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Diagnostic value of capnovolumetry in obstructive airway diseases

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1. Summary

Spirometry is internationally regarded as reference standard for the diagnosis of obstructive airway diseases such as asthma and COPD. It comprises the determination of forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC), as well as their ratio FEV_1/FVC. Besides spirometry, bodyplethysmography is helpful in the diagnosis of obstructive airway diseases via the assessment of airway resistance. Accordingly, in the present study both methods are used as reference standard for the presence of airway obstruction.

One of the known weaknesses of spirometric maneuvers is its dependence on patients' cooperation, which can only partially be alleviated by educational efforts. Therefore, less demanding methods might be of value in clinical practice. Among these, ultrasound-based capnovolumetry, i.e. the measurement of carbon dioxide (CO_2) in exhaled air, is promising as it requires only tidal breathing. As capnovolumetry is not yet commonly used for clinical purposes, its usefulness for the diagnosis of obstructive airway diseases should be evaluated.

The present doctoral thesis comprises three published studies on the value of capnovolumetry in the diagnosis of obstructive airway diseases. The dataset serving as basis for the studies was collected in a diagnostic study comprising a large sample of unselected patients recruited under ambulatory care conditions. The reference standard was spirometry and bodyplethysmography, while capnovolumetry was the index test. Study 1 aimed to assess the diagnostic accuracy of capnovolumetry for the diagnosis of airway obstruction. While the results of a previous pilot study could not be confirmed, other promising results were obtained that led to studies 2 and 3. Study 2 aimed to clarify the physiological meaning of capnovolumetric parameters, as these are not commonly known to clinicians. This was performed by identifying correspondences to conventional lung function parameters, using the statistical technique of path analysis. Study 3 investigated how to combine capnovolumetric data with clinical data and to optimize the diagnosis of obstructive airway diseases. This resulted in easy-to-understand decision trees that were verified by a machine learning approach.

In view of the low demands of capnovolumetry regarding patients' cooperation, the three studies demonstrated that it is an attractive lung function method. The three papers analyse its specific advantages and capabilities but also limitations in detail and might help to extend the set of diagnostic tools for obstructive airway diseases in particular for non-pulmonary specialists.

2. Introduction

2.1. Background of the present work

Obstructive airway diseases show a high prevalence worldwide and are frequently encountered in specialist and non-specialist practices [1, 2]. They comprise asthma and chronic obstructive pulmonary disease (COPD), which are commonly diagnosed by clinical signs and symptoms in combination with the results of spirometry [3, 4]. Spirometry, however, has methodological limitations mostly arising from a lack of patients' cooperation and thus tends to be prone to errors. Therefore, other methods requiring less cooperation are of interest, such as capnovolumetry [5]. This dissertation investigates the diagnostic accuracy of capnovolumetry for the diagnosis of obstructive airway diseases, as well as the interpretation and clinical use of the capnovolumetric parameters.

2.1.1. Chronic obstructive pulmonary disease (COPD)

2.1.1.1. Characteristics and causes of COPD

COPD is characterized by persistent respiratory symptoms and chronic airflow limitation. The most common respiratory symptoms are dyspnea, cough and sputum production [4]. In the majority of cases in Western countries, COPD is caused by cigarette smoking [6-9], while occupational and environmental exposures play a secondary role [10]. The disease is thought to be driven by airway inflammation triggered by the inhalation of noxious particles or gases. Lung inflammation is a normal protective response to inhaled toxins but seems to be modified in patients who develop COPD and appears to continue even after removal of the noxious stimuli [11, 12]. This chronic inflammatory response is associated with imbalances regarding the concentrations and activities of proteases and oxidants versus anti-proteases [13] and anti-oxidants [14], in combination with many other immunological and biochemical factors [15] and thus leading to parenchymal tissue destruction, and disruption of normal repair and defence mechanisms. Chronic airflow limitation that is not fully reversible is a major characteristic of COPD and is caused by a mixture of small airway disease and parenchymal destruction. Pathological changes in the small airways include the disruption of the epithelial barrier, mucociliary dysfunction resulting in accumulation of inflammatory mucous exudates in the lumen, infiltration of the airway walls by inflammatory cells, and deposition of connective tissue in the airway wall. This remodelling process thickens the airway walls and reduces its lumen [16]. Additionally, pathological changes in lung parenchyma lead to a destruction of alveolar

attachments and reduces lung elastic recoil [17]. These changes reduce the ability of the airways to remain open during expiration contributing to persistent airflow limitation.

COPD is also linked to systemic inflammation that has been discussed to be at least partially the result of "overspill" from the lung into the blood [18]. This factor, however, has remained controversial up to now, as well as the hypothesis that systemic inflammation contributes to the development of comorbidities, especially cardiovascular disorders that are frequently observed in patients with COPD [19, 20]. On the other hand, systemic inflammation may be primarily a marker of comorbidities elicited by cigarette smoke as common causal factor, as well as of the overall deterioration of health state as well as advanced age.

A large number of contributors and markers of inflammation have been identified in COPD, among which neutrophilic inflammation is most obvious [11]. Until now, most of these markers have not been shown to be clinically useful beyond established markers [21, 22], except the neutrophil number in peripheral blood and the serum level of C-reactive protein (CRP) [23]. Other biomarkers that are often or regularly assessed in COPD patients, in most cases refer to specific organ disorders, especially cardiovascular and metabolic disorders such as diabetes.

The two major phenotypes of COPD are chronic obstructive bronchitis and lung emphysema [24, 25]. These phenotypes show differences in their clinical and functional characteristics, with considerable variation, and are simultaneously present in the majority of COPD patients, however with different relative importance. Their differential diagnosis is relevant, as the most adequate treatment options differ between the two phenotypes [26, 27]. The bronchitis phenotype (airway-dominated) shows some similarities to various asthma phenotypes, whereas the emphysema phenotype is quite distinctive and characterized by a destruction of alveolar architecture resulting in impairments of gas exchange.

2.1.1.2. Role of lung function in COPD

The biochemical, immunological and cellular alterations found in COPD correspond to functional limitations that have a major impact on health status and prognosis. Most important of these functional limitations is that in lung function. Despite its importance, its role in the assessment of COPD has been questioned several times [28], and the role of imaging has increased over time as reflected in the use of chest computer tomography (CT) [29]. This method is increasingly used to recognize the presence and severity of lung emphysema or the presence of comorbidities such as bronchiectasis [29, 30]. In general, patients with COPD show airway obstruction and lung hyperinflation to a different degree. Lung hyperinflation can be defined as elevated functional

residual capacity (FRC). This is closely related to the fact that significant parts of the lung are not well ventilated (trapped air) as reflected in an increase of residual volume (RV) and its ratio to total lung capacity (RV/TLC) which can be estimated from spirometry [31].

Lung hyperinflation has multiple consequences for lung mechanics and gas exchange as well as the function of other organs. For example, in COPD it affects cardiac size and function, as well as characteristics of the electrocardiogram [32-34], mainly through alterations of volume and pressure inside the chest cavity, and these effects can be partially reversed through bronchodilator inhalation [35]. Regarding the lung, hyperinflation and trapped air describe an increase in not properly ventilated volume. This is commonly associated with inhomogeneity of ventilation, resulting in marked changes of gas concentrations over the course of expiration, especially the part reflecting alveolar ventilation.

