BMJ Open Respiratory Research

Predicting parameters of airway dynamics generated from inspiratory and expiratory plethysmographic airway loops, differentiating subtypes of chronic obstructive diseases

Richard Kraemer ,[1,2] Hans-Jürgen Smith,[3] Juergen Reinstaedtler,[4]
Sabina Gallati,[5] Heinrich Matthys[6]

To cite: Kraemer R, Smith H-J, Reinstaedtler J, *et al*. Predicting parameters of airway dynamics generated from inspiratory and expiratory plethysmographic airway loops, differentiating subtypes of chronic obstructive diseases. *BMJ Open Respir Res* Published Online First: [please include Day Month Year]. doi:10.1136/bmjresp-2023-002142

Received 18 October 2023
Accepted 9 February 2024

For numbered affiliations see end of article.

Correspondence to
Professor Richard Kraemer;
richard.kraemer@hirslanden.ch

ABSTRACT

Background The plethysmographic shift volume–flow loop (sR_{aw}-loop) measured during tidal breathing allows the determination of several lung function parameters such as the effective specific airway resistance (sR_{eff}), calculated from the ratio of the integral of the resistive aerodynamic specific work of breathing (sWOB) and the integral of the corresponding flow–volume loop. However, computing the inspiratory and expiratory areas of the sR_{aw}-loop separately permits the determination of further parameters of airway dynamics. Therefore, we aimed to define the discriminating diagnostic power of the inspiratory and expiratory sWOB ($sWOB_{in}$, $sWOB_{ex}$), as well as of the inspiratory and expiratory sR_{eff} (sR_{eff}^{IN} and sR_{eff}^{EX}), for discriminating different functional phenotypes of chronic obstructive lung diseases.

Methods Reference equations were obtained from measurement of different databases, incorporating 194 healthy subjects (35 children and 159 adults), and applied to a collective of 294 patients with chronic lung diseases (16 children with asthma, aged 6–16 years, and 278 adults, aged 17–92 years). For all measurements, the same type of plethysmograph was used (Jaeger Würzburg, Germany).

Results By multilinear modelling, reference equations of $sWOB_{in}$, $sWOB_{ex}$, sR_{eff}^{IN} and sR_{eff}^{EX} were derived. Apart from anthropometric indices, additional parameters such as tidal volume (V_T), the respiratory drive ($P_{0.1}$), measured by means of a mouth occlusion pressure measurement 100 ms after inspiration and the mean inspiratory flow (V_T/T_I) were found to be informative. The statistical approach to define reference equations for parameters of airway dynamics reveals the interrelationship between covariants of the actual breathing pattern and the control of breathing.

Conclusions We discovered that $sWOB_{in}$, $sWOB_{ex}$, sR_{eff}^{IN} and sR_{eff}^{EX} are new discriminating target parameters, that differentiate much better between chronic obstructive diseases and their subtypes, especially between chronic obstructive pulmonary disease (COPD) and asthma–COPD overlap (ACO), thus strengthening the concept of precision medicine.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Normative predicting equations for some parameters of the whole-body plethysmography are well established. However, yet hidden parameters of the plethysmographic shift volume–tidal volume (sR_{aw}-loop) may expect further insight into the pathophysiological behaviour of lung function in patients with lung diseases. However, normative predicting equations for these new parameters are needed.

WHAT THIS STUDY ADDS

⇒ The new defined normative reference equations provide the computation of z-scores transitional over a wide age range minimising the age- and growth-related variability between individuals in the distribution of the reference population.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The new defined normative predicting equations selectively for the inspiratory and expiratory parts of the sR_{aw}-loop ($sWOB_{in}$, $sWOB_{ex}$, sR_{eff}^{IN}, sR_{eff}^{EX}) are prerequisites for studies searching for target parameters, which serve to a much better differentiation between chronic obstructive diseases and their subtypes, especially between chronic obstructive pulmonary disease (COPD) and asthma–COPD overlap, improving the concept of precision medicine.

INTRODUCTION

There is growing interest in identifying specific functional patterns by standardised interpretation of pulmonary function tests in the diagnosis of respiratory diseases within a concept of precision medicine.[1–10] There are, however, mandatory prerequisites for studies predicting disease. For the calculation of individual z-scores, as recommended for the assessment of functional severity instead of percentage predicted values, the availability of normative reference equations applied transitionally over a wide age range is essential, especially when assessing lung function data within several diagnostic classes over a longer age range.[11–15] This takes into account the age- and growth-related variability between individuals in the distribution of the reference population.

Chronic obstructive pulmonary disease (COPD) is a common, complex and heterogeneous disorder, characterised not only by airflow limitation but also by small airway dysfunction,[16–19] pulmonary hyperinflation, gas trapping and gas exchange disturbances,[20–23] due to an increased inflammatory response of the lung. Although considerable individual heterogeneity within COPD is known, reflecting different physiological mechanisms, such as endotypes and phenotypes,[24] it is not surprising, that morbidity and mortality cannot be predicted from the degree of lung function impairment based only on spirometric airflow limitation in COPD alone.[3] There is a need for functional algorithms for homogeneous subgroups of patients,[25] as part of a concept of personalised medicine.[2 3 26 27]

In addition to spirometric measurements mainly obtained by forced expiratory flow-volume measurements, whole-body plethysmography is still widely used in many lung function laboratories of centres for respiratory diseases. There are numerous parameters that can be used to calculate functional characteristics of airway dynamics from the plethysmographic sR_{aw}-loops.[28–30] The most promising approach is based on the integral method, originally proposed by Matthys and Orth, which provides the integral of the $\oint \Delta V_{pleth} dV_T$ -loop (the so-called sR_{aw}-loop) as sWOB, from which the effective specific airway resistance (sR_{eff}) can be calculated.[31] We have recently demonstrated that good discrimination between asthma, asthma–COPD overlap (ACO)[32–34] and COPD is possible based on parameters obtained from the plethysmographic sR_{aw}-loop.[35] To visualise further information, not yet recognised in the sR_{aw}-loop, figure 1 shows a plethysmographic shift volume (V_{pleth}) and tidal flow (V′) plot of a patient with COPD, from which the inspiratory and expiratory parts of the breathing cycle are separately calculated. This results in parameters such as the inspiratory and expiratory sWOB ($sWOB_{in}$, $sWOB_{ex}$), as well as the inspiratory and expiratory sR_{eff} (sR_{eff}^{IN} and sR_{eff}^{EX}).

The aim of the present study was to establish reference equations for all parameters of the sR_{aw}-loop presented in figure 1, extended by parameters of central control of breathing such as the tidal volume (V_T), the respiratory drive ($P_{0.1}$) measured by means of a mouth occlusion pressure measurement 100 ms after inspiration, the mean inspiratory flow (V_T/T_I) and the ratio between inspiratory time and total respiratory time (T_I/T_{tot}) of each respiratory cycle, and hence to analyse them for their discriminatory power to define specific functional traits within the abovementioned obstructive lung diseases.

