

# Functional Predictors Discriminating Asthma–COPD Overlap (ACO) from Chronic Obstructive Pulmonary Disease (COPD)

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**Background:** A significant proportion of patients with obstructive lung disease have clinical and functional features of both asthma and chronic obstructive pulmonary disease (COPD), referred to as the asthma–COPD overlap (ACO). The distinction of these phenotypes, however, is not yet well-established due to the lack of defining clinical and/or functional criteria. The aim of our investigations was to assess the discriminating power of various lung function parameters on the assessment of ACO.

**Methods:** From databases of 4 pulmonary centers, a total of 540 patients (231 males, 309 females), including 372 patients with asthma, 77 patients with ACO and 91 patients with COPD, were retrospectively collected, and gradients among combinations of explanatory variables of spirometric (FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, FEF<sub>25-75</sub>), plethysmographic (sR<sub>eff</sub>, sG<sub>eff</sub>, the aerodynamic work of breathing at rest; sWOB), static lung volumes, including trapped gases and measurements of the carbon monoxide transfer (DL<sub>CO</sub>, K<sub>CO</sub>) were explored using multiple factor analysis (MFA). The discriminating power of lung function parameters with respect to ACO was assessed using linear discriminant analysis (LDA).

**Results:** LDA revealed that parameters of airway dynamics (sWOB, sR<sub>eff</sub>, sG<sub>eff</sub>) combined with parameters of static lung volumes such as functional residual capacity (FRC<sub>pleth</sub>) and trapped gas at FRC (V<sub>TG</sub><sup>FRC</sup>) are valuable and potentially important tools discriminating between asthma, ACO and COPD. Moreover, sWOB significantly contributes to the diagnosis of obstructive airway diseases, independent from the state of pulmonary hyperinflation, whilst the diffusion capacity for carbon monoxide (DL<sub>CO</sub>) significantly differentiates between the 3 diagnostic classes.

**Conclusion:** The complexity of COPD with its components of interaction and their heterogeneity, especially in discrimination from ACO, may well be differentiated if patients are explored by a whole set of target parameters evaluating, interactionally, flow limitation, airway dynamics, pulmonary hyperinflation, small airways dysfunction and gas exchange disturbances assessing specific functional deficits.

**Keywords:** COPD, COPD and coexisting asthma, ACO, aerodynamic work of breathing, airway dynamics, pulmonary hyperinflation, small airways dysfunction, precision medicine, multiple factor analysis, MFA, linear discriminant analysis, LDA

## Plan Language Summary

COPD is a complex and heterogeneous disease, making it difficult to understand disease etiology, detect early onset and define robust therapeutic strategies to reduce disease progression. Therefore, there is a dearth of information on understanding lung physiology of this disease because most functional assessment is only based on spirometric parameters, and the lack of reliable biomarkers for COPD emphasizes the inherent need for larger data evaluation and integration of

multiple implicated pathophysiological processes differentiating the various subtypes of COPD. Lung function trajectories in COPD differ significantly between patients, and currently cannot reverse lung damage. Moreover, the assessment of early onset COPD is critical in mitigating disease progression. Given the complexity of this disease, it has been anticipated to address innovative analytical methods in terms of an approach towards precision medicine in COPD, especially also between COPD and the asthma overlap in COPD. Therefore, we developed a concept to define discriminating functional markers, focusing on a whole set of spirometric, plethysmographic and gas-exchange parameters, featuring traits within a conditional inference tree to help in decision making.

## Introduction

Chronic obstructive pulmonary disease (COPD) is a common, complex and heterogeneous disease, characterized by an assortment of different functional disorders due to an increased inflammatory response of the lungs.<sup>1,2</sup> It is supposed that the complexity refers to components and their interactions, while heterogeneity occurs because not all especially functional components are present in all patients concurrently<sup>3,4</sup> throughout the whole lifetime.<sup>5</sup> In our understanding, therefore, physiologic management can hardly only be assessed by one or two spirometric parameters. Physiologically, COPD is a disease characterized by a combination of either pulmonary hyperinflation, small airways dysfunction, airway dysfunction, air trapping, and gas-exchange disturbances and, therefore, an attempt to objectify such interactive functional deficits implicates the assessment of a whole set of discriminating target parameters. Moreover, a substantial proportion of patients show characteristics of both asthma and COPD, referred to as the asthma–COPD overlap (ACO),<sup>6–12</sup> although the nosology of this overlap remains controversial.<sup>13–15</sup> ACO combines clinical and functional features of both diseases, asthma and COPD. Whereas COPD, depending on which lung function parameter is used,<sup>16</sup> is characterized by poorly reversible airflow limitation and airway obstruction, patients with ACO are thought to present a bronchodilator response (BDR) that serves as a major criterion for the diagnosis of ACO.<sup>11,13,17–20</sup> Although some consensus documents contain precise classification criteria for ACO,<sup>21,22</sup> there is still a lack of an internationally accepted definition of ACO and, in consequence, research into ACO has been.<sup>23</sup> Some physicians and researchers still consider ACO to be a specific syndrome,<sup>24</sup> whereas other physicians and researchers see ACO as a theoretical construct with no clear biological grounds.<sup>25</sup> However, in no longer referring to the term ACO but, instead, increasing emphasis on individual treatment approaches tailored to COPD and/or asthma, a focus on precision medicine in these patients should be adopted. It is important to recognize that there are differentiating features in asthma and AOC: from etiology, symptoms, type of airway inflammation, inflammatory cells and mediators, consequences of inflammation, response to therapy, and disease course.<sup>26</sup> For a patient with COPD, a diagnosis of concomitant asthma must be considered, based on an individualized assessment to assure adequate treatment.<sup>27,28</sup>

Until recently, the plethysmographic parameters, such as effective specific airway resistance ( $sR_{eff}$ ), its reciprocal parameter, the effective specific airway conductance ( $sG_{eff}$ ) and notably the plethysmographic parameter expressing the specific aerodynamic work of breathing at rest (sWOB), have not yet gained enough attention concerning their potential to differentiate COPD from ACO. This may be due to the fact that the relationship between parameters of airway dynamics and anthropometric measurements is rather complex, and hence only a few reference values are available.<sup>29–31</sup> There is, however, up-coming work indicating that the major mathematical component of airway dynamics ( $sR_{eff}$  and  $sG_{eff}$ ) is sWOB,<sup>32,33</sup> from which normalized reference equations have recently been defined.<sup>34</sup>

Therefore, the purpose of the present study was to address the complexity of chronic obstructive airway diseases physiologically, selecting specific target parameter values expressed in z-scores,<sup>35–38</sup> with proven discriminatory statistical power, and hence to present a multidimensional perception of a treatable trait strategy<sup>39</sup> within a new concept of precision.<sup>39,40</sup>

## Patients and Methods

### Study Design and Ethics

In the present study we refer to retrospectively evaluated data obtained from 4 Swiss centers (Center of Pulmonary Diseases, Hirslanden Private Hospital Group, Salem-Hospital, Bern, Switzerland; Clinic of Pneumology, Cantonal Hospital St. Gallen, Switzerland; Center of Pulmonology, Clinic Hirslanden, Zürich, Switzerland; Clinic of

Pneumology, Barmelweid Hospital, Switzerland). Patients' records were anonymized before analysis to maintain their confidentiality. The patients had been referred to the centers for extended pulmonary function testing and optimizing therapy. Data were collected from patients with a clinical diagnosis of chronic obstructive pulmonary diseases: (i) COPD, (ii) COPD with coexisting asthma (ACO), or (iii) bronchial asthma, according to international standards.<sup>1</sup> The anamnestic and clinical features were assessed by experienced pulmonary physicians based on history-taking, chest radiographs, high-resolution CT-scans, and functional investigations such as spirometry, whole-body plethysmography, measurements of carbon monoxide diffusion capacity ( $DL_{CO}$ ) and measurement of the fraction of exhaled nitric oxide ( $FeNO$ ).

The study was planned according to the Federal Law of Human Research, conceptualized 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 a part of the framework of the project entitled "Functional Diversification of the Asthma-ACO-COPD Multi-center Study" (ID 2017-00259), approved by the Governmental Ethics Committees of the State of Bern, St. Gallen, Solothurn, and Zürich (Project KEK-BE PB\_2017-00104). Written informed consent was waived because of the retrospective study design, which followed the institutional and national policies concerning research approvals.

## Differential Diagnosis and Patient Cohort

COPD was defined by a history of smoking (current or ex-tobacco smokers) or equivalent indoor/outdoor air pollution, with chronic cough, sputum and dyspnea, previously documented persistent airflow limitation with post-bronchodilator values of  $FEV_1/FVC < 70\%$  and  $FEV_1 < 80\%$ , not fully reversible with a bronchodilator.<sup>6,14</sup> Asthma was diagnosed based on a past history of atopy and/or allergies with symptoms such as wheezing, shortness of breath, chest tightness and cough that vary over time in their occurrence, frequency and intensity, and proven bronchial hyperreactivity (BHR),<sup>6</sup> or a positive bronchodilation test.<sup>41</sup> ACO was diagnosed when the subject had features of COPD and asthma, with documented bronchodilator response in a  $FEV_1 > 12\%$  and 200 mL.<sup>6</sup> Patients previously diagnosed with cystic fibrosis, interstitial lung disease, pulmonary thromboembolic disease, active tuberculosis, chest wall disease, neuromuscular disorder, malignant tumor, or a history of thoracotomy with pulmonary resection were excluded.

From the database of the 4 centers, 540 measurement-sets fulfilled the inclusion criteria of a correctly conducted post-bronchodilator response-test to 200 µg Salbutamol, defined as positive if the conditions  $\Delta FEV_1$  and/or  $\Delta FVC \geq 12\%$ , and  $\geq 200$  mL are fulfilled.<sup>42-44</sup> These data sets were obtained from a total of 540 patients, 231 males (42.8%) and 309 females (57.2%), containing 372 patients with asthma (68.9%), 77 patients with ACO (14.3%) and 91 patients with COPD (16.9%), with a mean age of 51.4 years (18.0–92.2 years). Patients with asthma were significantly younger than patients with ACO (mean difference 4.5±2.3 years) and COPD (mean difference 21.5±2.2 years).