2.1.1.3. Potential role of capnovolumetry in the assessment of COPD

Based on the arguments given before, the measurement of alveolar gas concentrations over the course of expiration offers the opportunity to assess the inhomogeneity of ventilation, as an indirect measure of airway obstruction. Among the gases suitable for this purpose, oxygen, nitrogen, carbon dioxide as well as tracer gases inhaled prior to expiration have been used as markers. Especially nitrogen washout has been performed for a long time in physiological studies to quantify the inhomogeneity of ventilation [36]. Recently, carbon dioxide (CO_2) that can be measured by capnographs over the course of expiration [5, 37] has gained much interest. If its concentration is plotted against expired volume instead of time, the method is called capnovolumetry. Capnovolumetry is of special interest in patients with COPD, as inhomogeneity of ventilation is often very pronounced in this disease [4]. These arguments suggest that capnovolumetry could significantly add to the diagnosis, phenotyping and monitoring of these patients. Despite this, it has not been sufficiently evaluated in the past and is currently not part of clinical routine assessments. As lung function measurements per se are not sufficient for a proper diagnosis, they must be combined with anamnestic data including clinical signs and symptoms. According to guidelines, spirometry remains an important part of the diagnosis and monitoring of COPD [4], thus the evaluation of capnovolumetry should include the assessment of its relationship to airway obstruction assessed by spirometry. Among the phenotypes of COPD, emphysema often shows the strongest signs of inhomogeneous ventilation. Thus, methods recording the concentration of gases, such as CO_2, during expiration should be sensitive in the detection of this phenotype. Based on this, the method of capnovolumetry that is the

topic of the present dissertation might be well suited for the diagnosis of COPD in general as well as its phenotypes.

2.1.2. Asthma

2.1.2.1. Characteristics and causes of asthma

Whereas in the clinical history of COPD cigarette smoking is of special significance, in asthma the history of allergic sensitization plays a major role [3]. Similarly to COPD, asthma is characterized by chronic airway inflammation but this is primarily linked to eosinophils and not to neutrophils [38]. Moreover, asthma typically involves episodes or attacks of airway obstruction; outside of these episodes lung function can be normal or close to normal. Symptoms include wheezing, shortness of breath, chest tightness and cough that are associated with the variable airflow limitation triggered by allergens, physical activity, changes in weather or viral respiratory infections [3]. Asthma often starts in childhood or adolescence, and in this case, it is commonly associated with allergies [39]. In many patients, symptoms persist and continue into adult life. Asthma can also develop de novo at any age, in some cases triggered by respiratory tract infections or occupational exposures. It is important to note that the frequency and severity of symptoms and airflow limitation typically vary over time. This implies that functional measurements might be less sensitive than in COPD if performed outside asthma attacks or in patients extensively treated with anti-asthma medication.

Despite common features, asthma is a heterogeneous disease with different clinical phenotypes, pathological features, clinical patterns and treatment responses. The most common phenotypes are allergic asthma, non-allergic asthma, adult-onset asthma, asthma with persistent airflow limitation and asthma with obesity [3, 40, 41]. Allergic asthma is the most easily recognized phenotype and also most common during childhood and young adulthood. Regarding risk factors, it is associated with a family history of allergic disease such as eczema or allergic rhinitis [42]. Biologically, it is characterized by eosinophilic airway inflammation. Patients with allergic asthma usually respond well to treatment with inhaled corticosteroids (ICS). Individuals suffering from non-allergic asthma usually have a negative history of allergy. Non-allergic factors like respiratory infection, physical exertion, air pollution and occupational exposures are associated with this phenotype of asthma [43]. Patients with non-allergic asthma often show a lower response to ICS than those with allergic asthma. Patients, particularly women, presenting with asthma for the first time in adult life are assigned to the phenotype of adult-onset asthma. These patients tend to be non-allergic and often require higher doses of ICS [44]. The group of patients with persistent airflow limitation comprises patients with long-

standing asthma who have developed airflow limitation that is incompletely reversible, probably due to long-term remodelling processes of the airways due to either intrinsic factors or inadequate treatment [45]. Finally, obese patients with asthma show prominent symptoms and little eosinophilic airway inflammation forming a further phenotype [46], although it is not clear, to which extent the airway obstruction is a result of a reduction of lung volume caused by obesity.

With the methods available in clinical practice, these phenotypes cannot be clearly distinguished in all patients and they also may overlap [3]. The specific consequences of asthma phenotypes for asthma treatment are currently unclear due to the limited spectrum of medication including bronchodilators and corticosteroids. On the other hand, the scope of interventions is steadily increasing, for example through the introduction of treatments specifically directed against eosinophils or other target cells [47, 48], therefore phenotyping of asthma might become more important in the future.

2.1.2.2. Role of lung function in asthma

In the absence of stimuli such as allergen exposure or viral infections, the functional state in asthma is stable and more or less normal in most cases [3], and the majority of patients visits the treating physicians in a stable state and not in an emergency situation. This implies that the role of lung function in the diagnosis and monitoring of asthma might differ from that in COPD. A normal lung function might indicate the absence of asthma, or the absence of an acute deterioration if asthma is present. This absence might be due to adequate treatment and/or the absence of a stimulus eliciting asthma. Diagnostic studies in asthma are handicapped by the fact that most patients are already treated and the rate of newly diagnosed patients in a typical practice is low.

2.1.2.3. Potential role of capnovolumetry in the assessment of asthma

As lung function of patients with asthma may be normal or close to normal owing to an efficient treatment, the proper diagnostic value of lung function may be underestimated. Regarding capnovolumetry, the consequences are that asthma might be more difficult to diagnose with this method compared to COPD. It also might be that other capnovolumetric parameters than those informative in COPD are relevant in asthma. Whereas in COPD parameters of the alveolar compartment are probably most informative, in asthma those of the bronchial compartment might be more relevant. Partially due to the limitations of lung function, other tests are considered as important in the diagnosis of asthma, such as bronchial provocation tests [49, 50]

or the assessment of exhaled nitric oxide (FeNO) [51]. These tests, however, are currently not part of the diagnostic procedures outside pneumological practices. In future studies, especially the assessment of FeNO may be combined with capnovolumetry in an attempt to maximize diagnostic accuracy. Despite the difficulties described above, patients with asthma were included in the analysis of capnovolumetry in this dissertation since they represent an important proportion of patients with obstructive airway diseases. Their inclusion also provided the opportunity to assess whether diagnostic strategies and the relevant capnovolumetric parameters were different between asthma and COPD.

2.1.3. Methods of lung function assessments

2.1.3.1. Spirometry

Among lung function assessments that are in widespread use, the major role is played by spirometry [3, 4]. Spirometry is a well-standardized, objective method for describing the functional state of the lung and internationally regarded as reference standard among the lung function tests used for the diagnosis of obstructive airway diseases. This is reflected, for example, in its role for COPD categorization according to the severity of airflow limitation [4]. According to international recommendations, the presence of COPD requires that the ratio of the forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) is below 0.70, whereas the severity of COPD is determined by FEV_1 as percent predicted [4]. Unfortunately, in practice spirometry shows limitations which are based on two factors.

The first factor is the fact that a number of interesting lung volumes, such as functional residual capacity (FRC), residual volume (RV) and total lung capacity (TLC), as well as their ratio RV/TLC, cannot be assessed by spirometry, since these volumes cannot be measured by inspiration or expiration alone, as evident for RV by definition. The numerical values for these volumes are provided by bodyplethysmography [52] or gas dilution methods [53, 54].