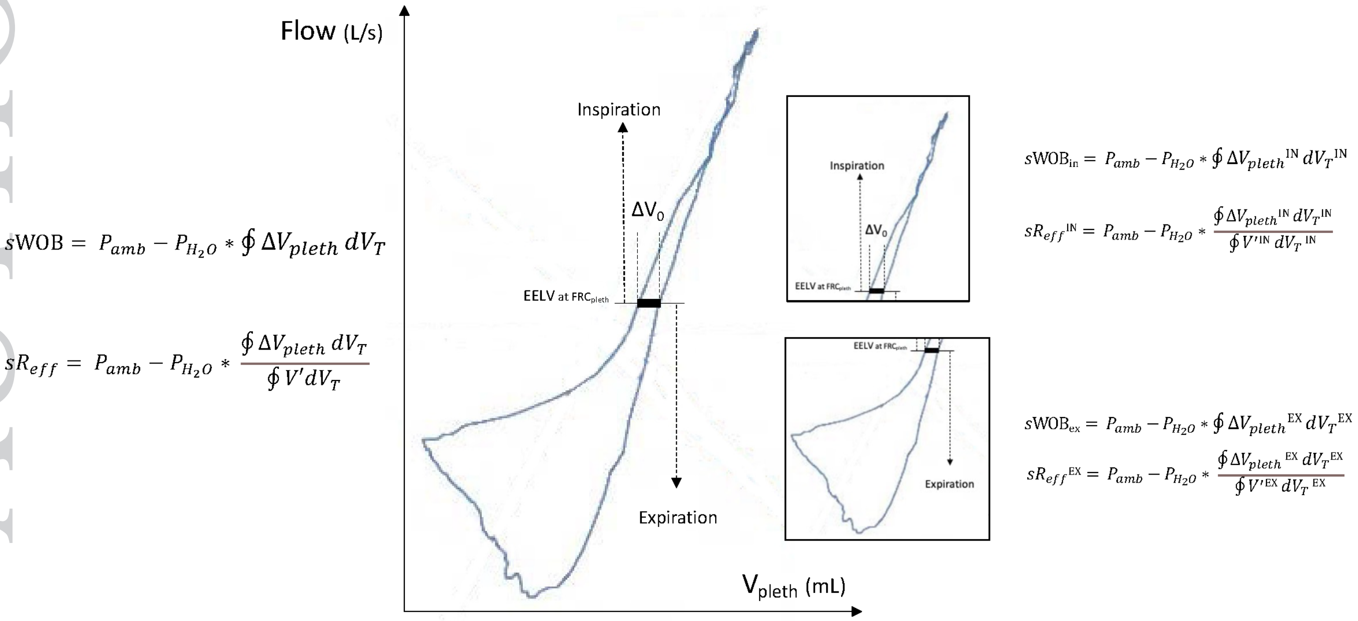

Figure 1 Aerodynamic parameters computed by integrals from a plethysmographic shift volume–tidal flow loop (sR_{aw}-loop) obtained from a patient with COPD, separated into the inspiratory and expiratory limb of the loop. EELV, end-expiratory lung volume; FRC_{pleth}, functional residual capacity; sR_{eff}, effective specific airways resistance; sR_{eff}^{EX}, expiratory, effective specific airways resistance; sR_{eff}^{IN}, inspiratory, effective specific airways resistance; sWOB, resistive aerodynamic work of breathing; $sWOB_{in}$, resistive aerodynamic work of breathing integrated from the inspiratory part of the R_{aw}-loop; $sWOB_{ex}$, resistive aerodynamic work of breathing integrated from the expiratory part of sR_{aw}-loop; V_{pleth} plethysmographic shift volume; ΔV_0, difference between inspiratory and expiratory shift-volume at FRC_{pleth}.

MATERIAL AND METHODS

Study design

In the present study, we refer to retrospectively evaluated data obtained from five Swiss centres (University Children's Hospital, Bern; Centre of Pulmonary Diseases, Hirslanden Hospital Group, Salem-Hospital, Bern, Switzerland; Clinic of Pneumology, Cantonal Hospital, St. Gallen, Switzerland; Centre of Pulmonology, Hirslanden Hospital Group, Clinic Hirslanden, Zürich, Switzerland; Division of Pulmonary Medicine, Clinic Barmelweid, Barmelweid, Switzerland), tested between 2006 and 2016. A healthy control collective of healthy children and adults comprises data of subjects participating in an epidemiologic study, in addition to data of healthy, no-smoking lab technicians, students, volunteers and hospital staff. The patients have been referred to the centres for extended pulmonary function testing and optimising therapy. Based on anamnestic, clinical features and functional criteria, the patients were classified by trained paediatric and adult pulmonologists into three diagnostic classes: (1) bronchial asthma, (2) COPD with coexisting asthma (ACO) and (3) COPD, the data have been exported between 2018 and 2022. The authors had no access to information that could identify individual participants during or after data collection.

Study collective

From the previously used database defining normative equations of sWOB, sR_{eff} and the effective specific airway conductance (sG_{eff}) (n=314; children and adults),[30] data from 194 healthy subjects (34 children, 19 males, 15 females, aged 6–16 years; 160 adults, 62 males, 98 females, aged 17–85 years) could be used to define the inspiratory ($sWOB_{in}$, $sReff^{IN}$) and the expiratory part ($sWOB_{ex}$, $sReff^{EX}$) of the sR_{aw}-loop.

From the previously used database defining functional predictors discriminating ACO from asthma and COPD,[35] data of 294 patients (16 children with asthma, 3 males, 13 females, aged 6–16 years; and 278 adults, 112 males, 166 females, aged 17–92 years) could be included to define the inspiratory ($sWOB_{in}$, $sReff^{IN}$) and the expiratory part ($sWOB_{ex}$, $sReff^{EX}$) of the sR_{aw}-loop.

Pulmonary function procedures

In all five centres, the same type of constant-volume whole-body plethysmographs (Master Screen Body, Jaeger Würzburg, Germany) was used by standard techniques according to ATS-ERS criteria[36] and revised Swiss guidelines.[37] The exported data were obtained from the same system software (JLAB V.5.2, SentrySuite V.1.29 resp.). Inclusion criteria were reproducible baseline measurements with at least five shift volume–tidal flow loops of comparable shapes and closed expiratory part of the shift volume–tidal flow loops. Moreover, in healthy subjects, the inspiratory capacity must be within the range of normal to achieve correct total lung capacity and vital capacity values. Apart from a daily calibration procedure given by the software of the Master Screen Body, monthly so-called 'biological controls' were performed measuring normal values of a healthy, non-smoking technician. Apart from the extension of parameters obtained by the sR_{aw}-loop, we found it important to introduce also parameters defining the control of breathing. As initially worked out by Whitelaw *et al*,[38] the respiratory drive ($P_{0.1}$) was measured by means of a mouth occlusion pressure measurement 100 ms after inspiration as automatic occlusion response during tidal breathing. This makes the $P_{0.1}$ effort-independent and reproducible and minimises vagal influences because pressure swings do not lead to corresponding changes in volume.[39] Since it starts from end-expiratory lung volume (EELV), any drop in $P_{0.1}$ is independent of the recoil pressure of the lung or thorax and airway resistance because the flow is interrupted.[40] Moreover, effective inspiratory impedance defined as product of $P_{0.1}$ and the ratio between V_T and the inspiratory time (T_I) was calculated.[41 42]

Mathematical and statistical approaches

To define the mathematical relationship between each lung function parameter as dependent parameters to be predicted, we first used the 'curve estimation' tool of the SPSS (V.29, IBM, Armonk, New York, USA) for linear, logarithmic, power and exponential regressions, as well as quadratic and cubic function for age, height and weight, as previously proposed.[43] It turned out that most mathematical relationships featured power associations. Therefore, our modelling used absolute values and their natural logarithm (ln). For the evaluation of the reference equations of sWOB, $sWOB_{in}$, $sWOB_{ex}$, sReff, sR_{eff}^{IN}, sR_{eff}^{EX} and sR_{tot} multilevel linear models with a two-level hierarchy was used, as previously presented.[30] By this mathematical modelling, the individual z-scores of each patient could be calculated instead of percentage predicted values as recommended to be used in the assessment of severity, especially if lung function data over a longer age range are assessed.[15] Previous work has shown that airway resistance is highly dependent on the breathing pattern and the EELV at functional residual capacity (FRC). We searched apart from anthropometric measures (gender, age and height), also for interrelationships with parameters of the breathing pattern and the timing of breathing ((V_T, V_T/FRC, T_I, V_T/T_I) at rest.