## Pulmonary Function Procedures

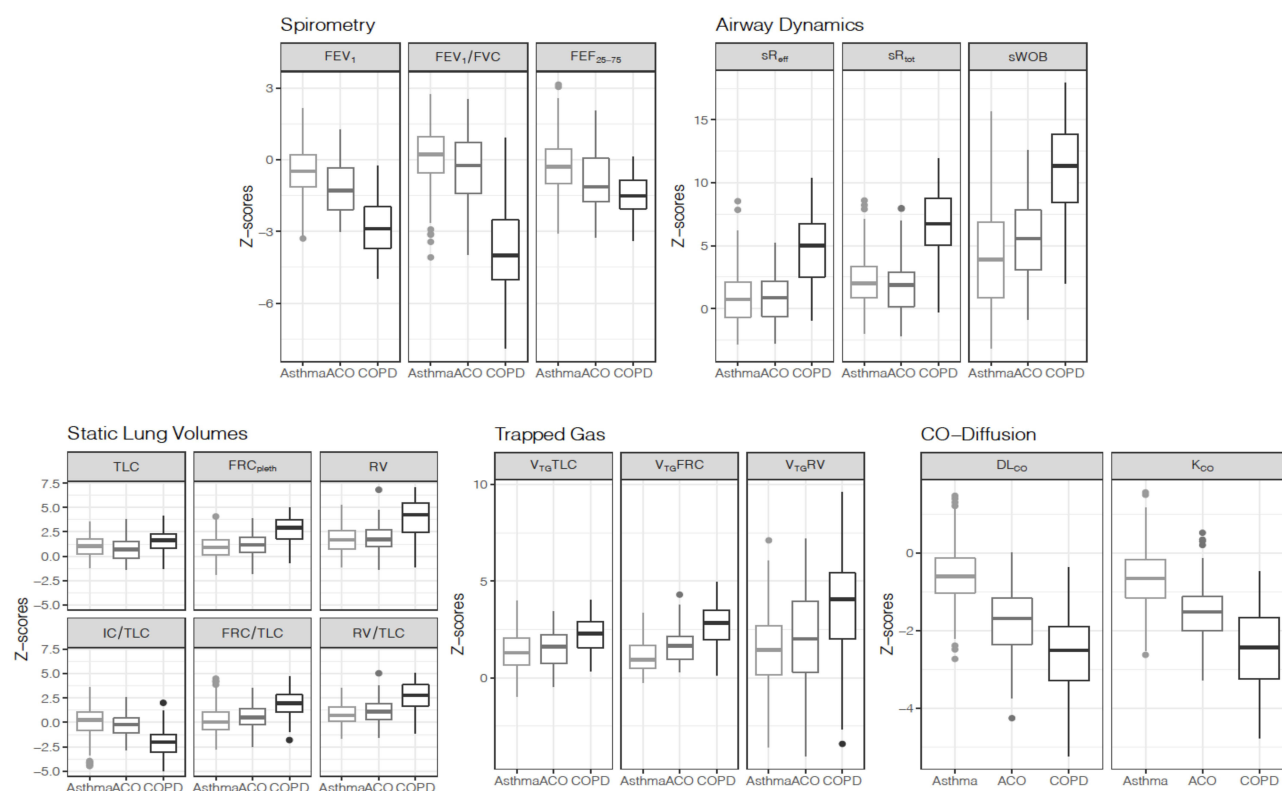
In all 4 centers, plethysmography including spirometry and diffusing capacity for carbon monoxide ( $DL_{CO}$ ), corrected for alveolar volume ( $K_{CO}$ ) by single breath analysis, was performed using a constant-volume body plethysmograph (Master Screen Body, Erich Jaeger GmbH, Würzburg, Germany) by standard techniques according to ATS-ERS criteria<sup>30,43,45,46</sup> and revised Swiss guidelines.<sup>28</sup> Apart from a daily calibration procedure given by the software of the Master Screen Body, monthly so-called "biological controls" were performed, measuring lung function in a healthy, non-smoking technician. The sequence of measurements was as follows. In the first step, measurements of airway dynamics giving the effective, specific airway resistance ( $sR_{eff}$ ), the reciprocal value of the specific airway conductance ( $sG_{eff}$ ), and the specific aerodynamic airway conductance ( $sWOB$ ), as well as the determination of the specific total resistance ( $sR_{tot}$ ) were conducted. Since the integral method evaluates changes of airway dynamics concomitantly with changes in the end-expiratory lung volume (EELV) at FRC,<sup>16,30,32,41,47,48</sup> it was important that parameters of airway dynamics were assessed in this first phase of plethysmographic assessment, and hence not influenced by deep inspiration or forced breathing maneuvers or other efforts.<sup>49-52</sup> In the second step, measurements of static lung volume such as functional residual capacity ( $FRC_{pleth}$ ) obtained by 3 shutter-closure maneuvers were applied, closely linked with the third step of slow maximal expiratory and inspiratory maneuver, giving the measures of residual lung volume ( $RV_{pleth}$ ), inspiratory capacity (IC), vital capacity (VC) and total lung capacity ( $TLC_{pleth}$ ). Only in the fourth and final step was forced spirometry recorded and presented as flow-volume-loop and volume-time-trend, deriving the forced expiratory volume in one second

(FEV<sub>1</sub>), the forced vital capacity (FVC) and its ratio to FEV<sub>1</sub> (FEV<sub>1</sub>/FVC) and the forced expiratory flows between 25% and 75% of exhaled FVC (FEF<sub>25-75</sub>). More detailed information regarding computation of the parameters of airway dynamics are given in the [Supplemental Material \(Section 1\)](#).<sup>32,33,53-63</sup> The plethysmographic and spirometric measurements were then followed by measurements of the diffusing capacity for carbon monoxide (DL<sub>CO</sub>) corrected for alveolar volume (K<sub>CO</sub>). The DL<sub>CO</sub> measurements were obtained by standard procedures,<sup>64</sup> as single breath-hold maneuver, calculated from the alveolar volume (VA) of the lung, breath-hold time, and the initial and final alveolar concentrations of carbon monoxide. The inhaled and exhaled helium concentrations are used to calculate a single breath estimate of the VA. Applying VA, the initial alveolar concentration of carbon monoxide can be calculated and TLC<sub>He</sub> is derived by adding the anatomic dead space to it. The parameter TLC<sub>He</sub> finally allows determination of FRC<sub>He</sub> and RV<sub>He</sub> by subtraction of IC, VC respectively. Inspiratory capacity (IC) was calculated indirectly by measuring the expiratory reserve volume (ERV) and vital capacity (VC) as the difference in predicted z-scores of TLC<sub>pleth</sub> and FRC<sub>pleth</sub>, respectively. Values were expressed as z-scores based on reference equations from Cotes et al.<sup>45</sup> Theoretically, the volumes of trapped gases (V<sub>TG</sub>) can be calculated on three levels of static lung volume. Combining the 3 static volume levels express as z-scores of TLC<sub>pleth</sub>, FRC<sub>pleth</sub> and RV<sub>pleth</sub> with the corresponding gas-dilution volume levels TLC<sub>He</sub>, FRC<sub>He</sub> and RV<sub>He</sub> enables the calculation of trapped gases defined as  $V_{TG}^{TLC} = TLC_{pleth} - TLC_{He}$ ,  $V_{TG}^{FRC} = FRC_{pleth} - FRC_{He}$  and  $V_{TG}^{RV} = RV_{pleth} - RV_{He}$ .<sup>65</sup> Since there is not yet a clear appreciation of how trapped gases should be defined, we tested the discriminative power of 3 V<sub>TG</sub>-ratios (V<sub>TG</sub><sup>TLC</sup>, V<sub>TG</sub><sup>FRC</sup>, V<sub>TG</sub><sup>RV</sup>) and perceived that the highest discriminative power was given by V<sub>TG</sub><sup>FRC</sup> (AUC 0.802±0.038; *p* < 0.0001). A special export software was developed by PanGas Ltd, Dagmersellen, Switzerland, enabling access to all routinely stored parameters in every JLab- and SENTRY-Suite databases.

**Z-score transformation.** All data were transformed to z-scores as a standardized measure of the positioning of an observed measurement in the distribution of the reference population, taking both between-subject and age- and growth-related variability into account.<sup>34-38,43,66-69</sup> To allow clinical interpretation of test results numerically independent from sex, age and ethnicity, measurement results were transferred into z-scores, as a standardized measure of the positioning of an observed measurement in the distribution of the reference population taking both between-subject as well as age- and growth-related variability into account.<sup>34-38,43,66-69</sup> Using this procedure, the lower limit of normal (LLN), identical with *z* = -1.645, or the 5th percentile in the distribution of FEV<sub>1</sub>, FEV<sub>1</sub>/FVC ratio, FEF<sub>25-75</sub>, as well as the upper limit of normal (ULN), identical with +1.645 z-scores or the 95th percentile for sR<sub>eff</sub>, sR<sub>tot</sub>, sWOB, TLC<sub>pleth</sub>, FRC<sub>pleth</sub>, RV/TLC and DL<sub>CO</sub>, K<sub>CO</sub> were obtained, respectively, and transformed into z-scores according to standard prediction equations<sup>45,70,71</sup> (Figure 1).