The second factor refers to the quality of measurements that may be questionable, at least outside specialists' practices [55-57]. This is often due to difficulties arising from patients' cooperation, in combination with insufficient training of the personnel that is often due to lack of time and opportunity. These two difficulties are linked, as untrained personnel will be less capable of properly instructing the patient. The difficulties from the patients' side mostly occur in children, older patients, and patients with language difficulties, all of whom are often not capable of performing adequate breathing maneuvers. One cannot over-emphasize the importance of trained and experienced technical personnel that is capable of explaining the

breathing maneuvers to the patient, as well as of recognizing errors [58]. This is the only way to obtain reliable and reproducible results. Thus, various training programs to improve and maintain the quality of spirometry have been implemented, but still the validity of its results in clinical practice remains a challenge [56, 59]. This is true even with perfectly trained personnel, as clinical experience shows that there are always patients who are not able to follow instructions referring to forced expiration.

2.1.3.2. Bodyplethysmography

Considering the arguments mentioned above, methods requiring a lower degree of cooperation than spirometry have their place for establishing a diagnosis, or at least for finding evidence for a suspected diagnosis. Pulmonary specialists can often rely on bodyplethysmography that does not require much cooperation and provides further measures beyond spirometry (FRC, TLC, sRaw (specific airway resistance) and RV) [60, 61]. Its frequency of clinical use differs between countries, with the most intensive application in Germany. A bodyplethysmograph is a volume-constant chamber and the measurement basically relies on detecting changes in box pressure in combination with either changes of mouth pressure or with flow rate under defined breathing conditions [52]. As bodyplethysmography is performed during tidal breathing, it can provide information on airway obstruction that is not equivalent to that provided by spirometry during forced expiration. There is also evidence indicating a superior diagnostic value of bodyplethysmography compared to spirometry regarding its use in bronchial provocation tests in patients with suspected asthma [50]. The application of bodyplethysmography is, however, unrealistic for non-pulmonary specialists, in particular general practitioners, due to the high investment in equipment and personnel.

2.1.3.3. Capnovolumetry

Alternative methods of lung function measurement requiring low demands of cooperation comprise capnography [37], the interrupter method [62] and impulse oscillometry [63]. The latter two methods need specific equipment with a substantial financial investment, whereas capnography can also be performed with ultrasound spirometers without need for special hardware. Capnography has been originally introduced for physiological studies and is currently in widespread clinical use in anaesthesiology for monitoring purposes [64, 65]. It has also been proposed as a method to assess lung function during resting ventilation with low requirements for cooperation [5, 37, 66, 67]. Patients only need to perform quiet tidal breathing over a number of breathing cycles, typically 10-20 cycles. In this type of application, usually the

concentration of exhaled CO_2 is plotted against expired volume instead of time. The resulting capnovolumetric curve can be described by a number of parameters (see figure 1 in [68]), and these parameters can be evaluated for diagnostic purposes [5, 67, 69, 70].

The expiratory curve is commonly divided into three parts (phases), the first being the upper dead space that is devoid of CO_2, the second representing the transition between the dead space and the alveolar space and comprising the airways, the third one referring to the alveolar space [66]. Phases 2 and 3 are usually described by their slopes (s2 and s3, respectively), as well as their volumes (see figure 1 in [68]). Slope s2 is always larger than slope s3, i.e. phase 2 is steeper than phase 3. The relationship between slopes can be described by their ratio, s3/s2, alternatively by the angle between the straight lines describing the slopes of these two phases. Normal subjects show a relatively steep phase 2 (high slope) and a flat curve in phase 3 (low slope). This indicates a low degree of mixing in the airways corresponding to a rapid increase of CO_2 concentration from zero to the alveolar value, and at the same time a fairly homogeneous alveolar compartment, with little inhomogeneity between alveolar compartments [66]. Correspondingly, the ratio s3/s2, with a low value of the numerator and a high value of the denominator, attains a low value. Therefore, the ratio of slopes and the angle are closely related to each other and describe the same phenomenon by different indices.

There are obstructive airway diseases associated with inhomogeneous ventilation, especially COPD and lung emphysema. Alveolar compartments are ventilated very differently and show different CO_2 concentrations that contribute differently over the course of expiration. Well-ventilated compartments with low CO_2 concentration contribute predominantly to the initial phase of expiration, whereas ill-ventilated compartments with high CO_2 concentration contribute predominantly to the final phase of expiration. As a result, the slope of phase 3 becomes steeper [71]. In addition, the mixing within the airways corresponding to phase 2 becomes stronger, so that the slope of phase 2 becomes less steep. In severe lung emphysema the transition between phases 2 and 3 may even become difficult to recognize. The result of increasing the numerator and decreasing the denominator is an increase in the ratio s3/s2 and correspondingly in the angle between the slope of the two phases [71, 72]. If slopes are very similar, the ratio approaches the value of 1 and the angle the value of 180 degree. These considerations indicate that the ratio s3/s2 should be a particularly sensitive parameter for the detection of airway obstruction linked to inhomogeneity of ventilation. This is typical for COPD. Indeed, the study performed by Ponto et al. [5] which particularly comprised COPD patients showed a high diagnostic accuracy for this ratio.

In asthma, it might be expected that the total volume of the bronchi is slightly reduced compared to normal subjects [73]. This would imply a reduced volume available for mixing and thus an increase in the slope of phase 2. If the slope of phase 3 should be unchanged, this would lead to a reduction of the ratio s3/s2, as the denominator becomes larger. Thus, in addition to s3/s2, the volume of phase 2 might be an informative parameter in patients with obstructive airway diseases.

Beyond the slopes s2 and s3, there are further parameters describing the shape of the capnovolumetric curve. Among these, the ratio of the area/volume of phase 3 is of special interest (see figure 1 in [68]). Formally, it is an average CO_2 concentration (CO_2 concentration times volume (=area of phase 3), divided by volume of phase 3). This parameter depends on the slope of phase 3 and thus the inhomogeneity of ventilation. It is linked to the amount of CO_2 attributable to the increase of CO_2 concentration over the alveolar phase, i.e. the amount of exhaled CO_2 due to the inhomogeneity of ventilation.

The reasons why capnovolumetry is not yet part of clinical routine seem to be twofold. Novel methods commonly enter clinical practice via their use by specialists and by showing a favourable cost-benefit ratio. Pulmonary specialists usually have bodyplethysmography, which renders additional methods of measurement during resting ventilation superfluous. Thus, the method is not commonly used among pneumologists, in contrast to anaesthesiologists who use capnography for several purposes [74, 75]. The second reason refers to the cost-benefit ratio that is relevant even if the diagnostic usefulness of capnovolumetry can be shown. Until recently, relatively expensive equipment in form of fast and precise CO_2 sensors was needed but this has changed, since the concentration of exhaled CO_2 can be estimated in commercially available ultrasound spirometers by software algorithms that do not require a CO_2 sensor [5]. This removes one important obstacle and renders it attractive to re-evaluate capnovolumetry for its diagnostic potential.