RESULTS

Healthy subjects and generation of normative predicting equations

The age distribution of the anthropometric measures and lung function data of the healthy subjects within six age classes expressed as per cent predicted

Table 1 Anthropometric and lung function data within six age classes in the healthy subjects

Healthy subjects n=194	**Age (years)**					
	6–12	12–18	18–24	24–48	48–66	>66 y
Gender						
Male/female	13/9	6/7	10/13	18/48	25/22	9/14
Anthropometric data						
Height (cm)	135.0±10.5	161.7±7.3	171.9±6.9	173.5±7.6	171.4±6.8	166.5±7.9
Weight (kg)	30.9±7.5	51.1±10.9	62.9±7.3	73.3±12.3	78.3±10.4	69.7±11.6
BMI (kg/m^2)	16.7±2.7	19.4±3.0	21.2±1.5	24.2±3.0	26.6±2.8	25.0±2.7
Static lung volumes						
TLC (% pred.)	98.4±5.7	102.1±6.1	101.0±4.5	104.9±8.0	101.7±8.5	97.3±11.2
FRC$_{pleth}$ (% pred.)	109.4±6.2	111.6±6.9	104.7±6.2	109.2±6.7	104.7±8.0	104.4±8.9
RV (% pred.)	111.7±21.1	118.1±24.1	116.1±21.7	105.3±21.0	113.2±16.9	103.1±16.2
Spirometry						
FEV$_1$ (% pred.)	102.8±10.3	97.0±8.5	95.1±8.2	103.912.5	97.2±11.5	104.8±13.2
FEV$_1$/FVC (% pred.)	105.8±7.3	106.0±5.0	107.4±8.9	106.7±10.0	110.5±9.1	114.0±9.7
FEF$_{25–75}$ (% pred.)	113.2±29.6	98.8±17.9	102±19.2	106.6±21.4	107.9±24.0	122.8±20.5
Airway dynamics						
sR$_{eff}$ (% pred.)	99.6±5.1	102.1±6.7	97.1±8.7	101.0±10.1	100.6±10.5	101.2±10.2
sR$_{tot}$ (% pred.)	100.6±9.0	103.3±10.8	96.2±8.9	101.0±8.6	100.6±8.8	100.9±9.0
sWOB (% pred.)	99.3±6.9	99.9±7.9	101.4±7.4	100.0±7.6	102.1±8.5	98.3±8.2

FEF$_{25–75}$, forced expiratory flow between 25% and 75% vital capacity; FEV$_1$, forced expiratory volume in 1 s; FRC$_{pleth}$, plethysmographic functional residual capacity; FVC, forced vital capacity; RV, reserve volume; sR$_{eff}$, effective specific airway resistance; sR$_{tot}$, specific total airway resistance; sWOB, specific aerodynamic work of breathing; TLC, total lung capacity.

are given in table 1. All lung function parameters presented with values within 95 percentiles equal to ±1.645 z-score of values predicted.[30 43 44]

Predictive data analysis of airway dynamic parameters of the sR$_{aw}$-loop

From the digitalised data points of each individual's sR$_{aw}$-loop shown in figure 1, we searched for inter-related parameters to define gender-specific interactions of parameters within four 'segments': (a) 'anthropometry': age, ln(age), (age)^2, height, ln(height) (height)^2, (b) 'static lung volumes': FRC$_{pleth}$, ln(FRC$_{pleth}$), (c) 'ventilation': V$_T$, ln(V$_T$) and (d) 'control of breathing': V$_T$/T$_I$, ln(V$_T$/T$_I$), T$_I$/T$_{tot}$. By multilinear modelling, we computed stepwise regressions within these 'segments' for sWOB and sR$_{eff}$ and their inspiratory (sWOB$_{in}$, sR$_{eff}$^{IN}) and expiratory parts (sWOB$_{ex}$, sR$_{eff}$^{EX}), resolving multicollinearity by analysis of variance (ANOVA), revealing the following normative equations:

$$\mathrm{sWOB} = \mathrm{EXP}\left(.072 + .116^{*}\ln\left(\mathrm{age}\right) + 1.235^{*}\ln\left(\mathrm{V_T}\right) - .574^{*}\mathrm{T_I/T_{tot}}\right) \pm .082964\ (\mathrm{SEE})$$

$$\left(F - \mathrm{value} : 690, \mathrm{p} < 0.001\right)$$

$$\mathrm{sWOB_{in}} = \mathrm{EXP}\left(-.675 + .024^{*}\ln\left(\mathrm{age}\right) + .966^{*}\ln\left(\mathrm{V_T}\right)\right) \pm .038671\ (\mathrm{SEE})$$

$$\left(F - \mathrm{value} : 2086, \mathrm{p} < 0.001\right)$$

$$\mathrm{sWOB_{ex}} = \mathrm{EXP}\left(-.677 + .065^{*}\ln\left(\mathrm{age}\right) + .723^{*}\ln\left(\mathrm{V_T}\right) - .269^{*}\mathrm{T_I/T_{tot}}\right) \pm .030865\ (\mathrm{SEE})$$

$$\left(F - \mathrm{value} : 1660, \mathrm{p} < 0.001\right)$$

$$\mathrm{sR_{eff}} = \mathrm{EXP}\left(-4.332 + .073^{*}\mathrm{gender} + .035^{*}\ln\left(\mathrm{age}\right) + 5.047^{*}\mathrm{V_T/FRC} - 1.736^{*}\ln\left(\mathrm{V_T/FRC}\right)\right) \pm .080672$$

$$*\mathrm{gender} : \mathrm{male} = 0; \mathrm{female} = 1; \left(F - \mathrm{value} : 21.2, \mathrm{p} < 0.001\right)$$

$$\mathrm{sR_{eff}^{ln}} = \mathrm{EXP}\left(-.443 + .008^{*}\mathrm{gender} - .051^{*}\ln\left(\mathrm{FRC}\right) + .370^{*}\mathrm{V_T/FRC}\right) \pm .011147\ (\mathrm{SEE})$$

$$\left(F - \mathrm{value} : 20.2, \mathrm{p} < 0.001\right)$$

$$\mathrm{sR_{eff}^{EX}} = \mathrm{EXP}\left(-.688 + .032^{*}\mathrm{gender} + .058^{*}\ln\left(\mathrm{age}\right) - .303^{*}\ln\left(\mathrm{FRC}\right) - .347^{*}\ln\left(\mathrm{V_T/FRC}\right)\right) \pm .067386\ (\mathrm{SE}$$

$$\left(F - \mathrm{value} : 15.1, \mathrm{p} < 0.001\right)$$

$$\mathrm{sR_{tot}} = \mathrm{EXP}\left(-.053 - .142^{*}\ln\left(\mathrm{FRC}\right) - .529^{*}\mathrm{V_T/FRC}\right) \pm .07647\ (\mathrm{SEE})$$

$$\left(F - \mathrm{value} : 7.9, \mathrm{p} < 0.001\right)$$

Moreover, the parameters of the control of breathing (P$_{0.1}$, V$_T$/T$_I$) and the inspiratory impedance defined as Z$_{in}$^{pleth}=P$_{0.1}$/V$_T$/T$_I$) were assessed, giving the following normative equations:

$$\mathrm{P_{0.1}} = \mathrm{EXP}\left(-2.283 + 0.325^{*}\ln\left(\mathrm{age}\right) - 3.536\mathrm{E} - 5^{*}\left(\mathrm{age}\right)^{2}\right) \pm .06488\ (\mathrm{SEE})$$

$$\left(F - \mathrm{value} : 760, \mathrm{p} < 0.001\right)$$

$$\mathrm{V_T/T_I} = 0.148 - 0.025^{*}\mathrm{gender}^{*} - 0.004^{*}\mathrm{age} + 0.202^{*}\ln\left(\mathrm{age}\right) \pm .0444258\ (\mathrm{SEE})$$