**Functional severity.** In order to upgrade the former issue of GOLD regarding functional severity, we replaced the fixed ratio of FEV<sub>1</sub>/FVC < 0.70 as criterium of functional severity by z-scores over the whole range of baseline z-scores for each lung function parameter, as previously presented in this journal.<sup>16</sup> By that the degree of functional severity of airflow limitation (FEV<sub>1</sub>, FEV<sub>1</sub>/FVC), small airways dysfunction (FEF<sub>25-75</sub>), dynamic airway dysfunction (sR<sub>eff</sub>, sR<sub>tot</sub>, sWOB), pulmonary hyperinflation (FRC<sub>pleth</sub>), trapped gases (V<sub>TG</sub><sup>FRC</sup>) and gas diffusion disturbance (DL<sub>CO</sub>, K<sub>CO</sub>) could be assessed within the 3 diagnostic classes, with the advantage that all parameters could functionally be comparable since they have been expressed as z-scores and, hence, gender-, age-, height- and ethnicity-corrected, as previously recommended.<sup>16,35-38</sup>

**Assessment of airway dynamics.** Although numerous parameters of airway dynamics can be calculated from the plethysmographic sR<sub>aw</sub>-loop,<sup>56</sup> we used the approach proposed by Matthys and Orth<sup>57</sup> defining the so-called “effective specific resistance” (sR<sub>eff</sub>) as the ratio of the area of the shift-volume versus tidal volume ( $\oint V_{pleth} dV_T$ ), to the area of the tidal flow/volume loop ( $\oint V_{pleth} dV_T$ ) (see [Figure S1](#)). The mathematical background of the integral technique to obtain parameters of airway dynamics (sR<sub>eff</sub>, sG<sub>eff</sub>, sWOB) has been previously established.<sup>33,41,57,65</sup> Details of the methodological and mathematical approach of the so-called “integral method” are given in the [Supplemental Material \(Section 1\)](#).<sup>32,33,53-63</sup> The advantage of this integral method compared with parameters of the two-point analysis defining sR<sub>aw</sub>, sG<sub>aw</sub>, respectively, is that data points throughout the entire respiratory cycle are evaluated. Moreover, the integral  $\oint V_{pleth} dV_T$  embodies the specific, aerodynamic work of breathing (sWOB) at rest.<sup>57</sup> For the parameters of airway



**Figure 1** Comparison of z-score distribution of initial values of all lung function parameters within the 3 diagnostic groups.

dynamics ( $sWOB$ ,  $sG_{eff}$  and  $sR_{eff}$ ), normative reference equations were used, recently worked out,<sup>34</sup> and provided in the [Supplemental Material \(Section 2\)](#).<sup>29,34,47,70–81</sup>

## Statistical Approach, Data Analysis and Statistical Methods

The distribution of all parameters presented as age- and gender-corrected z-scores is reported. Two-sided tests with a type-I error  $\alpha=5\%$  were used. *P*-values under 0.05 were considered statistically significant. There were 3 diagnostic classes (asthma, ACO, COPD) to be discriminated, and discrimination was based on 17 lung function parameters as potential predictors, separately evaluated within 5 lung function categories (flow limitation, airway dynamics, static lung volumes, trapped gases, CO-diffusion). Linear discriminant analysis was performed, and discriminate functions were identified. A confusion matrix summarizing the leave-one-out cross-validation classification accuracy of lung functions was created. Wilks's lambda ( $\Lambda$ ) test statistics was used for refined variable selection. The stepwise assessment of the R-statistics is given in the [Supplemental Material \(Section 3\)](#).

All analyses were done using the IBM SPSS software (version 28.0 (SPSS Inc., Chicago, IL), and R statistical software, version 4.1.2 (R Statistics, Vienna, Austria), together with the extension packages MASS, FactoMineR, caret and ade4.

## Results

### Assessment of Functional Deficits

The distribution of the lung function parameters expressed as z-scores within the 3 diagnostic classes, asthma, ACO and COPD, for spirometric flow limitation ( $FEV_1$ ,  $FEV_1/FVC$ ,  $FEF_{25-75}$ ), plethysmographic airway dynamics ( $sR_{eff}$ ,  $sR_{tot}$ ,  $sWOB$ ) static lung volumes ( $TLC$ ,  $FRC_{pleth}$ ,  $RV$ ,  $IC/TLC$ ,  $FRC/TLC$ ,  $RV/TLC$ ), trapped gases obtained on 3 lung volume levels ( $V_{TG}^{TLC}$ ,  $V_{TG}^{FRC}$ ,  $V_{TG}^{RV}$ ) and the CO-diffusion ( $DL_{CO}$ ,  $K_{CO}$ ) are given in [Figure 1](#). Highest range of z-score distribution was found within the diagnosis class “COPD”, especially for  $sWOB$  (asthma: 18.8; ACO: 13.5; COPD 15.9).



In Table 1 the prevalence of each parameter in this study is given, showing some unexpected new findings. In row a, the number (in %) of measurements of each parameter within its normal range is given. The prevalence of spirometric parameters (row b, all: FEV<sub>1</sub>: 25.4%; FEV<sub>1</sub>/FVC: 20.9%; FEF<sub>25-75</sub>: 15.9%) was significantly lower than those of

**Table 1** Prevalence and Functional Severity of All Lung Function Parameters Within 4 Indicator Sets for Flow Limitation (FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, FEF<sub>25-75</sub>), Airway Dynamics (sR<sub>eff</sub>, sR<sub>tot</sub>, sWOB), Static Lung Volumes (FRC<sub>pleth</sub>, V<sub>TG</sub><sup>FRC</sup>), and Gas Transfer (DL<sub>CO</sub>, K<sub>CO</sub>)

		Prevalence and Functional Severity Assessed by Different Lung Function Parameters				
		Asthma	ACO	COPD	All	F-value Between Groups
		n (%)	n (%)	n (%)	n (%)	
All measurements (%)		372 (68.9)	77 (14.3)	91 (16.9)	540 (100)	
FEV <sub>1</sub>						
Within range of normal ≥ LLN (%)	a	334 (89.8)	50 (64.9)	19 (20.9)	403 (74.6)	
Flow limitation < LLN (%) z-score (mean ± SD)	b	38 (10.2)	27 (35.1)	72 (79.1)	137 (25.4)	39.2 (p <0.0001)
	c	-2.20±0.45	-2.26±0.43	-3.29±0.87	-2.78±0.88	
FEV <sub>1</sub> /FVC						
Within range of normal ≥ LLN (%)	a	349 (93.8)	60 (77.9)	18 (19.8)	427 (79.1)	
Flow limitation < LLN (%) z-score (mean ± SD)	b	23 (6.2)	17 (22.1)	73 (80.2)	113 (20.9)	31.0 (p <0.0001)
	c	-2.43±0.61	-2.56±0.75	-4.51±1.54	-3.79±1.62	
FEF20-75						
Within range of normal ≥ LLN (%)	a	346 (93.0)	56 (72.7)	52 (57.1)	454 (84.1)	
Small airway dysfunction < LLN (%) z-score (mean ± SD)	b	26 (7.0)	21 (27.3)	39 (42.9)	86 (15.9)	1.07 (n.s.)
	c	-2.16±0.38	-2.35±0.62	-2.23±0.40	-2.24±0.46	
sR <sub>eff</sub>						
Within range of normal ≤ ULN (%)	a	290 (78.0)	60 (77.9)	17 (18.7)	367 (68.0)	
Bronchial obstruction > ULN (%) z-score (mean ± SD)	b	82 (22.0)	17 (22.1)	74 (81.3)	173 (32.0)	57.2 (p <0.0001)
	c	2.52±0.79	2.55±0.84	4.50±1.58	3.37±1.54	
sR <sub>tot</sub>						
Within range of normal ≤ ULN (%)	a	160 (43.0)	32 (41.6)	1 (1.1)	193 (35.7)	
Bronchial obstruction > ULN (%) z-score (mean ± SD)	b	212 (57.0)	45 (58.4)	90 (98.9)	347 (64.3)	156.4 (p <0.0001)
	c	3.38±1.31	3.19±1.55	6.98±2.31	4.28±2.31	
sWOB						
Within range of normal ≤ ULN (%)	a	122 (32.8)	11 (14.3)	1 (1.1)	134 (24.8)	
Increased work of breathing > ULN (%) z-score (mean ± SD)	b	250 (67.2)	66 (85.7)	90 (98.9)	406 (75.2)	214.1 (p <0.0001)
	c	1.98±1.79	1.89±1.94	6.89±2.49	3.05±2.85	
FRC <sub>pleth</sub>						
Within range of normal ≤ ULN (%)	a	268 (72.0)	57 (74.0)	21 (23.1)	346 (64.1)	
Pulmonary hyperinflation > ULN (%) z-score (mean ± SD)	b	104 (28.0)	20 (26.0)	70 (76.9)	194 (35.9)	33.7 (p <0.0001)
	c	2.43±0.56	2.42±0.62	3.31±0.92	2.75±0.83	

(Continued)

Table 1 (Continued).

		Prevalence and Functional Severity Assessed by Different Lung Function Parameters				
		Asthma	ACO	COPD	All	F-value Between Groups
		n (%)	n (%)	n (%)	n (%)	
V <sub>TG</sub> FRC						
Within range of normal ≤ ULN (%)	a	283 (76.1)	42 (54.5)	16 (17.6)	341 (63.1)	
Trapped gas > ULN (%) z-score (mean ± SD)	b	89 (23.9)	35 (45.5)	75 (82.4)	199 (36.9)	28.8
	c	2.25±0.53	2.36±0.64	3.13±1.01	2.60±0.87	(p <0.0001)
DL <sub>CO</sub>						
Within range of normal ≥ LLN (%)	a	347 (93.3)	37 (48.1)	16 (17.6)	400 (74.1)	
CO-transfer decreased < LLN (%) z-score (mean ± SD)	b	25 (6.7)	40 (51.9)	75 (82.4)	140 (25.9)	20.8
	c	-1.91±0.18	-2.37±.59	-2.94±0.90	-2.60±0.83	(p <0.0001)
KCO						
Within range of normal ≥ LLN (%)	a	342 (91.9)	42 (54.5)	22 (24.2)	406 (75.2)	
CO-transfer decreased < LLN (%) z-score (mean ± SD)	b	30 (8.1)	35 (43.5)	69 (75.8)	134 (24.8)	25.5
	c	-2.01±0.27	-2.16±.41	-2.90±0.85	-2.50±0.77	(p <0.0001)