This applies even more as the need for reliable lung function measurements in primary care increased over time. When relying only on spirometry, difficulties arise if spirometry fails due to insufficient cooperation from the patient. If capnovolumetry, as an alternative, should be useful for clinical practice, it should have sufficient sensitivity and specificity regarding the detection of impairments in lung function. A sufficient diagnostic accuracy might be assumed if in a receiver operating characteristics (ROC) analysis the area under the curve is >0.8, at least for well-defined subgroups of patients. Moreover, the interpretation and probably also the acceptance among clinicians would benefit if pathophysiological correspondences between the capnovolumetric parameters and conventional lung function measures can be shown. The

transfer into clinical practice would also benefit from simple algorithms demonstrating how to combine capnovolumetric and clinical data in order to achieve the highest diagnostic accuracy. These three topics were addressed in the present study.

2.2. Study questions

Based on the considerations outlined above, three studies constituting the basis of this dissertation were performed:

- The clinical setting most promising for capnovolumetry might be primary care, in which the most basic diagnostic question refers to the presence of airway obstruction. In a pilot study [5], a specific capnovolumetric parameter (ratio of capnovolumetric slopes of phases 2 and 3 (s3/s2)) showed a high diagnostic accuracy for the detection of airway obstruction with a sensitivity of 90% and a specificity of 86% at the cut-off s3/s2 ≥ 0.10, thereby recommending this parameter for further evaluation. So far, the parameter and the cut-off value proposed by Ponto et al. [5] have not been prospectively validated in a large group of patients.

  Based on the results of Ponto et al. [5], the first study aimed to prospectively and systematically assess the diagnostic accuracy of capnovolumetry for the detection of airway obstruction within a confirmatory study in order to prove its diagnostic value. Obstruction was defined via the methods available to a pulmonary specialist in order to have a reliable reference in each patient. This study was performed prospectively in a large sample of unselected patients recruited under ambulatory care conditions. For data evaluation, standard procedures of logistic regression and receiver operating characteristics (ROC) analysis were used. The dataset of this study population also served as basis for the other two studies that addressed further questions.
- The parameters of capnovolumetry are not commonly known among clinicians and might appear rather abstract. Any help in their interpretation would be clinically helpful and favour the use of capnovolumetry.

  Therefore, their physiological meaning was to be clarified, ideally by constructing physiologically meaningful correspondences to well-known lung function parameters. Such an interpretation should facilitate the use of capnovolumetry in clinical practice. This task was addressed in the second study by constructing an isomorphic mapping between the correlation structures of conventional and of capnovolumetric parameters, as a novel way to understand complex relationships. For this purpose, the statistical technique of path analysis was used.

- The establishment of a clinical diagnosis includes the evaluation of clinical history, signs and symptoms. A close analysis of the data obtained in the first study revealed that a small set of signs and symptoms appeared most relevant for diagnostic decisions. It was also found that only few capnovolumetric parameters were relevant. A clinical use of this information should be based on empirically justified, optimal combinations of data and result in algorithms that are easy to grasp and apply.

  The third study achieved this by using the technique of classification and decision trees that has not been previously used for capnovolumetry. Such trees were constructed for different diagnostic comparisons of interest. To account for the known risk of overfitting, the single trees were validated by the Random Forest approach, which is an established procedure of machine learning.

3. Methods used in the three studies

3.1. Detection of airway obstruction (first study)

3.1.1. Study design and population

Data of this study was obtained prospectively in a pulmonological practice in Augsburg between February and April 2018. This practice was led by six pulmonary specialists in primary care. Overall, 1400 consecutive patients were recruited. These patients were either diagnosed for the first time or, in the majority of cases, visited the practice for follow-up assessments. The exclusion criteria were an age of <18 years or an insufficient understanding of the German language, and there were no further inclusion or exclusion criteria. Patients with incomplete data were omitted, as well as patients with prior bronchial provocation or bronchodilator tests, in order to avoid potential interference with the aim of this diagnostic study. This resulted in a final population of 1287 patients who had the diagnosis of either COPD, or asthma, or other respiratory diseases, or no respiratory disease or other disorders that could interfere with respiratory function. Patients with COPD and concomitant asthma were assigned to the COPD group, as the COPD dominated function and symptoms.

The clinical diagnosis was based on all functional and clinical data available to the specialists. This included bronchial provocation challenges and bronchodilator tests as well as chest X-rays. None of these assessments was specifically performed for the purpose of the present study. It is important to note that all assessments specifically performed for the present study (especially capnovolumetry) were not part of the diagnostic process and their results not available to the treating physician.

The target number of 1400 patients was based on a power analysis that incorporated the estimated prevalence of patients with airway obstruction as well as estimates of the sensitivity and specificity of a specific capnovolumetric parameter for the detection of airway obstruction (ratio of slopes of phases 3 and 2) proposed by a pilot study [5]; details can be found in the paper [68]. The study was approved by the Ethical Committee of the TUM (Technical University of Munich), and the study protocol was supplied to the German Clinical Trials Register (DRKS 00013935).

3.1.2. Capnovolumetry as index test

In these measurements, patients were asked to perform tidal breathing over 10 or more breathing cycles, in a sitting position and with nose-clips. There were no further instructions

than to perform quiet breathing and to avoid panting or deep breaths. During the breathing cycles, the flow-rate was measured by ultrasound, as well as the molar mass, from which the CO_2 concentration could be computed taking into account temperature and humidity. This technique has been shown to provide reasonable accuracy compared to direct CO_2 measurements. Its advantage is that no additional CO_2 sensor is needed and potential problems concerning the variability of such a sensor do not exist, as the ultrasound signal does not need calibration. The computationally derived CO_2 signal was plotted against the expired volume, and the resulting curve was described by a number of capnovolumetric parameters (see figure 1 in [68]). Each parameter provided by the device represented a mean value of the last 5 recorded breathing cycles. The indices most important for the present study were the slopes of expiratory phases 2 and 3 (s2 and s3 respectively), as well as their ratio s3/s2. In addition, the expired volumes of the two phases and corresponding areas under the concentration-volume curve could be defined. Measurements were performed using the device SpiroScout (software LFX 1.8.0, Ganshorn, Niederlauer, Germany).

3.1.3. Spirometry and bodyplethysmography as reference standard

Spirometry and bodyplethysmography were routinely performed in all patients in the private practice, following established recommendations (see [68]). Their main purpose in the present study was to decide on the presence of airway obstruction by using criteria that are in widespread use and recommended. Regarding spirometry, airway obstruction was assumed, if the z-score of FEV_1/FVC (forced expiratory volume in one second / forced vital capacity) was below -1.645, corresponding to the lower 5-percentile (lower limit of normal, LLN) [76]. If the ratio was above, bodyplethysmography was used for decision, and obstruction was assumed if the value of specific airway resistance (sRaw) was above 1.2 kPa*s or that of airway resistance (Raw) was above 0.3 kPa*s/l [61]. These criteria could be easily checked in the database, and in cases of inconsistency the values were checked in order to decide on the presence of airway obstruction.

3.1.4. Data analysis

The values of the groups of patients with or without airway obstruction were compared with either the Mann-Whitney-U test or the Chi-square statistics, depending on the type of the data. Following the decision to evaluate the ratio s3/s2 as primary parameter, its value for the diagnosis of airway obstruction was evaluated by constructing a receiver operating characteristic (ROC) curve including quantification of the area under the curve (AUC) and its 95%

confidence interval. From the ROC curve, the optimal cut-off value could be derived via the maximal sum of sensitivity and specificity (Youden index). This was compared with the pre-specified value of 0.1 that was the basis of the power calculation. The results could be summarized in 2x2 contingency tables, indicating sensitivity and specificity for which 95% confidence intervals were computed.