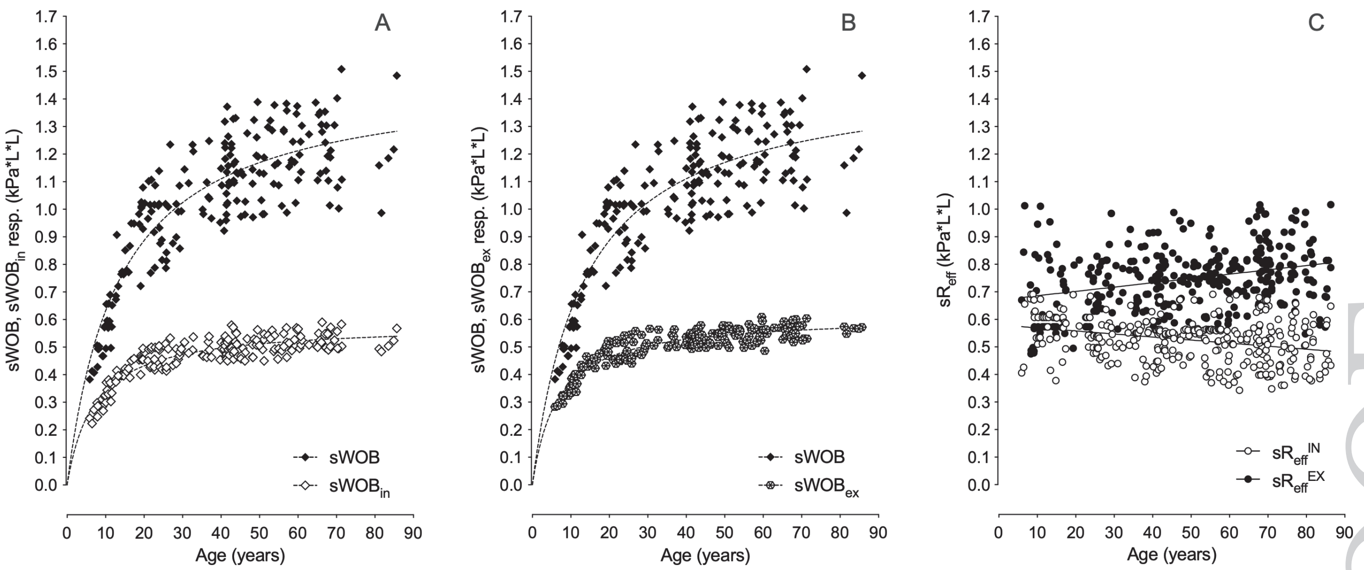

Figure 2 Age distributions of sWOB, in relation to sWOB$_{in}$ (A) and sWOB$_{ex}$ (B) and sR$_{eff}^{IN}$ in relation to sR$_{eff}^{EX}$ (C), over the age range of 6–86 years for healthy subjects in absolute terms. sWOB, resistive aerodynamic work of breathing; sWOB$_{ex}$, resistive aerodynamic work of breathing integrated from the expiratory part of sR$_{aw}$-loop; sWOB$_{in}$, resistive aerodynamic work of breathing integrated from the inspiratory part of the R$_{aw}$-loop; sR$_{eff}$, effective specific airway resistance; sR$_{eff}^{EX}$, expiratory, effective specific airways resistance; sR$_{eff}^{IN}$, inspiratory, effective specific airways resistance.

$$^{*}\text{gender} : \text{male} = 0; \text{female} = 1; \left(F - \text{value} : 131, \text{p} < 0.001\right)$$

$$T_I/T_{tot} = 0.347 - 0.010^{*}\text{gender}^{*} - 0.004^{*}\left(\text{age}\right) + 0.052^{*}\ln\left(\text{age}\right) + 3.641\text{E} - 5^{*}\left(\text{age}\right)^2 \pm .018294\ (\text{SEE})$$

$$^{*}\text{gender} : \text{male} = 0; \text{female} = 1; \left(F - \text{value} : 61, \text{p} < 0.001\right)$$

$$\text{d} - \text{P}_{ao}\text{x} = 0.6060 \pm 0.95537\ (\text{SD})$$

$$Z_{in}^{pleth} = 3.61 + 0.015^{*}\text{gender}^{*} + 0.066^{*}\ln\left(\text{age}\right) - 0.736^{*}\ln\left(\text{height}\right) + 1.268\text{E} - 5^{*}\left(\text{height}\right)^2 \pm .03086\ (\text{SEE})$$

$$^{*}\text{gender} : \text{male} = 0; \text{female} = 1; \left(F - \text{value} : 73, \text{p} < 0.001\right)$$

The age distributions of sWOB, in relation to sWOB$_{in}$ and sWOB$_{ex}$ on one side and sR$_{eff}^{IN}$ in relation to sR$_{eff}^{EX}$ on the other side, over the age range of 6–86 years for healthy males and females are given in figure 2. The inspiratory sWOB$_{in}$ contributed to 46.8%±5.8% of the sWOB (figure 2A), whereas sWOB$_{ex}$ provided 50.2%±7.2% to the sWOB (figure 2B). Regarding sR$_{eff}$, the inspiratory sR$_{eff}^{IN}$ was part of 25.5%±8.9% of sR$_{eff}$, whereas sR$_{eff}^{EX}$ contributed 43.0%±11.8% of sR$_{eff}$. Finally, sWOB$_{ex}$ was by the mean 9.4%±9.8% higher than sWOB$_{in}$, sR$_{eff}^{EX}$ by the mean 35.1% higher than sR$_{eff}^{IN}$, resp. (figure 2C).

Patients (asthma, ACO, COPD)

The age distribution of the anthropometric measures and lung function data of the patients within three diagnostic classes, expressed as z-scores, are given in table 2. The patients with asthma were significantly younger than those with ACO and COPD (p<0.001). The age distributions in the centres were similar. Regarding static lung volumes, patients with COPD presented with higher FRC$_{pleth}$ and hence incidence of pulmonary hyperinflation (asthma 19.8%; ACO: 32.8%; COPD 78.9%). Compared with the spirometric parameters (forced expiratory volume in 1 s (FEV$_1$), forced vital capacity (FVC)/FEV$_1$, forced expiratory flow between 25% and 75% vital capacity (FEF$_{25-75}$)), the plethysmographic parameters defining airway dynamics presented with much more pronounced differences between the three diagnostic groups, given by the *F*-value of the ANOVA, highest for sR$_{tot}$ (*F*=541), followed by sWOB$_{ex}$ (*F*=417).

Distributions of each lung function parameter

Regarding potentially discriminating parameters between the diagnostic classes using the *F*-statistic of ANOVA, the z-score distributions of each lung function parameter are synoptically presented in figure 3. There are quite great differences in the z-scores between the parameters and within the diagnostic classes. Whereas parameters of forced spirometry covered only a z-score range over 12, and of static lung volumes over 11, the z-score ranges for the work of breathing covered a z-score range over 75, and of the airway resistances over 40. Using one-way ANOVA to test the statistical differences among the means of the three diagnostic classes, highest ANOVA *F*-values were found for sR$_{tot}$ (540.9), followed by sWOB$_{ex}$ (416.8) and d-P$_{ao}$ (406.1). These three parameters showed also highest mean differences between ACO versus asthma and ACO versus COPD (p<0.01).

Table 2 The age distribution of the anthropometric measures and lung function data of the patients within three diagnostic classes, expressed as z-scores

Patients n=294	Asthma (n=154)	ACO (n=64)	COPD (n=76)	All (n=294)	F ANOVA	Sig. p value
Age (years)	40.9±20.0	58.5±17.6	69.2±10.9	52.1±21.4	71.2	<0.001
Male/female	44/110	34/30	37/39	115/179		
Anthropometric data						
Height (cm)	165.8±10.2	169.5±9.4	165.8±8.7	166.6±9.7	3.6	n.s.
Weight (kg)	69.2±16.1	74.3±14.6	71.7±1.2	71.0±16.6	2.3	n.s.
BMI (kg/m^2)	24.9±5.0	25.8±4.2	26.1±5.7	25.4±5.1	1.4	n.s.
Static lung volumes						
TLC (z-scores)	0.9±1.1	0.9±0.7	1.5±1.0	1.1±1.1	7.5	<0.001
FRC$_{pleth}$ (z-scores)	0.6±0.9	1.2±1.0	2.9±1.3	1.3±1.4	125.9	<0.001
RV (z-scores)	1.5±1.3	2.0±2.5	4.4±2.2	2.3±2.0	83.2	<0.001
Spirometry						
FEV$_1$ (z-scores)	−0.5±1.0	−1.0±1.2	−2.8±1.2	−1.2±1.5	116.6	<0.001
FEV$_1$/FVC (z-scores)	−0.1±1.0	−1.0±2.0	−4.0±2.0	−1.3±2.2	160.9	<0.001
FEF$_{25–75}$ (z-scores)	−0.4±1.0	−0.9±1.1	−1.5±0.9	−0.8±1.1	32.3	<0.001
Airway dynamics						
sWOB (z-scores)	2.6±4.7	7.8±4.0	16.2±3.8	7.2±7.1	254.8	<0.001
sWOB$_{in}$ (z-scores)	2.2±6.0	6.5±5.3	23.9±9.1	8.7±11.4	264.7	<0.001
sWOB$_{ex}$ (z-scores)	5.8±8.2	16.6±7.1	38.6±8.7	16.6±16.0	416.8	<0.001
sR$_{eff}$ (z-scores)	2.1±3.1	6.0±3.3	14.4±5.1	6.1±6.3	274.6	<0.001
sR$_{eff}^{IN}$ (z-scores)	4.3±17 5	34.8±25.7	97.2±31.5	37.5±50.8	360.6	<0.001
sR$_{eff}^{EX}$ (z-scores)	1.1±2.8	4.2±4.4	16.0±6.4	5.6±7.6	301.1	<0.001
sR$_{tot}$ (z-scores)	3.1±2.7	6.5±3.6	19.4±4.8	8.1±7.7	540.9	<0.001

ACO, asthma–COPD overlap; ANOVA, analysis of variance; BMI, Body Mass Index; COPD, chronic obstructive pulmonary disease; FEF$_{25–75}$, forced expiratory flow between 25% and 75% vital capacity; FEV$_1$, forced expiratory volume in 1 s; FRC$_{pleth}$, plethysmographic functional residual capacity; FVC, forced vital capacity; RV, reserve volume; sR$_{eff}$, effective specific airway resistance; sR$_{eff}^{EX}$, expiratory, effective specific airways resistance; sR$_{eff}^{IN}$, inspiratory, effective specific airways resistance; sR$_{tot}$, specific total airway resistance; sWOB, specific aerodynamic work of breathing; sWOB$_{ex}$, resistive aerodynamic work of breathing integrated from the expiratory part of sR$_{aw}$-loop; sWOB$_{in}$, resistive aerodynamic work of breathing integrated from the inspiratory part of the R$_{aw}$-loop; TLC, total lung capacity.