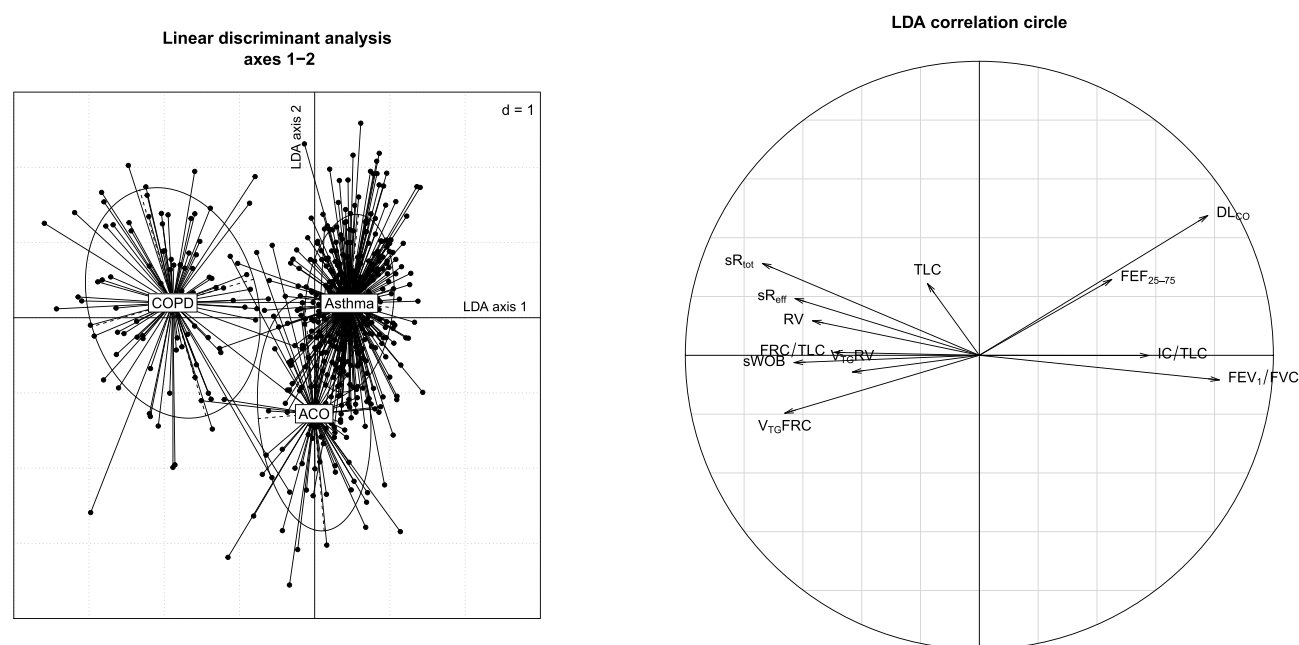
**Notes:** Prevalence: (a) measurements within the range of normal values predicted; (b) measurements lower than LLN, higher than ULN, respectively; (c) measurements of z-scores.

**Abbreviations:** LLN, lower limit of normal (-1.645); ULN, upper limit of normal (1.645); z, z-scores according to the Gaussian distribution of predicted values.

plethysmographic parameters (row b, all:  $sR_{eff}$ : 31.7%;  $sR_{tot}$ : 64.1%;  $sWOB$ : 75.2%;  $FRC_{pleth}$ : 35.9%;  $V_{TG}^{FRC}$ : 36.9%). Moreover, z-scores of spirometric parameters (row c, all:  $FEV_1$ :  $-2.78 \pm 0.88$ ;  $FEV_1/FVC$ :  $-3.79 \pm 1.62$ ;  $FEF_{25-75}$ :  $-2.24 \pm 0.46$ ) were significantly lower and less widespread than those of plethysmographic parameters (row c, all:  $sR_{eff}$ :  $-2.52 \pm 0.79$ ;  $sR_{tot}$ :  $3.38 \pm 1.31$ ;  $sWOB$ :  $3.05 \pm 2.85$ ;  $FRC_{pleth}$ :  $2.75 \pm 0.83$ ). Accordingly, the *F*-statistic of ANOVA differentiating between the 3 diagnostic classes was highest for  $sWOB$ , followed by  $sR_{tot}$  and  $sR_{eff}$ . Noteworthy is that a high prevalence was found for  $sWOB$  (asthma: 67.2%; ACO: 85.7%; COPD: 98.9%), with highest z-scores in patients with COPD (asthma:  $1.98 \pm 1.79$ ; ACO:  $1.89 \pm 1.94$ ; COPD:  $6.89 \pm 2.49$ ), significantly different between the 3 diagnostic classes ( $F=214.1$ ,  $p < 0.001$ ). Remarkably, the prevalence of pulmonary hyperinflation in COPD patients was high and severe (76.9%;  $z = 3.31 \pm 0.92$ ) and also in combination with trapped gases ( $V_{TG}^{FRC}$ : 82.4%  $z = 3.13 \pm 1.01$ ). Expectedly, prevalence and severity of CO-transfer disturbances were considerably pronounced in patients with COPD ( $DL_{CO}$ : 82.4%;  $z = -2.94 \pm 0.90$ ,  $K_{CO}$ : 75.8%;  $z = -2.90 \pm 0.85$ , respectively).

MANOVA followed by a stepwise forward variable selection was applied to the original 17-variable dataset. The 17 original variables (predictors) were grouped within 5 categories (spirometry:  $FEV_1$ ,  $FEV_1/FVC$ ,  $FEF_{25-75}$ ; airway dynamics:  $sR_{eff}$ ,  $sR_{tot}$ ,  $sWOB$ ; static lung volumes: TLC,  $FRC_{pleth}$ , RV, IC/TLC,  $FRC/TLC$ , RV/TLC; trapped gases:  $V_{TG}^{TLC}$ ,  $V_{TG}^{FRC}$ ,  $V_{TG}^{RV}$ ; and CO-diffusion:  $DL_{CO}$ ,  $K_{CO}$ ) (Figure S2). Following the variable selection based on Wilks's lambda statistics ( $\Lambda$ ),  $FEV_1$ ,  $FRC_{pleth}$ , RV/TLC,  $V_{TG}^{TLC}$  and  $K_{CO}$  were excluded from the model. Details are given in the Supplemental Material (Section 3). A linear discriminant analysis based on the remaining 12 variables is given in Figure 2, demonstrating that the first function discriminated COPD from asthma, and the second function differentiated asthma from ACO, with a classification accuracy of 90% (asthma: 87%; ACO: 75%; COPD: 94%).

This evaluation of the probability of the group membership between the 3 diagnostic classes (asthma, ACO, COPD) revealed that 12 parameters,  $DL_{CO}$  ( $\Lambda$ : 0.489),  $FEV_1/FVC$  ( $\Lambda$ : 0.328),  $sR_{tot}$  ( $\Lambda$ : 0.267),  $sWOB$  ( $\Lambda$ : 0.244),  $FEF_{25-75}$  ( $\Lambda$ : 0.227),  $V_{TG}^{FRC}$  ( $\Lambda$ : 0.214),  $sR_{eff}$  ( $\Lambda$ : 0.204), RV ( $\Lambda$ : 0.215197), TLC ( $\Lambda$ : 0.190), IC/TLC ( $\Lambda$ : 0.187),  $V_{TG}^{RV}$  ( $\Lambda$ : 0.186) and  $FRC/TLC$  ( $\Lambda$ : 0.185), significantly entered the model ( $p < 0.001$ ).



**Figure 2** Linear discriminant analysis (LDA) discriminating COPD from asthma (first function, x-axis) and asthma from ACO (second function, y-axis), based on 12 lung function parameters selected from the 17 original variables by MANOVA.

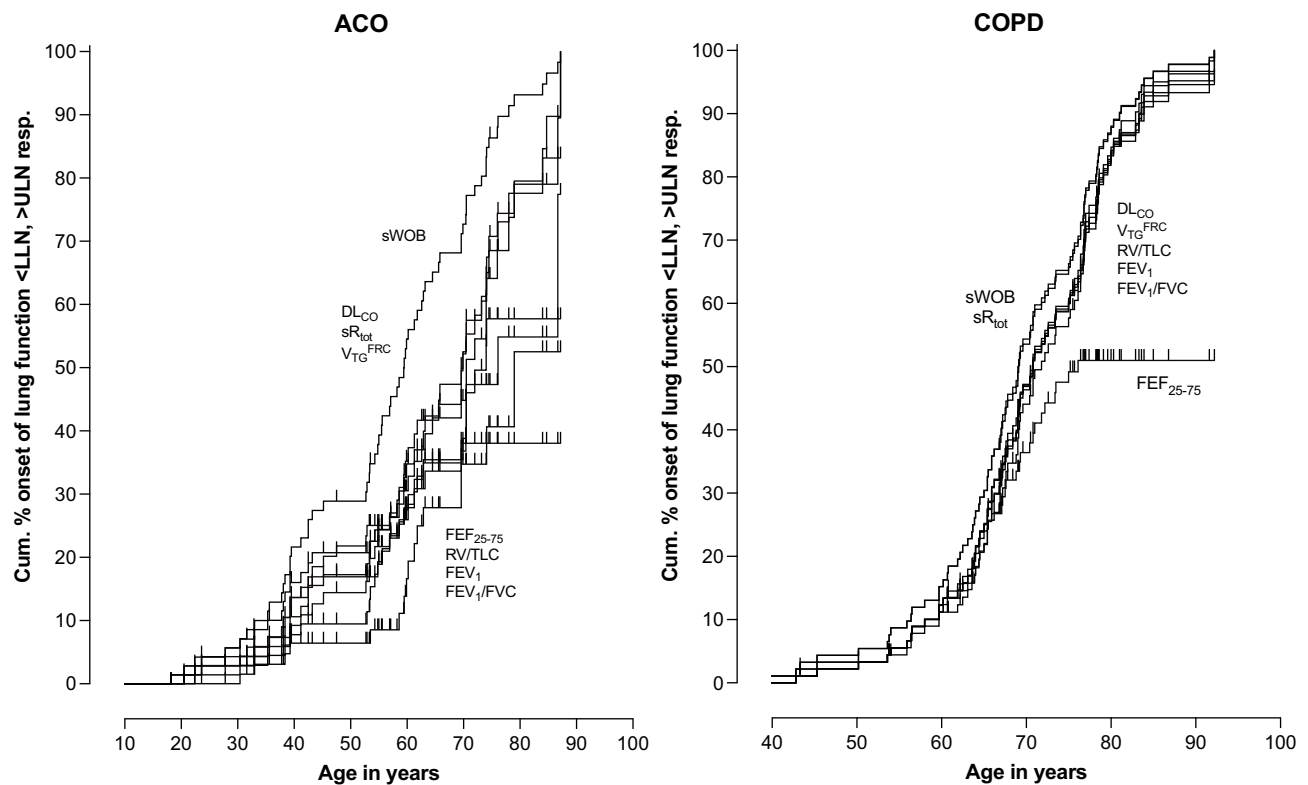
## Onset of Lung Function Deterioration in ACO and COPD