This primary analysis was followed by two types of secondary analysis. The first of these aimed to determine to which extent the diagnostic accuracy of capnovolumetry depended on the degree of airway obstruction quantified by spirometry. For this purpose, separate analyses of s3/s2 were performed in the groups of patients with values of FEV_1 in percent predicted being either 80%, 50% or 30% at maximum. This distinction was made in analogy to the categorization of COPD patients according to GOLD [4]. The second analysis aimed to evaluate parameters that were informative regarding airway obstruction beyond s3/s2 and to combine them in order to reveal which maximum gain of diagnostic accuracy could be achieved compared to s3/s2 alone. For this purpose, multiple logistic regression was used, limiting the maximum number of predictors to four. Moreover, the ratio s3/s2 was log-transformed after adding 0.05 to approximate a normal distribution as far as possible. In an analogous way, the slope s3 was log-transformed after addition of 0.03. The logistic regression analyses were performed with different sets of predictors, among which the four capnovolumetric parameters with the highest predictive value were chosen and the remaining parameters were omitted irrespective of the fact that they could provide a further contribution. This was done to reduce potential problems from overfitting and multi-collinearity. The logistic regression analyses provided predictive scores (probability for belonging to the group with airway obstruction), and these scores were used in ROC analysis in the same way as had been done for s3/s2. This included the analysis in the three sub-populations showing a different degree of airway obstruction.

It is known that capnovolumetric parameters, just as other lung function parameters, depend on anthropometric measures as well as the breathing pattern, especially tidal volume. To determine a potential gain in diagnostic accuracy from taking into account these dependences, a sensitivity analysis was performed. For this purpose, the dependence of capnovolumetric parameters on age, height, sex and tidal volume was determined in multiple linear regression analyses, and the predicted values from these regression analyses were used for normalization of the measured values. The above-mentioned analyses were then repeated using these adjusted parameter estimates.

All statistical analyses of the first study were performed using the package SPSS (Version 25, IBM, Armonk, NY, USA), and an error of the first kind of $p<0.05$ was assumed as level of statistical significance.

3.2. Interpretation of capnovolumetric parameters (second study)

3.2.1. Study design and population

This study relied on the same population as the first study, however with the difference that patients were additionally analysed according to their clinical diagnoses. This, however, referred only to the groups with COPD or asthma, as well as the group of patients without respiratory disease or disorder potentially affecting respiratory function (control group). The group of patients with other respiratory diseases (such as restrictive disorders, pneumonia or other infections, pleural diseases, lung tumor, bronchiectasis) was omitted, as this heterogeneous group was difficult to fit into the analysis. Only patients with full data were included in this analysis in order to avoid problems from data imputation in methods requiring complete data. Overall, 978 patients fulfilled these criteria, among them 259 patients with COPD, 401 patients with asthma and 318 control subjects. As in the first study (see 3.1.), the clinical diagnoses were taken from the patients' files on the basis of already existent findings, without reference to the assessments in the present study.

3.2.2. Assessments

In this study, spirometry and bodyplethysmography were not only used to decide on the presence of airway obstruction but also to provide parameters that could be helpful in the interpretation of capnovolumetry. The parameters were forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), their ratio (FEV_1/FVC), forced expiratory flow at 50 and 25% of vital capacity (FEF_{50}, FEF_{25}), residual volume (RV), and the ratio RV to total lung capacity (RV/TLC), as well as specific airway resistance (sRaw) and airway resistance (Raw), both as effective values. These parameters were chosen in order to cover a broad range of functional deteriorations and thereby to enhance the likelihood to find a set of conventional lung function parameters that could be brought in correspondence with capnovolumetric parameters. The set comprised parameters indicative of lung hyperinflation that might correlate with parameters of the capnovolumetric phase 3, as well as parameters of flow rate that might reflect airway obstruction and correlate with parameters of the capnovolumetric phase 2. All assessments of either conventional lung function or capnovolumetry were the same as in the first study, and

the same quality criteria applied. The definition of airway obstruction was the same as in the first study.

3.2.3. Data analysis

The present study relied on the three diagnostic categories asthma, COPD and control. Accordingly, the statistical comparisons between groups were performed by the Kruskal-Wallis test or Chi-square statistics of contingency tables. Regarding capnovolumetry, the analysis relied on the four parameters slope of phase 3 (s3), ratio of slopes of phases 3 and 2 (s3/s2), volume of phase 2 (Vol s2), and the ratio area/volume of phase 3 (AreaVol s3), that had been identified as most important in the first study (see [68]), regarding the detection of airway obstruction irrespective of the underlying diagnosis.

To achieve the aim of the study, in a first step the multiple relationships within each set of parameters (conventional lung function or capnovolumetry) were investigated. This was done by logistic regression analysis with the diagnosis of asthma or COPD as outcomes, as well as multiple linear regression analyses, with one of the parameters as outcome and the others as predictors. As in the first study (see [68]), the slope of phase 3 was log-transformed after addition of 0.03, and the ratio s3/s2 was also log-transformed after addition of 0.05, in order to achieve a distribution as close to normal as possible. The results of these analyses served as a starting point for the construction of advanced statistical models and are not shown in detail, since they were not suitable for a comprehensive depiction due to their complicated structure that largely was due to multi-collinearity.

As a result of these facts, direct and indirect relationships were mixed. This could be addressed by the advanced technique of structural equation modelling which was used in the traditional form of path analysis, involving only observed (manifest) variables without reference to unobserved (latent) variables. Path analysis is an extension of conventional linear regression and well-suited to describe a network of interdependences, taking into account that some of the observed correlations may be indirect and some of them may be direct. For this purpose, the procedures as implemented in the SPSS extension AMOS (Version 25, IBM, Armonk, NY, USA) were used.

For the parameters of capnovolumetry there are no reference values that are generally accepted. Moreover, their dependence on anthropometric characteristics and tidal volume was weak, and taking into account this dependence did not lead to improvements in the first study (see [68]). Therefore, the capnovolumetric parameter values were used in all analyses as

measured values without any attempt of adjustment or normalization. As it is known that lung function parameters depend on anthropometric characteristics and these were not included in the capnovolumetric model, z-scores normalizing for age, height and sex were used for lung function parameters. Using the results of logistic regression analyses in combination with pathophysiological insight, a path analysis model comprising the four selected capnovolumetric parameters was constructed in consecutive steps. The robustness of this model was affirmed by systematically changing relationships between parameters, especially removing or inverting relationships, and comparing the goodness of fit.

The final capnovolumetric model served as reference for the construction of the model describing the relationships between lung function parameters. The guiding principle was to conserve the structure of the path model as much as possible and to find substitutions of capnovolumetric parameters by conventional lung function parameters that preserved the network structure. This novel approach turned out to be much superior to all attempts to express capnovolumetric as function of conventional lung function parameters, which always led to difficulties from collinearity that could not be resolved. The approach followed in this work was much more elegant as it aimed to preserve the multiple relationships between parameters and thus to map them on each other as precisely as possible.

