 6B, about a fraction of 0.16 of the average distances). The group structure was still significant ($P = 0.006$; Fig. 6D), even under a lower within-group agreement $A=0.023$. The classification accuracies for the full contrast attained their maximum of 0.54 for two dimensions and for the asthma/COPD contrast in five reconstruction dimensions (Fig. 6E), which resulted in an accuracy of 0.84, sensitivity 0.83, and specificity 0.85 in five reconstruction dimensions (Fig. 6, G–H).

**DISCUSSION**

We have attempted to distinguish between asthma, COPD, and healthy controls either by assessing fluctuations and scaling behavior or by robustly comparing probability distributions of the dynamic behavior of $R_{rs}$ and $X_{rs}$, implicitly assuming an underlying dynamic system.

**Main Findings**

Evidence for the controversial power-law hypothesis (45) was found. That is, the power-law null hypothesis could not be rejected for 17/35 subjects at the 5 percent significance level, and their $Z_{tar}$ fluctuations were consistent with power-law behavior when this was fitted to the tail of the distributions. However, although there was no evidence against the power-law distribution, the two- or three-parameter log-normal distribution described the tail almost equally well. Without larger time series it is difficult to conclude this issue.

Consistent with earlier findings we did not detect significant changes between power-law exponents for asthmatics vs. controls ($P > 0.99$), but COPD showed significantly different exponents. In contrast to Que et al. (45), we did not detect significant differences in power-law intercepts between asthmatics and controls, although the extrapolated intercepts were significantly larger for COPD. The earlier analysis was done with methods that are now known to be potentially unreliable (60), and these earlier findings should therefore be reconsidered. The final analysis of this data in Que et al. (44) in terms of log-normal distributions is consistent with our results.

Detrended fluctuation analysis did not obtain any significant differences in scaling exponents. Moreover, the scaling exponents were close to 0.5, the value obtained for Brownian motion, although it seems that exponents in COPD might be somewhat closer to 0.5 than for asthma and controls, indicating increased randomness. Due to the quasi-periodic nature of breathing, DFA exhibited two different scaling regimes. For scales lower than the average breathing period the DFA exponent depends strongly on the method of detrending and has to be considered unreliable. For scales above the breathing period, we have considered the exponents to be reliable. At even larger time scales it seems likely that respiratory impedance exhibits yet another crossover into scaling exponents significantly larger than 0.5, since similar phenomena were found in time series of tidal breathing parameters (6). However, to conclude this issue necessitates much longer recordings than presently available.
The distance-based analysis between probability distributions further evidenced that there exist subtle differences in respiratory properties. Since the $R_{rs}$ and $X_{rs}$ time series were normalized for this analysis, only differences in the shape of the dynamic behavior were thereby quantified. Interestingly, these were sufficiently large to allow robust (cross-validated) classification of 80 percent of subjects in the asthma/COPD contrast, which was better than classification based on mean $Z_{rs}$, $\ln Z_{rs}$, skewness and kurtosis of $Z_{rs}$, etc., individually.

Only the estimated intercept of the power-law behavior of the tail resulted in similar classification between asthma and COPD. This finding confirms our hypothesis that the two diseases differentially affect the within-breath dynamics of respiratory impedance.

Regarding the $3+3$ dimensional delay embedding and its Wasserstein distances, these did only improve classification marginally (to 84 percent of subjects in the asthma/COPD contrast, which was better than classification based on mean $Z_{rs}$, $\ln Z_{rs}$, skewness and kurtosis of $Z_{rs}$, etc., individually. Only the estimated intercept of the power-law behavior of the tail resulted in similar classification between asthma and COPD. This finding confirms our hypothesis that the two diseases differentially affect the within-breath dynamics of respiratory impedance.

In contrast to the largely successful classification of asthma vs. COPD, predictive classification of asthmatics vs. healthy controls was problematic due to large overlap between those two groups, in both the statistical properties of $Z_{rs}$ as well as their dynamic behavior.

**Clinical Implications**

The distance-based time series analysis of respiratory impedance led to a correct distinction between patients with asthma and COPD in at least 80 percent of cases, i.e., the forced oscillation technique can capture discriminative aspects of airway disease from recordings during simple, tidal breathing. The differential diagnosis of asthma and COPD can be a challenge in clinical practice (23) as it appears that both diseases can exhibit overlapping pathological and physiological features (16). Part of this overlap may be due to real coexistence of both diseases in some patients, whereas in others the current diagnostic techniques apparently fail to pick up the difference (16). Alternatively, it cannot be excluded that the classical diagnoses of asthma and COPD are not capturing...
existing and clinically relevant phenotypic differences among patients with obstructive airway diseases. Our data suggest that characterization of patients based on evidence from objective measurements, such as respiratory impedance time series, may become more informative in clinical assessment than traditional diagnostic labels.

Our patients were used as a so-called “training set” (27), thereby being representative of gold-standard patients of either disease. The presently observed discriminative capacity of the dynamic time series analysis is, therefore, promising with regard to differential diagnosis and monitoring of asthma and COPD. The fully noninvasive nature of the measurements, without the requirement of artificial breathing maneuvers, offers great prospect for clinical application in chronic, often elderly patients. However, this still requires validation experiments, in independently recruited patients with an intention-to-diagnose (27), to establish the diagnostic accuracy of the dynamic time series analysis of respiratory impedance in clinical practice.

Conclusion

Instead of evaluating Zrs signals with respect to the mechanical properties of airways, we have attempted a stochastic and nonlinear analysis. The distance analysis showed that there exist subtle differences in these signals that can only be partially attributed to statistical properties, such that the nature of the differential behavior of respiratory impedance is mostly unclear. Self-similar fluctuations were not detected in the signals at this time scale, and the evidence for power-law behavior was not conclusive. The distance-based analysis, however, has proved useful and detected clustering in functional space, indicating functional changes in respiratory impedance that are characteristic with respect to disease. Reverse engineering of these patterns is a possibility, since the interpopulation properties of Wasserstein distances (58, ch. 5.1), in combination with nonlinear modeling techniques (22), probably allow to compute characteristic dynamic models for each group of subjects. This would potentially lead to further insights into how the respiratory system is affected in disease and possibly also allow to assess and track changes in airway caliber over the course of time.

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Present address of M. Muskulus: Department of Civil and Transport Engineering IVT-BAT, Norwegian University of Science and Technology NTNU, Lerkendalsbygget, 7491 Trondheim, Norway (e-mail: michael.muskulus@ntnu.no).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

REFERENCES