Recent evidence shows that failure to attain peak lung function is a risk factor for early onset of COPD.<sup>82,83</sup> However, it is well known that, even with normal attainment of lung function, the risk of COPD is significantly increased among patients with accelerated lung function decline.<sup>84</sup> Although we do not dispose over repeated measurements over the life course, we have been interested to evaluate comparatively our parameters as potential predictors that influence underlying disease onset. In Figure 3, the most significant parameter onsets within the data set of ACO compared to COPD are shown. Whereas in ACO a substantial splitting of parameter onsets can be observed, such a separation (apart from FEF<sub>25-75</sub>) cannot be found in COPD. A comparison of ACO versus COPD within parameter-specific cumulative percentage onset of abnormal lung function is shown in Figure 4. As most sensible trajectory parameters classify sWOB with cumulative percentage onsets of 5–10%, respectively, in ACO at age 27.8–33.0 years and COPD at 50.2–56.4 years ( $\chi^2=23.6$ ,  $p<0.0001$ ), followed by  $V_{TG}^{FRC}$  at 35.3–38.1 years for ACO and 54.0–58.0 years for COPD, respectively ( $\chi^2=6.2$ ,  $p<0.02$ ), and  $DL_{CO}$  at 31.6–39.3 years for ACO and 54.0–58.0 years for COPD, respectively ( $\chi^2=5.6$ ,  $p<0.02$ ). Whereas in patients with ACO a certain diversity of parameter onsets could be observed, such distinction could not be found in patients with COPD. FEV<sub>1</sub> and FEV<sub>1</sub>/FVC are presented as late onset parameters (FEV<sub>1</sub>: 38.4–52.9 years in ACO and 54.0–58.0 years in COPD; FEV<sub>1</sub>/FVC: 39.3–58.6 in ACO and 54.0–58.0 years in COPD). Noteworthy is that abnormal lung function started much earlier in patients with ACO (age 20–30 years) than in COPD (age 45–55 years).

## Discussion

For years there has been ongoing and growing interest in characterizing functional diversities between asthma, ACO and COPD by lung function assessment. Specific efforts were to define discriminating factors for demarcation of ACO from COPD.<sup>11,13,17-20</sup> A further task should be to identify within these diseases the onset of abnormal lung function and to assess its progression in functional severity<sup>85-89</sup> for appropriate scheduling of treatment.<sup>28,90</sup> In most studies, however, exclusively spirometric parameters are used. In contrast, the present study focuses on a multivariate approach of a whole set of parameters, looking at the various functional facets of the physiological complexity within and between the 3 diagnostic classes of asthma, ACO and COPD.



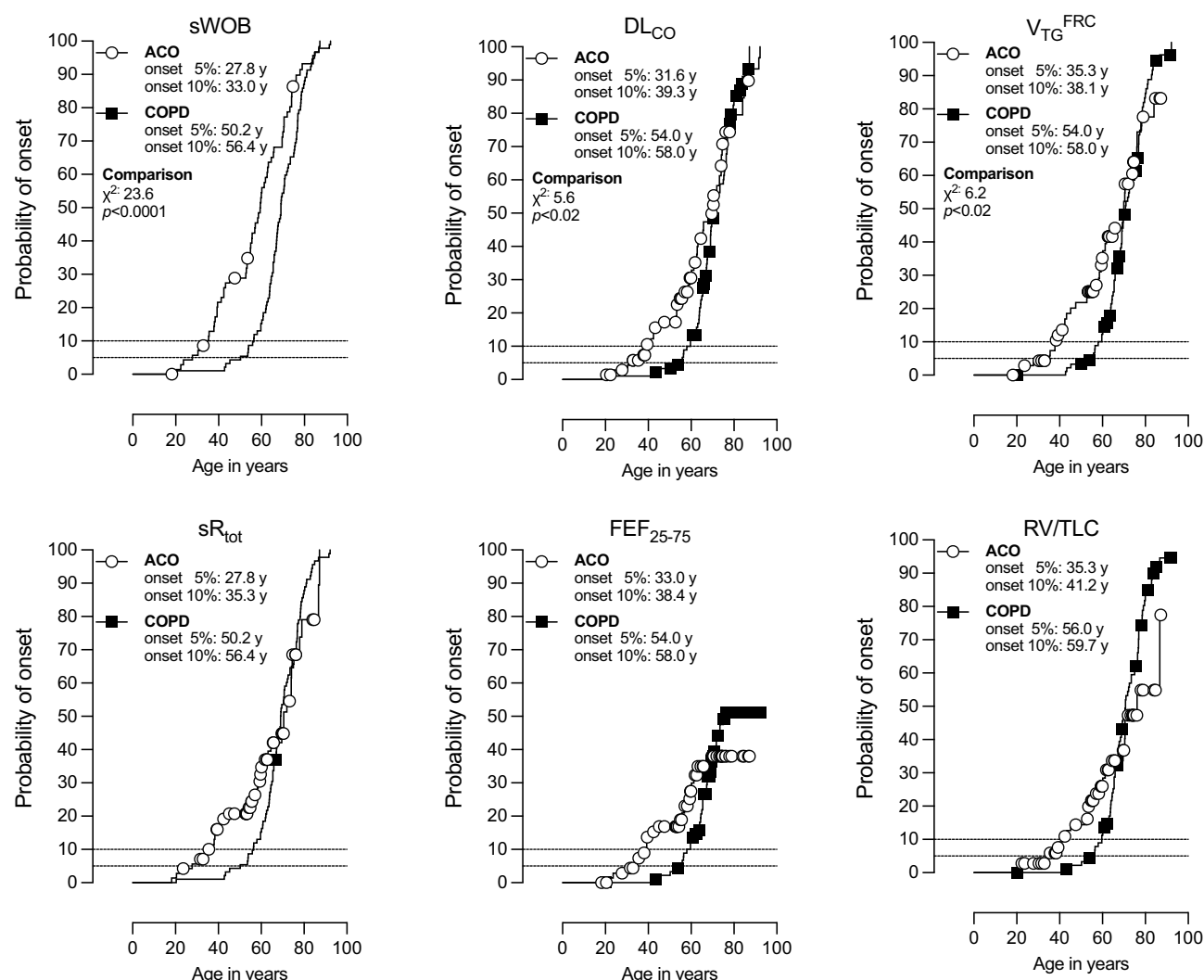


**Figure 3** Cumulative present onset of the most significant lung function parameters within COPD compared to ACO exceeding the lower limit of normal (LLN) for  $DL_{CO}$ ,  $FEV_1$ ,  $FEV_1/FVC$ ,  $FEF_{25-75}$ , or exceeding the upper level of normal (ULN) for  $sWOB$ ,  $sR_{tot}$ ,  $V_{TG}^{FRC}$  and  $RV/TLC$ .

## Findings of the Present Study

The main findings of the present study are that, in addition to spirometric parameters ( $FEV_1$ ,  $FEV_1/FVC$ ,  $FEF_{25-75}$ ), plethysmographic parameters, especially parameters of airway dynamics ( $sR_{eff}$ ,  $sR_{tot}$ ,  $sWOB$ ), and parameters of monoxide gas exchange are important trajectories for differentiating the different subtypes of COPD. In addition to diffusion capacity for carbon monoxide, the aerodynamic work of breathing at rest ( $sWOB$ ) substantially contribute to differentiating the different types of obstructive airway diseases.