Linear discriminant analysis (LDA)

Potentially discriminating parameters of airway dynamics (FEV$_1$, FVC/FEV$_1$, FEF$_{25–75}$, sWOB, sWOB$_{in}$, sWOB$_{ex}$, sR$_{eff}$, sR$_{eff}^{IN}$, sR$_{eff}^{EX}$, sR$_{tot}$, all parameters expressed as z-scores) were included into the model of an LDA, using the Canonical Discriminant Function tool of SPSS. The LDA based on all 10 parameters from which by stepwise exclusion 6 remained in the model is graphically represented in figure 4. The overall prediction accuracy was 84.7% (asthma: 81.2%, ACO: 81.3%, COPD: 94.7%). Based on Wilks' lambda (Λ) test statistics six parameters sR$_{tot}$ (Λ=0.185), sWOB$_{ex}$ (Λ=0.163), sR$_{eff}$ (Λ=0.152), sWOB$_{in}$ (Λ=0.153), sR$_{eff}^{IN}$ (Λ=0.151) and sR$_{eff}^{EX}$ (Λ=0.146) discriminated between the three diagnostic classes.

DISCUSSION

The shape of the sR$_{aw}$-loop is quite complex and not a simple narrow oval loop, especially not in patients with obstructive lung diseases. Consequently, different investigators have used different portions of the loop to approximate a representative value for the entire breathing cycle. The effective specific resistance (sR$_{eff}$) and the total specific resistance (sR$_{tot}$), have been well established,[31 45 46] although they have not received sufficient attention in the literature.

The specific work of breathing assessed by plethysmography

A major step in the assessment of airway dynamics throughout the entire plethysmographic shift volume–tidal flow loop and its mathematical understanding of loop shaping was first elaborated by Matthys and Orth.[31] They extended the dimensional analysis applied by Jaeger and Otis,[47] to integrate these contributions to an 'effective resistance' that included the effects of the entire range of variable flows during tidal breathing and non-linearities of the breathing loop. The outstanding feature of these of airway dynamic parameters is their reflection of an integrative assessment of airway behaviour throughout the tidal breathing cycles.

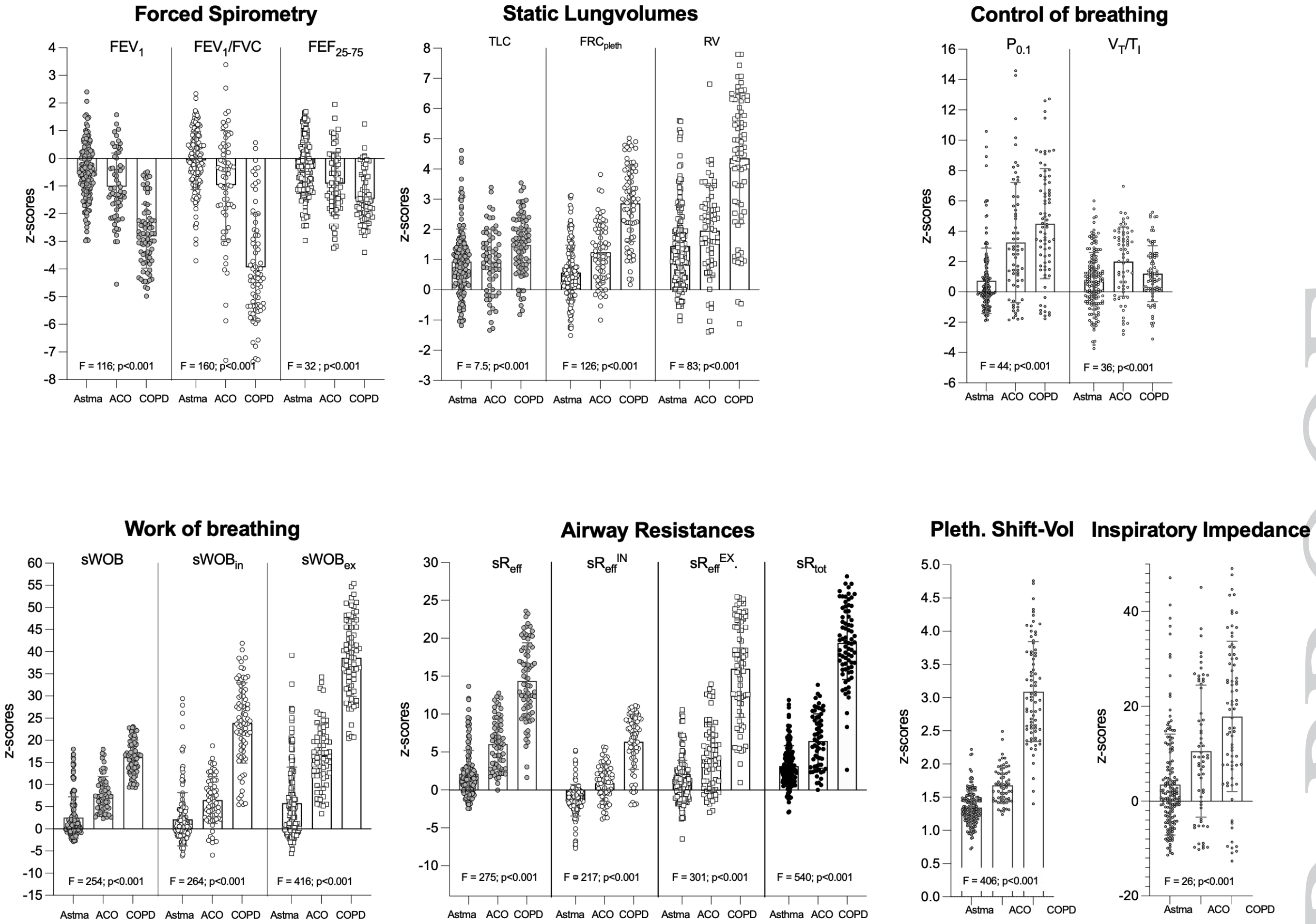

Figure 3 Z-score distribution of each lung function parameter within the three diagnostic classes. ACO, asthma–COPD overlap; COPD, chronic obstructive pulmonary disease; $FEF_{25–75}$, forced expiratory flow between 25% and 75% vital capacity; FEV_1, forced expiratory volume in 1 s; FRC_{pleth}, plethysmographic functional residual capacity; FVC, forced vital capacity; $P_{0.1}$, respiratory drive; RV, reserve volume; sR_{eff}, effective specific airway resistance; sR_{eff}^{EX}, expiratory, effective specific airways resistance; sR_{eff}^{IN}, inspiratory, effective specific airways resistance; sWOB, resistive aerodynamic work of breathing; $sWOB_{ex}$, resistive aerodynamic work of breathing integrated from the expiratory part of sR_{aw}-loop; $sWOB_{in}$, resistive aerodynamic work of breathing integrated from the inspiratory part of the R_{aw}-loop; TLC, total lung capacity; V_T/T_I, mean inspiratory flow.

The digital integration of the respective loops improves the signal-to-noise ratio.