It did not appear a sensible approach to substitute each conventional parameter for each capnovolumetric parameter, since some of them were obviously less adequate from a physiological point of view as others. Thus, in the first step, sets of parameters were defined that could be reasonably associated with each of the capnovolumetric parameters, based on both physiological arguments and the results of the regression analyses. These considerations motivated the following correspondences. The slope of phase 3 was coordinated with RV/TLC, RV and FEV_1 as potential counterparts; the ratio of slopes s3/s2 with RV/TLC, RV and FEV_1; the volume of phase 2 with FEF_{50}, FEF_{25} and FEV_1; the ratio area/volume of phase 3 with RV/TLC, FVC and FEV_1.

Based on these sets, capnovolumetric parameters were consecutively replaced by conventional lung function parameters within the path analysis model provided by capnovolumetry. Using this stepwise approach, those lung function parameters were identified that were most suitable to substitute capnovolumetric parameters in the path model. The criteria were that the parameter resulted in a good fit and at the same time preserved the structure of the model as far as possible in the sense that the basic structure remained and at most single dependences (arrows) between the parameters were modified.

Path analysis was performed with AMOS (Version 25, IBM, Armonk, NY, USA) and the generalized least squares estimation criterion was used. The goodness of fit was judged by the Chi-square statistics that describes the deviation of the data from the model. Therefore, this statistics indicates a good fit if it is as low as possible and the correspondent p-value signifies no statistical difference ($p>0.05$). It is known, however, that this statistics may be over-sensitive in samples of large size. Therefore, the primary criteria were the comparative fit index (CFI) that should be >0.95, as well as the root mean square error of approximation (RMSEA) that should be <0.05. All other statistical tests were performed with SPSS (Version 25, IBM, Armonk, NY, USA) and statistical significance was assumed for $p<0.05$.

3.3. Integration into diagnostic algorithms (third study)

3.3.1. Study design and population

The third study was based on the same data as the first study but only patients with asthma or COPD and the control group (patients without respiratory disease or disorder potentially affecting respiratory function) were included in the analysis. Patients with other respiratory diseases than COPD or asthma (such as restrictive disorders, pneumonia or other infections, pleural diseases, lung tumor, bronchiectasis) were excluded. As described in the second study (see 3.2.), the physician-based diagnoses relied on already existing findings, without reference to the assessments in the present study. Overall, 1057 patients fulfilled the inclusion criteria, among them 260 patients with COPD, 433 patients with asthma, and 364 control subjects, with potentially incomplete data.

3.3.2. Assessments

The study had the aim to reveal whether capnovolumetric data can be combined with basic anamnestic information to support the diagnosis of obstructive airway diseases. Anamnestic information was taken from a questionnaire covering clinical history, signs and symptoms. The items were a subset of those used in the initial study (see 3.1.), in which only capnovolumetric measures were analysed. The set of questions was selected on the basis of a preliminary analysis of the whole data set. This analysis focused on two questions, first whether data for the questionnaire item was available in all or nearly all patients, thereby removing a number of items that were conditional on the answers of previous items. Second, statistical tests (contingency tables) were performed to remove those items that did not show significant differences between the diagnostic groups. Using this selection procedure, a set of seven items remained.

It comprised questions on dyspnea upon either mild or strong exertion, cough, phlegm, wheezing in the last 12 months, as well as smoking status (current, ex-smoker). Capnovolumetric measurements were the same as in the first study and the same quality criteria applied. Only the parameters s3/s2, s3, area/volume phase 3 and volume phase 2 were included in the present analysis as these had been identified as relevant in the first study for the detection of airway obstruction (see 3.1.) and in the second study (see 3.2.) had allowed a meaningful interpretation.

3.3.3. Data analysis

The three diagnostic groups (asthma, COPD and control) were compared with each other using Chi-square statistics for categorical variables (anamnestic information) and with the non-parametric Kruskal-Wallis test for continuous parameters (capnovolumetric parameters). In addition, binary logistic regression analyses were performed for the comparison of COPD versus controls, asthma versus controls, and asthma versus COPD. These analyses provided a first overview on the relationship between questionnaire items, capnovolumetric parameters and diagnostic groups. Multinomial logistic regression was not found adequate, as it did not lead to statistically robust results, and was therefore not used.

In the next step, the multiple correlations between anamnestic information, capnovolumetric parameters and the diagnoses of asthma and COPD were delineated as a quantitative network diagram. For this purpose, correlations were expressed via an adjacency matrix based on phi-coefficients describing the strength of associations; the control group served as reference. Anamnestic information, i.e. questionnaire items, was integrated into the diagram as binary variables. To reduce complexity, only the capnovolumetric parameters s3/s2 and volume of phase 2 were used. These had been identified previously (see 3.2.) as carrying information on both asthma and COPD. To convert the continuous capnovolumetric data into binary variables, a predefined (see 3.1.) cut-off value of 0.10 for s3/s2 [5] was used. For the volume of phase 2, the optimal cut-off value was identified by ROC analysis regarding the detection of asthma versus control. Please note that this parameter was the only one that had been found to be specifically related to asthma (see 3.2.).

While the network diagram described the different associations found for asthma and COPD, it did not provide specific information that could be used for diagnostic purposes. In principle, logistic regression could be employed for this, using the predicted probabilities for a specific diagnostic group, or via considering the odds ratios provided by the method. This, however, is a rather abstract approach and also requires the numerical implementation of the regression function, if probabilities are to be used.

An alternative are decision algorithms. These are easy to comprehend and apply, as tree-based procedures, and mimic the consecutive decision process implicitly or explicitly followed by many physicians. In the present study, such decision trees were computed and provided for the diagnosis of asthma and COPD (see below). Single trees are, however, well known to bear the risk of overfitting, even with cross-validation, and therefore the results should be checked with more robust methods. This can be done by using large ensembles of decision and classification trees that are constructed by a systematic process. The aim is to mimic the variability arising from the use of different data sets and different sets of available variables by random selection.

One of the common methods to achieve this is the Random Forest approach. In principle, the method samples random subsets of the existing data sets and then constructs a tree for each subset, again on a random basis. This is done by randomly selecting variables at each node of the tree, with the result that a large variety of trees is built, each of them with different performance in different data sets. The final decision is usually taken as a majority decision over all trees, after the data of an individual have been evaluated by all trees. The disadvantage of the method compared to single trees is that its application requires a software object in which the ensemble of trees has been implemented as algorithm. This renders it more difficult to understand the decision process.

In the present study, the Random Forest approach was used for two purposes. The first one was to reveal whether the parameters identified as significant in single trees (see below) coincided with those showing the highest importance in the ensembles of trees. This was done to reduce the risk of error in single trees due to overfitting. The second purpose was to compare the classification accuracy between the Random Forest approach and single trees. If a single tree would show much higher accuracy than the ensemble, this would point towards overfitting. If, on the other hand, the ensemble would be much better than the single trees, this would indicate that a significant gain in accuracy could be achieved by the ensemble approach that would, however, require a software tool.

Different ensembles of Random Forest trees were constructed for COPD versus control, asthma versus control and asthma versus COPD. Anamnestic information and capnovolumetric parameters s3/s2, s3, area/volume phase 3 and volume phase 2 were offered to the search algorithm. In contrast to the network analysis, capnovolumetric parameters were given without predefined cut-off values, since the optimal cut-off values were identified by the Random Forest algorithm. The trees were constructed from the data by random selection of 500 subsets of patients (with replacement). The random sets of variables at each node comprised three parameters each, a number that was derived via the square root of the number of variables

offered. The patients not included in a specific tree (called “out of bag”) enabled the evaluation of accuracy by using them for prediction as test sets. The relative importance of parameters within the Random Forest procedure was described by two criteria: the mean decrease in accuracy and the GINI criterion referring to the impurity of categorizations. The final results were evaluated in terms of 2x2 contingency matrices and ROC analyses. Random Forest ensembles were constructed using the package “randomForest” in R, Version 4.0.2. The same was true for the network analysis that was performed with the package “igraph” from R.