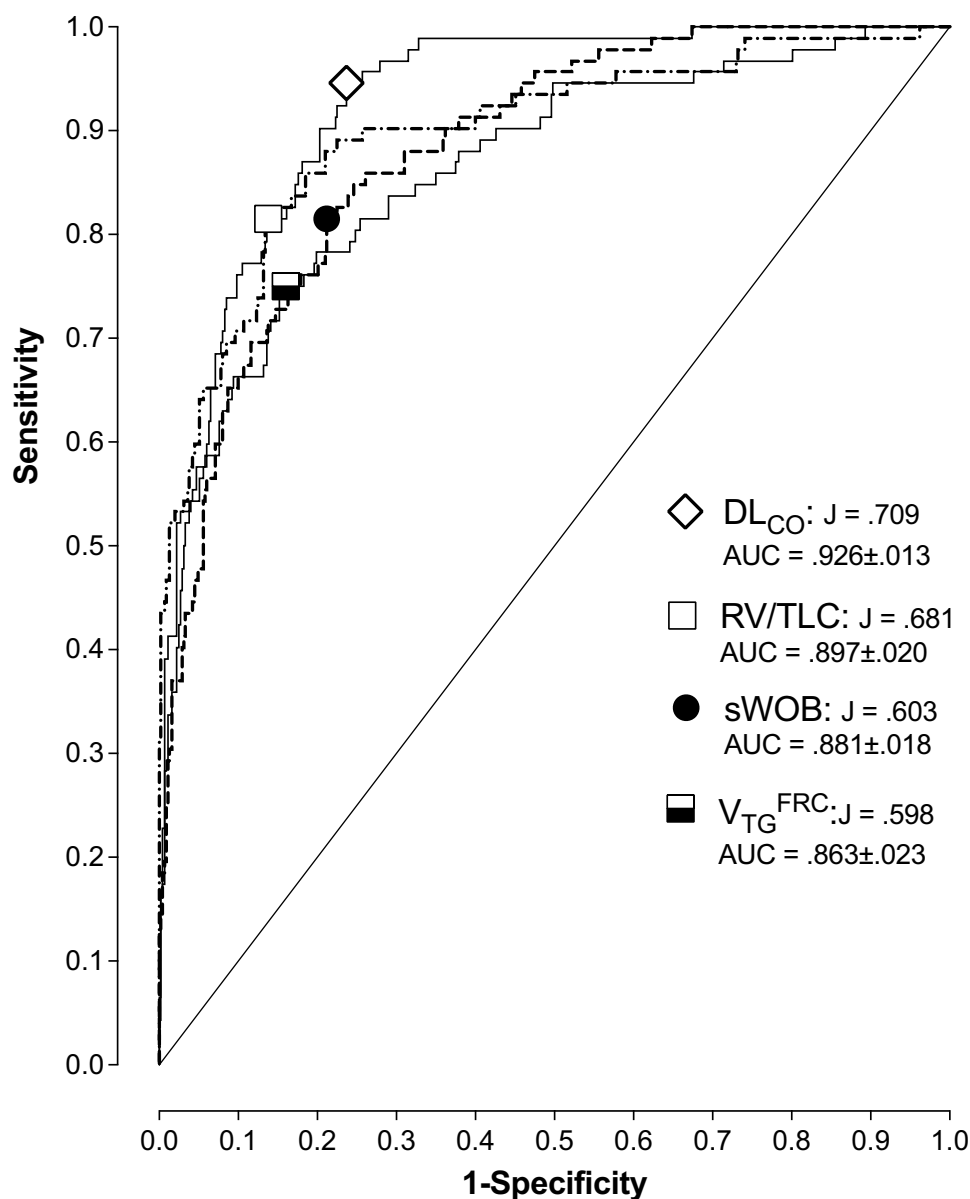
There are two components to the gas-dynamic work of breathing during respiration in patients with severe obstructive ventilatory defects and a closing volume above FRC level, which can be assessed with the plethysmograph: the aerodynamic work of breathing and the gas-dynamic work of breathing, performed on a trapped air volume which exceeds the ERV during spontaneous breathing at FRC level. The former refers to the work to overcome the frictional (aerodynamic) resistance of gas flow within the ventilated airways, whereas the latter is a waste of muscle force to compress non-ventilated lung volumes, so called trapped air. This can be recognized by a shift-volume difference between the end-inspiratory and end-expiratory zero-flow points. The new finding is that  $sWOB$  increases significantly in parallel with the deterioration of all parameters (Figure 3) but much earlier in ACO (Figure 4). Significant earlier percentage onset in ACO compared to COPD was also found for  $DL_{CO}$  and  $V_{TG}^{FRC}$  (Figure 4). Interestingly, if  $sWOB$  is taken as primary parameter expressing functional severity, it could be shown that, in patients with COPD,  $sWOB$  increased in parallel with the significant deterioration of 3 other parameters (Figure 5:  $DL_{CO}$ ,  $RV/TLC$ ,  $V_{TG}^{FRC}$ ;  $p < 0.0001$ ). Such an association, however, was not found in patients with ACO. Moreover, our study also shows, that the deployment of trapped gas territories calculated as difference between the z-scores of plethysmographic  $FRC_{pleth}$  and the  $FRC_{He}$  obtained by gas dilution in the lung may be a surrogate of what is already known through histologic studies.<sup>89,91-93</sup> Briefly, these main findings clearly feature arguments that a discrimination between ACO and COPD can be achieved if a modelling profile of multidimensional acting outcome parameters is applied.



**Figure 4** Probability of onset of disease at ages in years calculated at 5%- and 10%-levels of 6 lung function parameters (sWOB, DL<sub>co</sub>, V<sub>TG</sub><sup>FRC</sup>, sR<sub>tot</sub>, FEF<sub>25-75</sub>, an RV/TLC comparing ACO with COPD.

In the following, we discuss some important features which discriminate ACO from COPD. Numerous comprehensive reviews of the natural history of COPD have been published.<sup>83,87,88,93</sup> Early COPD diagnosis has remained challenging due to the small impact of early lung function loss within spirometric target parameters.<sup>94</sup> Some studies reported relatively few cases diagnosed before the age of 50 years,<sup>85</sup> and that patients started inhaled medication for COPD only at an average of 67.8 years.<sup>86</sup> Therefore, several population-based studies have shown that underdiagnosis of COPD is substantial,<sup>95</sup> and many experts consider the late diagnosis of COPD as the most important factor responsible for the poor outcome in a substantial proportion of patients. Both cross-sectional and longitudinal studies have identified numerous factors associated with the risk of being diagnosed with COPD, mainly in association with active smoking.<sup>89</sup> In none of these studies, however, was lung function assessed by lung function parameters other than FEV<sub>1</sub>, and in none of these studies was a distinction between ACO and COPD identified.

The Copenhagen City Heart Study followed up lung function trajectories, exacerbations and survival in individuals with ACO with early-onset asthma (<40 years of age), and ACO with late-onset asthma (>40 years of age).<sup>96</sup> Patients with late-onset asthma experienced a FEV<sub>1</sub> decline at a faster rate than those with early-onset asthma, and an increased risk of hospital admissions and reduced life expectancy, which was even more pronounced than in those with COPD and, hence, without asthma. We cannot comment on that phenomenon because we have no information regarding the onset of asthma in COPD patients. However, the observation that in our data sWOB presented a 5% cumulative percentage onset



**Figure 5** Sensitivity and specificity of the two gas-dynamic components of the work of breathing: (i) the specific aerodynamic work of breathing (sWOB) to overcome the frictional (aerodynamic) resistance of gas flow within the ventilated airways, on the one hand, and (ii) the trapped air at FRC ( $V_{TG}^{FRC}$ ) indicating the waste of muscle forces to compress non-ventilated airways, on the other hand.

in asthmatics 30 years earlier than in those with COPD (53.6 minus 23.4 years), and a notation of the cumulative decrease in  $DL_{CO}$  in ACO patients 23.4 years earlier than in COPD patients (55.0 minus 31.6) confirms previous findings, that COPD evolving from early-onset asthma is in a more benign condition than COPD that is complicated by the development of late-onset asthmatic features.<sup>96</sup>

It is estimated that patients with ACO are prone to experiencing more frequent and more severe exacerbations, and evidence-based effective treatments for ACO have yet to be defined. One problem with ACO is still that there have been many clinical trials performed in patients with chronic obstructive lung diseases, excluding patients with ACO, mainly because no definitive inclusion criteria have been developed for this subtype of disease. Therefore, ACO refers to a group of poorly studied and characterized patients making both diagnosis and treatment challenging for the clinicians. It is our understanding and belief that this uncertainty regarding the diagnosis of ACO could be resolved and the elaboration of an adequate study-based treatment of patients with ACO could be found if a discrimination between ACO and COPD is

achieved by a modelling profile of multidimensional acting outcome parameters, including those separate from spirometric parameters and the addition of parameters of the airway dynamics.

Only a limited number of studies evaluate functional severity by combining spirometric and plethysmographic assessment in COPD patients.<sup>16,97–100</sup> To our knowledge, only our previous study evaluated airway dynamics ( $sR_{\text{eff}}$ ,  $sR_{\text{tot}}$ , and especially  $sWOB$ ) by the plethysmographic integral method.<sup>16</sup> By using such an approach, a much more profound insight into lung physiology is provided, insofar as not only the degree of flow limitation ( $FEV_1$ ,  $FEV_1/FVC$ ) but also the degree of bronchial obstruction ( $sR_{\text{eff}}$ ,  $sR_{\text{tot}}$ ) and the costs of breathing at rest ( $sWOB$ ) are specified. In addition, the magnitude of pulmonary hyperinflation ( $FRC_{\text{pleth}}$ ), the occurrence of gas trapping ( $V_{\text{TG}}^{\text{FRC}}$ ) due to bronchial collapse inclination, and the degree of small airways dysfunction ( $FEF_{25-75}$ ,  $sG_{\text{eff}}$ ) may lead to intrabronchial gas distribution dysfunction, which can be estimated by  $DL_{\text{CO}}$  and  $K_{\text{CO}}$ , respectively. Although parameters of airway dynamics and parameters of CO-diffusion capacity may overlap with the disturbed pattern of a respiratory disorder, they may reveal unique components in the differentiation of diagnosis, if it is assumed that a distinction can be made between ACO and COPD, on the one hand, and ACO and asthma on the other. Our multifunctional assessment demonstrates that certain combinations of target parameters significantly contribute to the discrimination of these respiratory diseases.

## Small Airways Dysfunction (SAD)

There is considerable evidence that, pathologically, both small airways disease and emphysema are related to airflow limitation in COPD,<sup>101</sup> suggesting that SAD is present at all stages of COPD. Therefore, the detection of SAD in early stages of COPD should be an important target. SAD appears to be a precursor to the development of emphysema,<sup>91,101–103</sup> and pharmacological targeting should be focused earlier rather than later in the natural history of COPD. Most of the available information derives from either pathological studies or review articles, and there is little data on the natural history of small airways dysfunction in the onset or progression of asthma and COPD. Labaki et al<sup>104</sup> showed that regions with SAD on CT-scans are subsequently converted into emphysema after 5 years, supporting the concept that small airways are a primary pathological site for all COPD phenotypes. Several lung function indices have been proposed and evaluated as markers of small airways function. Among these, the  $FEF_{25-75}$  is the most cited indicator of small airways dysfunction, although the literature on its reliability is not conclusive. One problem with  $FEF_{25-75}$  is related to alteration of the so-called “volume history” that occurs with air trapping and bronchodilation by shifting the lung volume range at which the  $FEF_{25-75}$  is computed. According to Sorkness et al,<sup>105</sup> the characteristics of small airways dysfunction include premature airway closure, dynamic airway compression and air trapping, leading to regional heterogeneity and exaggerated volume dependence of airway dynamics. The question, however, is how progression of such combined structural alterations can be assessed physiologically. RV/TLC has been proposed as a potential marker for small airways function.<sup>106–109</sup> However, RV/TLC varies with age and sex, implicating that the RV/TLC must be evaluated as z-scores from reference equations. If we select patients with presumed SAD according to the criteria proposed by Sorkness et al,<sup>105</sup> combining abnormal z-scores of RV/TLC,  $V_{\text{TG}}^{\text{FRC}}$  and  $DL_{\text{CO}}$  in our data collective, SAD could be attributed to 63.0% of patients with COPD (11.3% in ACO, 0.8% in asthmatics), highly correlated with all spirometric parameters and with  $sG_{\text{eff}}$ , and, interestingly, with highest z-score mean difference between SAD and non-SAD of 2.9.