Findings of the present study

Normative values of the airway dynamic parameters depend not only on anthropometric measures but also on parameters of the breathing pattern, timing of breathing and central control of breathing. This applies not only to sWOB and sR_{eff}, as previously reported,[30] but also to the inspiratory and expiratory parts of the sR_{aw}-loop, which are indicated by $sWOB_{in}$, $sWOB_{ex,}$ sR_{eff}^{IN} and sR_{eff}^{EX}. Therefore, we postulate, that the effort of breathing to move the lung, and hence the sWOB obtained by plethysmography allows an estimation of the gas dynamic, resistive effort integrating the needed plethysmographic shift volume over the tidal volume. In a constant volume whole-body plethysmograph, the shift volume refers to the size of the lung volume that decreases on compression and increases on decompression, and is proportional to the underpressure and overpressure in the lung and the absolute, ventilated and non-ventilated, lung volume. It follows that the specific gas-dynamic work performed during tidal breathing at rest can be estimated by simultaneously assessing the plethysmographic shift volume and the corresponding tidal volume. By this way, the sWOB can be considered as an approximation of the total gas-dynamic work, performed during a complete breathing cycle.

Most importantly, this kind of modelling has been shown to be predictive for a large age range from childhood to adulthood.[35] In fact, the healthy human body has a wide range of regulatory mechanisms during normal breathing and can serve as a model to understand what the interactions would look like in patients with respiratory disorders. The pattern of breathing and airway resistance during exercise in terms of the relationships between inspiratory time (T_I), tidal volume (V_T) and EELV has been studied in detail by Hesser and Lind,[48–50] showing the interrelationship between T_I and V_T at different ranges. This is important for assessing the overall understanding of how airway dynamics relate

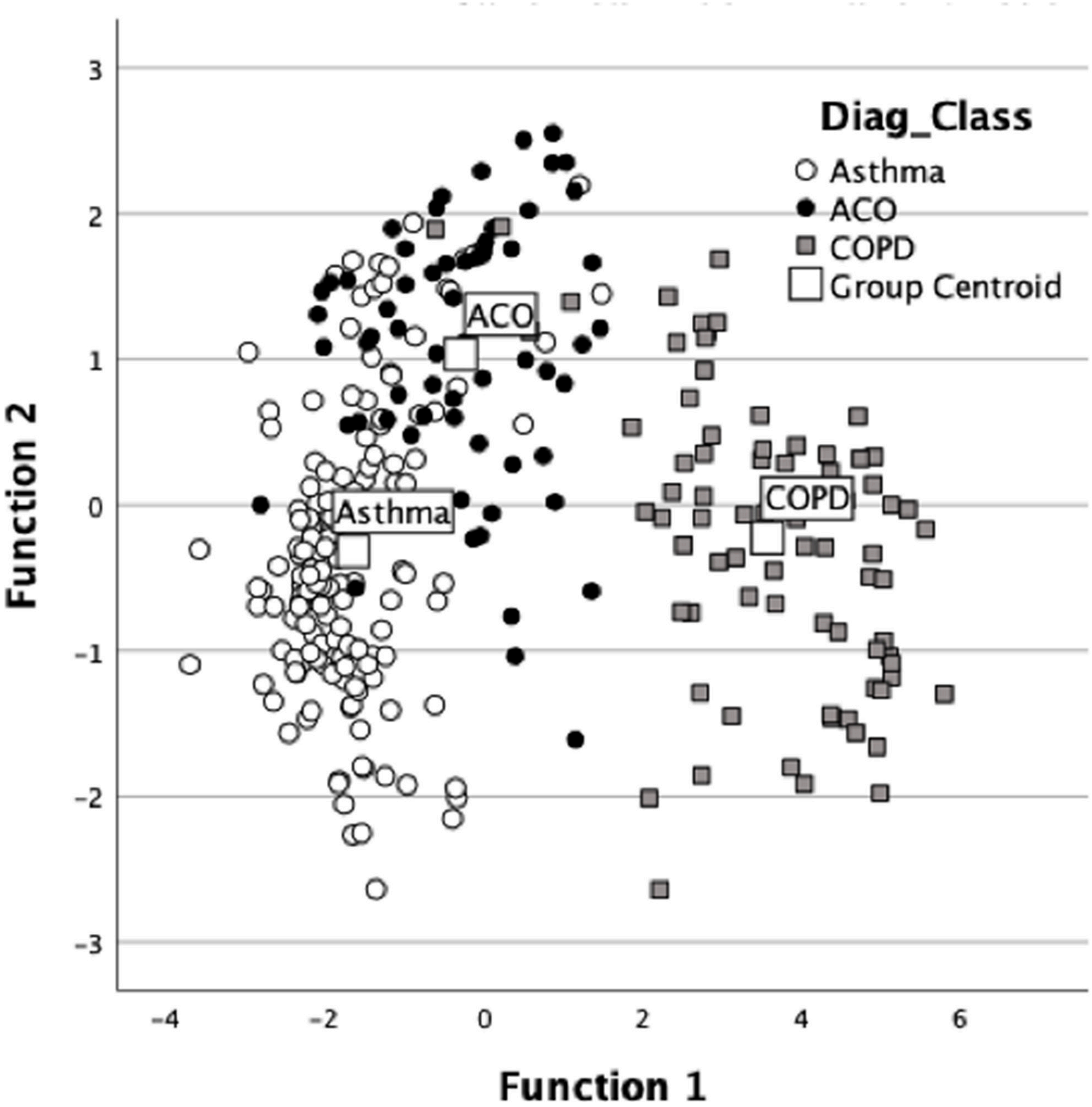

Figure 4 Linear discriminant analysis based on all 10 parameters from which by stepwise exclusion 6 remained in the model (sR_{tot}, $sWOB_{ex}$, sR_{eff}, $sWOB_{in}$, sR_{eff}^{IN} and sR_{eff}^{EX}), differentiating between asthma, ACO and COPD. ACO, asthma–COPD overlap; COPD, chronic obstructive pulmonary disease; sR_{eff}, effective specific airway resistance; sR_{eff}^{EX}, expiratory, effective specific airways resistance; sR_{eff}^{IN}, inspiratory, effective specific airways resistance; $sWOB_{ex}$, resistive aerodynamic work of breathing integrated from the expiratory part of sR_{aw}-loop; $sWOB_{in}$, resistive aerodynamic work of breathing integrated from the inspiratory part of the R_{aw}-loop.

to the distending forces of the thoraco-pulmonary system, especially in diseased subjects with pulmonary hyperinflation, small airway dysfunction and/or pulmonary restriction. Apart from the advantage that airway dynamics can be assessed in close relation to these promoting factors of actual breathing, plethysmographic measurements offer the advantage that they can be performed during tidal breathing, requiring little cooperation from the subject and, therefore are effort independent. For such measurements, deep inspiration and forced breathing manoeuvres that influence the regional distribution of the air are not required, and such side effects can be avoided.

Impact of the ageing pulmonary system on airway dynamics

Ageing is associated with the loss of lung elastic recoil and stiffening of the chest wall as well as decreased maximum respiratory pressure-generating capacity, airway calibre and expiratory flow rates during exercise.[51–54] The mechanisms responsible for the elevated sWOB with age can be better understood, if sWOB is partitioned into the inspiratory ($sWOB_{in}$) and expiratory ($sWOB_{ex}$) part, related to age and other linked parameters. In fact, as shown in figure 2 both $sWOB_{in}$ and $sWOB_{ex}$ significantly increase with age curvilinearly (F=16.7; p<0.001), and additionally, $sWOB_{ex}$ increases significantly more than $sWOB_{in}$ (F=378.9; p<0.001). This finding confirms previous results obtained in exercise studies, that the smaller airways and greater mechanical constraints during exercise likely result in increased aerodynamic sWOB in the older compared with the younger adults.[54] It is well documented that in normal subjects at rest, $sWOB_{in}$ and sR_{eff}^{IN} and hence the work needed against lung and chest wall inspiratory resistance is a minor component of the work of breathing.[55] The effective resistance of the relaxed chest wall is caused by pressure–volume hysteresis measured as sR_{eff}^{IN}. However, sR_{eff}^{IN} is small at normal breathing rates,[56] the diameter of the bronchi enlarges during inspiration and consequently $sWOB_{in}$ is lower than $sWOB_{ex}$. As the regression analyses indicate, there are two other mechanisms, which must be considered. The ratio between V_T and FRC_{pleth} (ventilation in relation to the EELV) decreases dramatically in young age, remaining thereafter more or less stable. This parameter could play an important role in patients with obstructive lung disease, if the EELV is increased due to pulmonary hyperinflation, or trapped gases are present.