As we aimed at practical applications, the Random Forest approach was supplemented by the construction of single decision trees. These trees allowed to illustrate typical tree structures by specific examples. For this purpose, an established procedure based on Chi-square statistics (CHAID) as implemented in SPSS was used. To reduce errors, a Bonferroni correction was taken into account, and all results were based on tenfold cross-validation. In analogy to the Random Forest approach, separate trees were constructed for COPD versus control, asthma versus control and asthma versus COPD, and these trees are presented in the paper. All statistical analyses referring to CHAID were performed with SPSS (Version 25, IBM, Armonk, NY, USA). The level of statistical significance was assumed at $p<0.05$.

4. Results of the three studies with author's contributions

4.1. Detection of airway obstruction (first study)

Citation: Kellerer C, Jankrift N, Jörres RA, Klütsch K, Wagenpfeil S, Linde K, et al. Diagnostic accuracy of capnovolumetry for the identification of airway obstruction–results of a diagnostic study in ambulatory care. Respiratory Research. 2019;20(1):92.

Spirometry is the most common lung function method used in clinical practice, including general practitioners. The method is extremely valuable but also has its weaknesses. While technical issues can be easily solved, one major issue remains if there is lack of sufficient cooperation by the patient. Such cooperation is required for the forced breathing maneuvers. Experience shows that this difficulty can only partially be resolved by educational efforts. It implies that in a significant proportion of patients no valid information from spirometry can be gained. This might be partially alleviated by the use of alternative methods that require less cooperation, for example because measurements are performed during resting ventilation. One of these methods is capnovolumetry, i.e. the measurement of exhaled carbon dioxide as a function of expired volume, that is available in ultrasound spirometers, thus not requiring additional technical equipment. Whether ultrasound-based capnovolumetry is sufficient to recognize the presence of airway obstruction, as a most basic diagnostic feature, remained to be clarified. A pilot study performed by Ponto et al. [5] showed a high diagnostic accuracy for a specific capnovolumetric parameter (ratio of capnovolumetric slopes of phases 2 and 3 (s3/s2)) regarding the detection of airway obstruction. So far, the parameter and the cut-off value proposed by Ponto et al. [5] have not been prospectively validated in a large group of patients. Therefore, the first study aimed to prospectively and systematically assess the diagnostic accuracy of capnovolumetry for the detection of airway obstruction within a confirmatory study.

For this purpose, consecutive patients from a pneumologists' practice were studied. The presence of airway obstruction was inferred from spirometry and bodyplethysmography, and this information served as reference standard. The index test was capnovolumetry performed with an ultrasound spirometer. Data was evaluated by receiver operating characteristics (ROC), in which a fixed ratio of slopes of the expiratory phases 3 and 2 was used, as well as logistic regression analyses.

Overall, 1400 patients were recruited of whom 1287 patients fulfilled the inclusion criteria. These criteria comprised completeness of functional data and the absence of interventions that

could have affected the results. In total, 371 patients (29%) of 1287 patients included showed signs of airway obstruction according to the reference standard comprising spirometry and/ or bodyplethysmography. Regarding baseline characteristics (sex, age, BMI) and lung function parameters, patients with airway obstruction showed significant differences compared to those without airway obstruction in all measures except BMI (see table 1 in the publication). Moreover, the major capnovolumetric parameters except the volume of phase 2 were significantly different between the groups of patients with and without airway obstruction (see table 2 in the publication).

The primary target parameter s3/s2 showed significantly higher values in patients with airway obstruction compared to those without. When using the ratio of slopes of the expiratory phases 3 and 2 (s3/s2) as primary outcome parameter of capnovolumetry, ROC analysis showed an area under the curve (AUC) of 0.678, with a 95% confidence interval (95%CI) from 0.645 to 0.710. The predefined cut-off value (=0.10) for s3/s2 resulted in a sensitivity of 47.7 (95%CI 42.7, 52.8) % and a specificity of 79.0 (95%CI 76.3, 81.6) %, indicating a considerably lower sensitivity in the present study compared to previous data [5]. The result could be improved when using a slightly different cut-off value of 0.08 that was derived via the maximum of the Youden index, with a sensitivity of 59.0 (95%CI 54.0, 63.9) % and a specificity of 68.7 (95%CI 65.6, 71.6) %.

Further analyses were performed to assess whether the diagnostic accuracy depended on the degree of airway obstruction (see table 3 in the publication). When requiring severe obstruction in terms of the forced expiratory volume in one second (FEV_1) ≤ 50% of its individual predicted value, the sensitivity of the criterion of s3/s2 ≥ 0.10 increased to 75.9 (95%CI 67.1, 83.0) %, with a specificity of 75.8 (95%CI 73.3, 78.1) %. When requiring very severe obstruction in terms of FEV_1 ≤ 30% of predicted, the sensitivity of the criterion of s3/s2 ≥ 0.10 was further raised to 86.7 (95%CI 70.3, 94.7) %, with a specificity of 72.8 (95%CI 70.3, 75.2) %. Logistic regression analyses revealed other parameters beyond s3/s2 as informative, especially the ratio area/volume phase 3, the slope of phase 3 and the volume of phase 2. When using these four parameters to establish a combined capnovolumetric score for the prediction of airway obstruction, an AUC of 0.772 (95%CI 0.743, 0.801) was achieved in the total population. The maximum Youden index corresponded to a sensitivity of 69.8 (95%CI 65.1, 74.7) % and a specificity of 71.7 (95%CI 67.7, 73.7) %, indicating a gain in diagnostic accuracy compared to s3/s2 regarding sensitivity, however partially at the cost of specificity.

In summary, the method of capnovolumetry that requires minimal cooperation by the patient showed a statistically significant albeit moderate ability in the recognition of airway obstruction defined via spirometry and bodyplethysmography. Its diagnostic accuracy increased when the

severity of airway obstruction increased, and its sensitivity could be increased by the use of multiple parameters from capnovolumetry. As these results were obtained in a population from a pneumological practice with a high prevalence of obstructive airway diseases, it remains to be determined whether the criteria identified as optimal have to be modified when the method is applied in circumstances with a lower prevalence of airway obstruction and how it can be combined with anamnestic information.

Author's contribution

The author performed the measurements in all 1400 patients, together with another medical doctoral student. Moreover, she was responsible for the establishment, completion and quality control of the data base comprising a multitude of parameters. The author also performed the statistical analyses using the SPSS statistical package and was involved in all stages of the interpretation of the data and manuscript preparation, as well as the submission, reviewing process and proofreading. Based on this, the position as leading author is appropriate.

4.2. Interpretation of capnovolumetric parameters (second study)

Citation: Kellerer C, Schneider A, Klütsch K, Husemann K, Sorichter S, Jörres RA. Correspondence between Capnovolumetric and Conventional Lung Function Parameters in the Diagnosis of Obstructive Airway Diseases. Respiration. 2020;99(5):389-97.