## Pulmonary hyperinflation (PHI)

Pulmonary hyperinflation, defined as an increased volume of air remaining in the lungs at end-expiration, is present when resting end-expiratory lung volume (EELV) is increased above normal.<sup>110–112</sup> PHI is a key feature in the disease course of COPD, and clinically important, because it contributes to dyspnea and reduced physical activity.<sup>106,111–113</sup> In healthy individuals, the level of EELV remains positioned on the steep portion of the respiratory PV-compliance curve, and hence the static recoil-tidal volume relationship is favorable. In patients with obstructive pulmonary diseases, however, the tidal breathing may be shifted upwards to TLC, especially during an exacerbation or when exercising. Although by increasing distending forces on the bronchial tree expiratory flows may be optimized, it has the detrimental effect of forcing the respiratory system to operate on the flatter part of the compliance-PV curve, where the progressive pressure increases but generates smaller incremental volume changes. It follows that pulmonary hyperinflation imposes

a restraining mechanical constraint on the respiratory system, where tidal volume expansion is limited in relation to increasing inspiratory effort, and hence the resistive work of sWOB.

Changes in static lung volume, especially trapped gases, may well disclose unrecognizable underlying disease processes, with functional consequences. An increase of  $FRC_{pleth}$  above the upper limit of natural variability detects pulmonary hyperinflation, suggestive of the presence of emphysema and may hence be present as an early sign already in ACO. Defining patients with presumed PHI according to criteria proposed by different authors,<sup>114–118</sup> we combined abnormal z-scores of  $FRC_{pleth}$  with RV/TLC, and  $V_{TG}^{FRC}$ . PHI including trapped gas could be attributed in 70.1% of patients with COPD (8.0% in ACO, 21.8% in asthmatics). Moreover, sWOB demonstrated highest z-score mean difference between PHI and non-PHI of 5.4.

## Airway Dynamics

A decrease in airway radius may be the result of increased amount of mucus and inflammatory cells obstructing the airway lumen, increased thickness of the submucosa related to inflammation, fibrosis or increase in smooth muscle mass, and distortion and narrowing of the lumen by the loss of alveolar attachments. Therefore, it is important to assess parameters reflecting these progressive processes, such as parameters of airway dynamics (sWOB,  $sG_{eff}$  and  $sR_{eff}$ ), measurements obtained by the integral method and hence independent of the value of  $FRC_{pleth}$ . What was previously anticipated for the measurement of specific airway resistance (sRaw) regarding strength, repeatability and inter-dependence from the breathing pattern<sup>119–121</sup> was no longer valuable, and has been resolved by the introduction of the integral method featuring airway dynamics such as sWOB,  $sR_{eff}$  and  $sG_{eff}$ .<sup>32,34,57,122</sup> It follows that, due to the proven clinical usefulness of airway resistance measurement in COPD patients, airway dynamic measurements deserve to be investigated.<sup>106</sup> Moreover, since bronchodilator response (BDR) is considered an important potential phenotypic marker for several subtypes of COPD, dynamic tests (post-bronchodilation and/or provocations tests) could well serve as candidates for COPD subtyping. We have recently demonstrated that the discriminating power of BDR distinguishing asthma from ACO and COPD is significantly better achieved by  $sG_{eff}$  than  $FEV_1$ .<sup>16</sup> Moreover, sWOB also improved in asthma by 76.2%, in ACO by 47.8%, and in COPD by 46.9%, compared to  $FEV_1$  (asthma: 21.8%; ACO: 18.6%; COPD: 4.2%).<sup>16</sup> BDR assessed by several advanced lung function parameters was recently also studied by Jarenbäck et al,<sup>99</sup> suggesting that in addition to flow-response, volume-response should also be evaluated. The overall clinical aim in COPD is to improve function in the small peripheral airways by improving flow (flow responders), as well as decreasing air trapping and pulmonary hyperinflation (volume responders). The evaluation of BDR is thus important and goes beyond the information provided by  $FEV_1$ , which mainly reflects flow limitation in the central airways.<sup>123</sup> The conclusion of Jarenbäck et al was that volume- and resistance-responses do not follow the flow response measured with  $FEV_1$ .<sup>99</sup>

The content of the sRaw-loop consisting of the shift volume ( $V_{pleth}$ ) and the tidal flow ( $V'$ ) plot seems to be rather complex, especially in COPD patients when the sRaw-loop becomes the shape of a golf club within the expiratory limb, and a disease of the peripheral airways must be assumed. Consequently, different investigators have utilized different portions of the loop to approximate a representative value for the entire cycle. The  $sR_{eff}$  and  $sR_{tot}$  have been well established as functional characteristics approximating the shape of such sRaw-loops.<sup>16,32,33,41,106,124</sup> Noteworthy, is that, in contrast to the previously used  $sR_{aw}$  reflecting proximal airway abnormalities,  $sR_{eff}$  and the reciprocal value  $sG_{eff}$  were proven to be a target parameter reflecting small airways function.<sup>16,97,98,125</sup> Moreover, Mahut et al suggested that  $sR_{tot}$  and  $sR_{eff}$  can be considered equivalent and correlated with indices that explore peripheral airways (RV/TLC), and that these two parameters are statistically linked to activity-related dyspnea in COPD patients.<sup>106</sup> The open shape of the sRaw-loop is associated with changes in the elastic recoil pressure and collapse during quiet tidal breathing due to the changes in airway resistance exhibited between inspiratory and expiratory flow. The shape also indicates unequal ventilation of the lung areas, which is a typical early sign of a pulmonary disease. Moreover, we have shown previously that the area of the sRaw-loop is related to the flow-resistive work of breathing sWOB,<sup>16</sup> which may explain its correlation with activity-related dyspnea; as demonstrated by Mahut et al,<sup>106</sup>  $sR_{eff}$  is a better descriptor of lung function due to its dual nature, eg, including resistance and volume components that may be related to the viscoelastic behavior of the lung. In COPD patients with nonhomogeneous small airway partial obstruction, the sRaw-loop area increases during expiratory flow, representing expiratory flow limitation and/or dynamic airway compression, the former being clearly



linked to activity-related dyspnea in COPD patients.<sup>126</sup>  $sR_{\text{eff}}$  and  $sR_{\text{tot}}$ , therefore, represent surrogates of activity-related dyspnea in moderate to severe COPD patients.<sup>106</sup>

Regarding results of airway dynamics obtained in the present study, an important new finding can be presented insofar as sWOB was detected as the most sensible trajectory parameter, demonstrating much earlier onset of abnormal z-scores with cumulative percentage onsets of 5–10% in ACO at age 27.8–33.0 years and COPD at 50.2–56.4 years ( $p < 0.0001$ ), followed by  $DL_{\text{CO}}$  at 31.6–39.3 years for ACO and 54.0–58.0 years for COPD ( $p < 0.02$ ), and  $V_{\text{TG}}^{\text{FRC}}$  at 35.3–38.1 years for ACO and 54.0–58.0 years for COPD ( $p < 0.02$ ).

## Gas Exchange Disturbance

Diffusing capacity of the lung for carbon monoxide is a measure of gas exchange reflecting the complex interactions occurring at the alveolar–capillary interface. The analyses of Ni et al<sup>127</sup> showed that diffusion capacity may be a useful objective assessment criterion for COPD. As diffusion capacity incorporates pulmonary ventilation and perfusion at the same time, it may be able to explain why some patients have more symptoms while their  $FEV_1$  is not very low. In their meta-analysis,  $DL_{\text{CO}}$  was an important measurement for COPD patients in terms of severity, exacerbation risk, mortality, emphysema domination, and presence of pulmonary hypertension.<sup>127</sup> In a similar context, Yanagisawa et al<sup>128</sup> plead that COPD should be assessed by using  $DL_{\text{CO}}$  and CT, because this variable in combination with this imaging method are strongly associated with the destruction of the alveolar wall.