Relevance to differentiate parameters of the inspiratory and expiratory parts separately

As it could be shown by the canonical discriminant analysis and based on Wilks' lambda (Λ) test statistics, sR_{tot} presented with the most discriminative power followed by $sWOB_{ex}$, sR_{eff}, $sWOB_{in}$, sR_{eff}^{IN} and sR_{eff}^{EX} differentiating between the three diagnostic classes. Noteworthy, the three spirometric parameters FEV_1, FEV_1/FVC and $FEF_{25–75}$ were excluded from the model. Furthermore, the rating list of discriminative lung function parameters revealed that the inclusion of aerodynamic parameters separating the inspiratory from the expiratory limb of the sR_{aw}-loop is highly recommended.

Limits of the methods

In modern plethysmographs, the thermos-hygrometric artefact from inspiration to expiration is automatically corrected by algorithms however, different depending on the manufacturers. It is understandable that the details of these algorithms are not published or provided with the manuals of the plethysmograph. Therefore, it was essential to have in each centre the same plethysmograph and the same software. It follows that the reference equations are valid only for the Jaeger plethysmograph used to collect these data.

Perspectives and clinical implications

We have recently demonstrated that parameters of airway dynamics are important diagnostic tools as target parameters both, the assessment of the bronchodilator response[39] and the assessment of airway hyper-reactivity by methacholine challenge test in patients with asthma, ACO and COPD.[57] Both test techniques are principally based on defining airway patency, and hence changes of airway dynamics during these test procedures. In so far, the specific aerodynamic work of breathing could well be a new reliable parameter to define specific disease endophenotypes.

The availability of normative reference equations applied over a wide age range are prerequisites for studies predicting disease progression in obstructive lung diseases. Not only spirometric parameters but also plethysmographic parameters of airway dynamics evaluated from the sR_{aw}-loop feature new insights into the physiopathology of these diseases. There is increasing interest in incorporating independent discriminatory parameters within new concepts of 'artificial intelligence',[4 58] highlighting and comparing the various functional facets and the physiological complexity within obstructive lung diseases. Using extended sets of spirometric and plethysmographic parameters in a multivariate approach, thus enabling the identification of functional traits within the diagnosis of obstructive pulmonary diseases. A new option now is to use these normative equations for target parameters to differentiate the functional physiopathology between different airway diseases. Preliminary results of an ongoing study reveal that, if a whole set of holistically evaluated parameters of spirometry and plethysmography are well-tailored and introduced within a multidimensional perception, treatable trait strategies as new concepts towards precision medicine can be developed.[7 10] It follows that the analysis of new parameters obtained by the plethysmographic sR_{aw}-loop may well discriminate between different obstructive lung diseases and their subtypes.

CONCLUSIONS

There are many advantages using the plethysmographic parameters (sWOB, sR_{eff}) derived from the sR_{aw}-loop subdividing the inspiratory from the expiratory part of the breathing cycle. Our work presented here provides normative equations allowing the introduction of new parameters such as $sWOB_{in}$, $sWOB_{ex}$, sR_{eff}^{IN} and sR_{eff}^{EX}. Moreover, the study demonstrates that parameters of airway dynamics are highly inter-related with parameters of the central control of breathing such as $P_{0.1}$, V_T/T_I and T_I/T_{tot}. Depending on which functional characteristics are evaluated in the assessment of functional derangements in patients with obstructive lung diseases, we discovered that $sWOB_{in}$, $sWOB_{ex}$, sR_{eff}^{IN} and sR_{eff}^{EX} are new discriminating target parameters, which serve as a much better differentiation between chronic obstructive diseases and their subtypes, especially between COPD and ACO, improving the concept of precision medicine.

Author affiliations
[1]Center of Pneumology, Hirslanden Salem-Spital, Bern, Switzerland
[2]School of Biomedical and Precision Engineering, University of Bern, Bern, Switzerland
[3]Research in Respiratory Diagnostics, Medical Development, Berlin, Germany
[4]Vyaire Medical GmbH, Höchberg/Würzburg, Germany
[5]Hirslanden Precise, Genetic Medicine, Zollikon/Zürich, Switzerland
[6]Department of Pneumology, University of Freiburg, Freiburg im Breisgau, Germany

Acknowledgements We thank all the participants, the parents of children and the technicians who volunteered for lung function testing diligently devoting their time.

Contributors RK designed, coordinated and analysed the data, and drafted the manuscript. H-JS and JR gave advice on the technical parts of the data acquisition and took part in the interpretation of data and revising. SG and HM edited and revised the manuscript. All authors approved the final version of the manuscript.

Funding The data collection was part of various research projects, supported by grants of the Swiss National Science Foundation (SNF 32-040681.94 and SNF 32-040562.95).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study was planned according to the Federal Law of Human Research, conceptualised according to the Swiss Ethics Committees on research involving humans and was conducted in accordance with the tenets of the Declaration of Helsinki. The study is part of the framework of the project entitled “Functional diversification of the Asthma-ACO-COPD multi-centre study” (ID 2017-00259), approved by the Governmental Ethics Committees of the State of Bern, the State of St. Gallen and the State of Zürich (Project KEK-BE PB_2017-00104). Written informed consent was waived because of the retrospective study design, which follows the institutional and national policies concerning research approvals. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Master files have been stored and secured in the Clinical Trial Unit, Hirslanden Corporate Office, CH-8152 Glattpark, Switzerland.