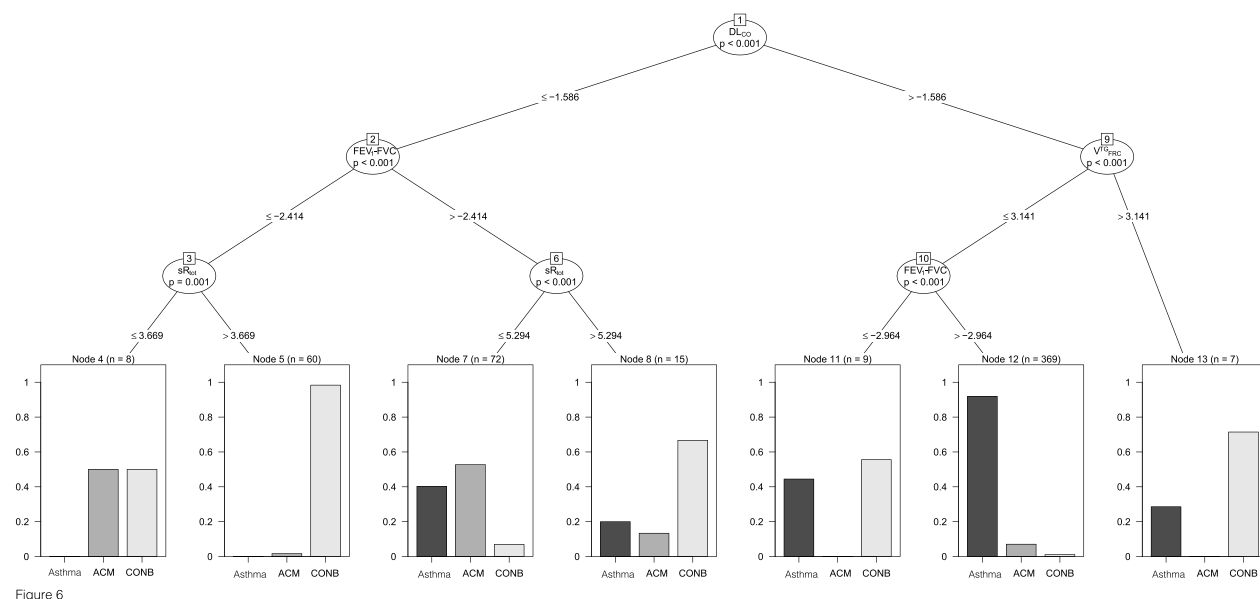
The cascade of physiological events and their influence on expiratory flow limitation leading to pulmonary hyperinflation appears to be the pivotal abnormality and this has disastrous implications with respect to the mechanical and gas exchange functions of the respiratory system. While there are some studies evaluating  $DL_{\text{CO}}$  as a predictor in COPD, especially to assess the integrity of the alveolar–capillary interface,<sup>129,130</sup> only the study of Perez de Llano et al refers to the accuracy of algorithms to identify it in ACO.<sup>129</sup> However, in that study, neither by a single variable nor by any combination of clinical, functional or inflammatory variables could the authors distinguish ACO patients from those in other categories of chronic obstructive airway disease.<sup>129</sup> In contrast, however, applying the same technique using ROC data analyses we could define quite interesting target parameters discriminating between asthma, ACO and COPD. Figure 6 shows an ROC analysis of 4 prioritized lung function parameters presenting an area under the curve (AUC) of  $>0.80$ , dissociating the 3 diagnostic classes. The most pronounced dissociation was found for  $DL_{\text{CO}}$  ( $\text{AUC} = 0.926 \pm 0.013$ ), followed by  $RV/\text{TLC}$  ( $\text{AUC} = 0.897 \pm 0.020$ ), sWOB ( $\text{AUC} = 0.881 \pm 0.018$ ) and  $V_{\text{TG}}^{\text{FRC}}$  ( $\text{AUC} = 0.863 \pm 0.023$ ). In contrast to previous studies, these ROC curves are computed based on z-scores and using the LLN of  $-1.645$  SDS of predicted normal as the cut-off.

## Conditional Inference Tree

To define and select the most discriminating lung function parameters within their functional severity (z-scores) to differentiate between asthma, ACO and COPD, a decision tree using the 4 highest discriminating parameters ( $DL_{\text{CO}}$ ,  $FEV_1/\text{FVC}$ ,  $sR_{\text{tot}}$ ,  $V_{\text{TG}}^{\text{FRC}}$ ) obtained by the MANOVA was constructed. The recursive partitioning by conditional inference (implemented in the R package party) of dependent variables based on the value of correlations is provided in Figure 6. The first split is given by the z-score of  $DL_{\text{CO}} \leq$  or  $>1.586$ , separating  $DL_{\text{CO}}$  from asthma and ACO. In a second split ( $FEV_1/\text{FVC} \leq -2.414$  SDS) and in a third split COPD can be significantly distinguished from ACO if  $sR_{\text{tot}} > 3.669$  SDS (60/91) and if  $sR_{\text{tot}} > 5.294$  SDS (15/91) and hence in the total of 82.4%. If  $DL_{\text{CO}} > -1.586$  SDS  $V_{\text{TG}}^{\text{FRC}} >$  or  $\leq 3.141$ , SDS primarily differentiates between asthma and ACO, especially if, in addition,  $FEV_1/\text{FVC} > -2.964$  SDS (369/372) in 99.2% of cases.

## Limitations and Strengths of the Study

Several limitations need to be mentioned: The present study is a retrospective evaluation of lung function data obtained using various parameters and there are no longitudinal observations, a feature that can only be achieved by a prospectively designed study. Our actual challenge was to find surrogate markers superior to  $FEV_1$  and/or  $FEV_1/\text{FVC}$ , to establish functional parameters significantly helping differentiation between COPD and ACO. As it turned out, such an evaluation based on various functional parameters of airway dynamics, static lung volume and gas transfer disclosed a variety of fundamentally different archetypes, which thus requires new definitions of functional assessment in COPD.



**Figure 6** "Conditional Inference Tree" as a trait for decision making in the pathways of "precision medicine" distinguishing asthma and ACO from COPD, represented by the 4 most discriminating lung function parameters ( $DL_{CO}$ ,  $FEV_1/FVC$ ,  $sR_{tot}$ ,  $V_T^{FRC}$ ).

The main limitation of our study is that it addresses functional trajectories representing the complex lung physiology in COPD, not directly linked to clinical settings. However, the aerodynamic specific work of breathing at rest (sWOB) features presumably the closest parameter associated with clinical signs such as wheezing, shortness of breath, chest tightness and cough, and could well be taken as a marker for longitudinal follow-up and treatment efficacy. Other limitations are the relatively small number of subjects per center and within the subgroups of COPD. However, there were no differences if the centers were compared to one another (data not shown). Therefore, the population-based retrospective nature of our study and its highly standardized multicenter framework has a reliable force of expression.

The strengths of the present study are that we used pulmonary function data from well-characterized spirometric and plethysmographic target parameters, which allowed us to examine the interrelationships between several facets of lung function trajectory through early adulthood. We used an unsupervised modeling strategy that did not require arbitrary cut-offs to define "abnormal" lung function. In addition, our model was flexible in that it allowed the changes in lung function over time to vary between the different lung function trajectory classes.

## Conclusion

Being aware of the enormous functional, structural, and biological heterogeneities occurring in patients with COPD, we like to anticipate considerable interest in evaluating the discrimination between COPD and ACO by a whole set of target parameters evaluating, interactionally, flow limitation, airway dynamics, small airways dysfunction, pulmonary hyperinflation, airway gas trapping, and gas-exchange characteristics, and hence assessing specifically the complex diagnostic class-specific functional deficits. The summary of these various ventilatory defects in COPD and their combination and interactions underscores the heterogeneous physiological mechanisms of this complex disease.<sup>131</sup> Extended lung function testing could presumably be helpful in the tracking of dynamics and changes over time in patients with COPD. In view of the serious disease burden in COPD, a more sophisticated assessment of functional deficits and their reversibility would be justified, and not only because treatment could be adequately adjusted. Moreover, a further step in diagnosing the different phenotypes and corresponding treatment strategies could be provided.<sup>3,28</sup> Noteworthy is that, despite the disagreement on the definition and recognition of ACO as a distinct pathophysiological entity,<sup>132,133</sup> it seems important to us to identify ACO patients by highly discriminating factors of lung physiology, in order to allow better-targeted therapy, and, hopefully, improved clinical course. Moreover, this subgroup of ACO patients deserves to be included in therapeutic trials, to enable individualized management.

## Abbreviations

ACO, asthma–COPD overlap; ATS, American Thoracic Society; AUC, area under the curve (ROC analysis); BDR, bronchodilator response; COPD, chronic obstructive pulmonary disease;  $DL_{CO}$ , carbon monoxide diffusion capacity;  $\Delta V_{pleth}$ , plethysmographic shift volume; EELV, end-expiratory lung volume; ERS, European Respiratory Society; FEF<sub>25–75</sub>, forced expiratory flow between 25 and 75% vital capacity; FeNO, fraction of exhaled nitric oxide; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; FRC<sub>pleth</sub>, plethysmographic functional residual capacity; FRC<sub>He</sub>, functional residual capacity obtained by helium dilution technique; FVC, forced vital capacity; IC, inspiratory capacity; KCO, carbon monoxide transfer factor; LDA, linear discriminant analysis; LLN, lower limit of normal; Ln, natural logarithm; MFA, multiple factor analysis; MMEF, maximal mid-expiratory flow;  $P_{amb}$ , ambient pressure;  $P_{H_2O}$ , water pressure; PHI, pulmonary hyperinflation; ROC, receiver operating characteristics; RV<sub>He</sub>, total lung capacity obtained by helium dilution technique; RV<sub>pleth</sub>, plethysmographic residual volume; SAD, small airways dysfunction; SD, standard deviation;  $sG_{aw}$ , specific airway conductance (angle method);  $sG_{eff}$ , effective specific airway conductance (integral method);  $sR_{eff}$ , effective specific airway resistance (integral method); sWOB, effective resistive work of breathing (integral method); TLC<sub>He</sub>, total lung capacity obtained by helium dilution technique; TLC<sub>pleth</sub>, plethysmographic total lung capacity; ULN, upper limit of normal; VC, vital capacity; VIF, variance inflation factor;  $V'$ , flow;  $V_T$ , tidal volume;  $V_{TG}^{TLC}$ , trapped gas on the level TLC, defined as  $TLC_{pleth} - TLC_{He}$ ;  $V_{TG}^{FRC}$ , trapped gas on the level FRC, defined as  $FRC_{pleth} - FRC_{He}$ ;  $V_{TG}^{RV}$ , trapped gas on the level RV, defined as  $RV_{pleth} - RV_{He}$ .

## Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics Approval and Informed Consent

The study was planned according to the Federal Law of Human Research, conceptualized by the Swiss Ethics Committee on Research involving humans, and approved by the Governmental Ethics Committees of the State of Berne, Zürich, and St. Gallen. Master-files have been stored and secured in the REDCap-system of the Clinical Trial Unit, Medical Faculty, University of Berne, Switzerland. Written informed consent was waived because of the retrospective study design, which is following the institutional and national policies concerning research approvals.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors have no conflicts of interests to declare in this work.

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