ORCID iD

Richard Kraemer http://orcid.org/0000-0002-1542-2420

REFERENCES

1 Agusti A, Bel E, Thomas M, *et al*. Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J* 2016;47:410–9.
2 Wouters EFM, Wouters BBREF, Augustin IML, *et al*. Personalised pulmonary rehabilitation in COPD. *Eur Respir Rev* 2018;27:170125.
3 Franssen FM, Alter P, Bar N, *et al*. Personalized medicine for patients with COPD: where are we. *Int J Chron Obstruct Pulmon Dis* 2019;14:1465–84.
4 Lopez-Campos JL, Centanni S. Current approaches for phenotyping as a target for precision medicine in COPD management. *COPD* 2018;15:108–17.
5 Brightling C, Greening N. Airway inflammation in COPD: progress to precision medicine. *Eur Respir J* 2019;54:1900651.
6 Lopes-Pacheco M. CFTR Modulators: the changing face of cystic fibrosis in the era of precision medicine. *Front Pharmacol* 2019;10:1662.
7 McDonald VM, Fingleton J, Agusti A, *et al*. Treatable traits: a new paradigm for 21st century management of chronic airway diseases: treatable traits down under international workshop report. *Eur Respir J* 2019;53:1–16.
8 Leung JM, Obeidat M, Sadatsafavi M, *et al*. Introduction to precision medicine in COPD. *Eur Respir J* 2019;53:1802460.
9 Brandsma C-A, Van den Berge M, Hackett T-L, *et al*. Recent advances in chronic obstructive pulmonary disease pathogenesis: from disease mechanisms to precision medicine. *J Pathol* 2020;250:624–35.
10 Cardoso J, Ferreira AJ, Guimarães M, *et al*. Treatable traits in COPD - A proposed approach. *Int J Chron Obstruct Pulmon Dis* 2021;16:3167–82.
11 Pauwels RA, Buist AS, Calverley PM, *et al*. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO global initiative for chronic obstructive lung disease (GOLD) workshop summary. *Am J Respir Crit Care Med* 2001;163:1256–76.
12 Swanney MP, Ruppel G, Enright PL, *et al*. Using the lower limit of normal for the Fev1/FVC ratio reduces the misclassification of airway obstruction. *Thorax* 2008;63:1046–51.
13 Quanjer PH, Enright PL, Miller MR, *et al*. The need to change the method for defining mild airway obstruction. *Eur Respir J* 2011;37:720–2.
14 Scholes S, Moody A, Mindell JS. Estimating population prevalence of potential airflow obstruction using different spirometric criteria: a pooled cross-sectional analysis of persons aged 40-95 years in England and Wales. *BMJ Open* 2014;4:e005685.
15 Stanojevic S, Graham BL, Cooper BG, *et al*. Official ERS technical standards: global lung function initiative reference values for the carbon Monoxide transfer factor for caucasians. *Eur Respir J* 2017;50:1–13.
16 Burgel PR. The role of small airways in obstructive airway diseases. *Eur Respir Rev* 2011;20:23–33.
17 Usmani OS, Barnes PJ. Assessing and treating small airways disease in asthma and chronic obstructive pulmonary disease. *Ann Med* 2012;44:146–56.
18 Perez T, Chanez P, Dusser D, *et al*. Small airway impairment in moderate to severe asthmatics without significant proximal airway obstruction. *Respir Med* 2013;107:1667–74.
19 Usmani OS, Singh D, Spinola M, *et al*. The prevalence of small airways disease in adult asthma: a systematic literature review. *Respir Med* 2016;116:19–27.
20 Hogg JC, Macklem PT, Thurlbeck WM. The resistance of small airways in normal and diseased human lungs. *Aspen Emphysema Conf* 1967;10:433–41.
21 Macklem PT, Mead J. Resistance of central and peripheral airways measured by a retrograde catheter. *J Appl Physiol* 1967;22:395–401.
22 Hogg JC, Macklem PT, Thurlbeck WM. Site and nature of airway obstruction in chronic obstructive lung disease. *N Engl J Med* 1968;278:1355–60.
23 Bates JHT, Suki B. Assessment of peripheral lung mechanics. *Respir Physiol Neurobiol* 2008;163:54–63.
24 Agustí A, Celli B, Faner R. What does Endotyping mean for treatment in chronic obstructive pulmonary disease. *Lancet* 2017;390:980–7.
25 Vanfleteren L, Spruit MA, Wouters EFM, *et al*. Management of chronic obstructive pulmonary disease beyond the lungs. *Lancet Respir Med* 2016;4:911–24.
26 Agusti A, Sobradillo P, Celli B. Addressing the complexity of chronic obstructive pulmonary disease: from phenotypes and biomarkers to scale-free networks, systems biology, and P4 medicine. *Am J Respir Crit Care Med* 2011;183:1129–37.
27 Topalovic M, Das N, Burgel P-R, *et al*. Artificial intelligence outperforms pulmonologists in the interpretation of pulmonary function tests. *Eur Respir J* 2019;53:1–11.
28 Ulmer WT, Marek W, Rasche K. Airway resistance curves in obstructive respiratory tract diseases. 8 types of airway resistance curves in spontaneous respiration. *Fortschr Med* 1988;106:663–4,
29 Criée CP, Sorichter S, Smith HJ, *et al*. Body plethysmography--its principles and clinical use. *Respir Med* 2011;105:959–71.
30 Kraemer R, Smith HJ, Matthys H. Normative reference equations of airway dynamics assessed by whole-body plethysmography during spontaneous breathing evaluated in infants, children, and adults. *Physiol Rep* 2021;9:e15027.
31 Matthys H, Orth U. Comparative measurements of airway resistance. *Respiration* 1975;32:121–34.
32 Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it *Thorax* 2009;64:728–35.
33 Adrish M, Anand MP, Hanania NA. Phenotypes of asthma-chronic obstructive pulmonary disease overlap. *Immunol Allergy Clin North Am* 2022;42:645–55.
34 Alsayed AR, Abu-Samak MS, Alkhatib M. Asthma-COPD overlap in clinical practice (Aco_Cp 2023): toward precision medicine. *J Pers Med* 2023;13:677.
35 Kraemer R, Gardin F, Smith H-J, *et al*. Functional predictors discriminating asthma-COPD overlap (ACO) from chronic obstructive pulmonary disease (COPD). *Int J Chron Obstruct Pulmon Dis* 2022;17:2723–43.
36 Pellegrino R, Viegi G, Brusasco V, *et al*. Interpretative strategies for lung function tests. *Eur Respir J* 2005;26:948–68.
37 Stolz D, Barandun J, Borer H, *et al*. Diagnosis, prevention and treatment of stable COPD and acute exacerbations of COPD: the Swiss recommendations 2018. *Respiration* 2018;96:382–98.
38 Whitelaw WA, Derenne JP, Milic-Emili J. Occlusion pressure as a measure of respiratory center output in conscious man. *Respir Physiol* 1975;23:181–99.
39 Kraemer R, Smith H-J, Sigrist T, *et al*. Diagnostic accuracy of methacholine challenge tests assessing airway hyperreactivity in asthmatic patients - a multifunctional approach. *Respir Res* 2016;17:154.
40 Telias I, Damiani F, Brochard L. The airway occlusion pressure (P(0.1)) to monitor respiratory drive during mechanical ventilation: increasing awareness of a not-so-new problem. *Intensive Care Med* 2018;44:1532–5.
41 Dreher M, Doncheva E, Schwoerer A, *et al*. Preserving oxygenation during walking in severe chronic obstructive pulmonary disease: noninvasive ventilation versus oxygen therapy. *Respiration* 2009;78:154–60.

42 Windisch W, Dreher M, Storre JH, *et al*. Nocturnal non-invasive positive pressure ventilation: physiological effects on spontaneous breathing. *Respir Physiol Neurobiol* 2006;150:251–60.

43 Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179–87.

44 Stocks J, Quanjer PH. Reference values for residual volume, functional residual capacity and total lung capacity. ATS workshop on lung volume measurements. *Eur Respir J* 1995;8:492–506.

45 Bisgaard H, Nielsen KG. Plethysmographic measurements of specific airway resistance in young children. *Chest* 2005;128:355–62.

46 Kirkby J, Stanojevic S, Welsh L, *et al*. Reference equations for specific airway resistance in children: the asthma UK initiative. *Eur Respir J* 2010;36:622–9.

47 JAEGER MJ, OTIS AB. Measurement of airway resistance with a volume displacement body Plethysmograph. *J Appl Physiol* 1964;19:813–20.

48 Lind F, Hesser CM. Breathing pattern and lung volumes during exercise. *Acta Physiologica Scandinavica* 1984;120:123–9. 10.1111/j.1748-1716.1984.tb07381.x Available: https://onlinelibrary.wiley.com/toc/1365201x/120/1

49 Lind F, Hesser CM. Breathing pattern and occlusion pressure during moderate and heavy exercise. *Acta Physiologica Scandinavica* 1984;122:61–70. 10.1111/j.1748-1716.1984.tb07482.x Available: https://onlinelibrary.wiley.com/toc/1365201x/122/1

50 Hesser CM, Lind F, Linnarsson D. Significance of airway resistance for the pattern of breathing and lung volumes in exercising humans. *J Appl Physiol (1985)* 1990;68:1875–82.

51 Knudson RJ, Clark DF, Kennedy TC, *et al*. Effect of aging alone on mechanical properties of the normal adult human lung. *J Appl Physiol Respir Environ Exerc Physiol* 1977;43:1054–62.

52 Johnson BD, Badr MS, Dempsey JA. Impact of the aging pulmonary system on the response to exercise. *Clin Chest Med* 1994;15:229–46.

53 Harik-Khan RI, Wise RA, Fozard JL. Determinants of maximal Inspiratory pressure. The Baltimore longitudinal study of aging. *Am J Respir Crit Care Med* 1998;158(5 Pt 1):1459–64.

54 Smith JR, Cross TJ, Van Iterson EH, *et al*. Resistive and elastic work of breathing in older and younger adults during exercise. *J Appl Physiol (1985)* 2018;125:190–7.

55 Loring SH, Garcia-Jacques M, Malhotra A. Pulmonary characteristics in COPD and mechanisms of increased work of breathing. *J Appl Physiol (1985)* 2009;107:309–14.

56 Barnas GM, Yoshino K, Stamenovic D, *et al*. Chest wall impedance partitioned into rib cage and diaphragm-abdominal pathways. *J Appl Physiol (1985)* 1989;66:350–9.

57 Kraemer R, Smith H-J, Gardin F, *et al*. Bronchodilator response in patients with COPD, asthma-COPD-overlap (ACO) and asthma, evaluated by plethysmographic and spirometric Z-score target parameters. *Int J Chron Obstruct Pulmon Dis* 2021;16:2487–500.

58 Topalovic M, Derom E, Osadnik CR, *et al*. Airways resistance and specific Conductance for the diagnosis of obstructive airways diseases. *Respir Res* 2015;16:88.