Among the methods for the assessment of lung function, capnovolumetry is of special interest owing to its minimal cooperation requirements from the patients. It has been previously shown to be suitable for the diagnosis of airway obstruction (see publication 1). The parameters describing capnovolumetry are, however, not commonly known and may appear rather abstract, although most of them have a very clear and intuitive interpretation. Regarding the use and acceptance of capnovolumetry it would be of advantage to know, in which way the parameters are related to those of conventional lung function, especially spirometry and bodyplethysmography that are in widespread use and well known to many clinicians. The present study therefore aimed to identify possible correspondences between the two sets of parameters.

In order to avoid statistical complications from idiosyncratic disorders not fitting into standard categories, the analysis was restricted to a subset of the 1400 patients recruited in study 1. This subset comprised 978 patients with complete datasets and either asthma (n=401), or chronic obstructive pulmonary disease (COPD) (n=259), or without respiratory disease or conditions affecting respiratory function (n=318). The method of evaluation followed the approach to construct a path analysis model for the capnovolumetric parameters that took into account their multiple relationships to each other. In the next step, a path analysis model was constructed for the conventional lung function parameters, starting from the capnovolumetric model and replacing capnovolumetric by conventional parameters, with the aim to keep the structure of the model the same as far as possible, i.e. to obtain an isomorphic model. This approach was superior to conventional regression analysis that was handicapped by the high degree of collinearity between most variables. Path analysis is an extension of conventional linear regression analysis, allowing for the description of networks comprising both direct and indirect effects.

The capnovolumetric path diagram included the four parameters slope of expiratory phase 3, ratio of slopes of phases 3 and 2, volume of phase 2, and the ratio area/volume of phase 3 that had been identified as most important in the first study. It additionally comprised the diagnostic categories of asthma, COPD and airway obstruction. Asthma was dependent on s3/s2 and the volume of phase 2, COPD on the slope of phase 3, s3/s2, the ratio area/volume of phase 3 and

the presence of airway obstruction. Airway obstruction depended on s3, s3/s2, the volume of phase 2 and the ratio area/volume of phase 3. s3 depended on the ratio s3/s2 and the volume of phase 2, while the area/volume of phase 3 depended on s3/s2 and s3. The important point was the relationship between the volume of phase 2 and asthma as well as obstruction, which was consistent with results of the first study. The same was true for the dominant role of s3/s2. The ratio area/volume which had been identified as important in the first study turned out to be a mediator between s3 or s3/s2 and the diagnostic categories of airway obstruction and COPD, underlining the distinction between direct and indirect effects in the path analysis model.

Using the described technique of sequential replacement, an analogous path analysis model could be constructed for the conventional lung function parameters, and this model kept the basic structure of the capnovolumetric model, with few modifications that were physiologically plausible. The ratio of slopes s3/s2 corresponded to the z-score of the forced expiratory volume in one second (FEV_1), reflecting their central role for the detection of airway obstruction. The slope s3 corresponded to the z-score of the ratio of residual volume to total lung capacity (RV/TLC). Thus, hyperinflation or trapped air indicated by RV/TLC and indirectly linked to inhomogeneous ventilation, were reflected in the slope of the alveolar phase s3 that directly indicates the inhomogeneity of ventilation. The capnovolumetric volume of phase 2 that probably indicates a residual airway obstruction, corresponded to the z-score of the mid-expiratory flow rate (FEF_{50}) that is commonly considered as a sensitive indicator of airway obstruction. The ratio of area/volume of phase 3 describes a change in absolute CO_2 concentration over this phase that should be inversely related to the ventilatory capacity of the patient; indeed, the lung function parameter that corresponded best to this capnovolumetric parameter was the forced vital capacity (FVC), a marker of ventilation capacity.

These findings underlined that within the set of capnovolumetric parameters and within the set of conventional lung function parameters intricate relationships could be identified that included relationships to diagnostic categories. Furthermore, the proper selection of conventional lung function parameters allowed a mapping to capnovolumetric parameters including their mutual relationships that was nearly 1:1. The four pairs of capnovolumetric and conventional parameters could be interpreted as reflecting the entities of lung hyperinflation, overall ventilatory impairment, bronchoconstriction, and ventilated lung volume. Beyond providing physiological insight, these findings might help the users of capnovolumetry in the clinical interpretation of the measurements.

Author's contribution

The analysis was based on the measurements in 1400 patients, that the author had performed together with another medical doctoral student. The responsibility for the establishment, completion and quality control of the data base extended to the present study. The author performed the statistical analyses using the AMOS and SPSS statistical packages and was involved in all stages of the work, from the design of the analysis, interpretation of the data, manuscript preparation, submission and reviewing process to the proofreading. Based on this, the position as leading author is appropriate.

4.3. Integration into diagnostic algorithms (third study)

Citation: Kellerer C, Klütsch K, Husemann K, Sorichter S, Jörres R, Schneider A. Capnovolumetry in combination with clinical history for the diagnosis of asthma and COPD. NPJ primary care respiratory medicine. 2020;30(1):1-9.

The previous two studies had shown that capnovolumetry was informative in the detection of airway obstruction and that its major parameters could be interpreted in a physiologically meaningful way with regard to obstruction and the diagnosis of asthma and COPD. In practice, the diagnosis of respiratory diseases always involves the assessments of clinical signs and symptoms. Thus, the question arises in which way capnovolumetric data can be combined with anamnestic data to support the diagnosis of asthma or COPD. For this purpose, different analytic strategies may be used which differ in their usability and complexity. Experience shows that most physicians prefer simple, easy-to-comprehend diagnostic algorithms and that abstract formulas are not in favour. The present study therefore aimed to evaluate the usefulness of decision trees intuitively mimicking diagnostic decision processes but being based on statistical evidence instead of experts' recommendations. As a first step, however, a more robust but not as easy comprehensible machine learning algorithm was used. In addition to the trees, a network diagram was constructed on the basis of the data in order to understand the mutual relationships between variables.

The database was the same as in the previous two studies. From the 1400 patients, 1057 patients with asthma (n = 433), COPD (n = 260), or without respiratory disease (n = 364, control) were selected. Completeness of datasets for each patient was not required. The analysis was based on capnovolumetric data and seven anamnestic questions regarding symptoms and smoking status. These questions had been selected from a larger number of questions following the requirement that questions with a large number of missing values were excluded, as well as questions that turned out to be far from informative in logistic regression analyses regarding asthma or COPD. The selection comprised seven questions covering wheezing in the last 12 months, dyspnea upon strong and mild exertion, cough, phlegm, current and ex-smoking status. These questions also had the advantage to be within the range of common anamnestic questions. The algorithms that could be graphically shown were modelled as single decision trees using an established procedure (CHAID). Prior to this, random ensembles of trees were constructed from the dataset using the Random Forest approach to verify the order of most relevant parameters in a statistically robust fashion and to compare predictive accuracy.

Regarding the decision between COPD and control, the variables area/volume of phase 3, dyspnea upon strong exertion, the ratio s3/s2, and current smoking were identified as relevant in the Random Forest approach. Regarding asthma vs control, the relevant variables were wheezing, volume of phase 2, dyspnea upon strong exertion and current smoking. When COPD was compared with asthma, the most relevant variables were s3/s2, current smoking and ex-smoker history. The diagnostic capability of the ensembles of trees was quantified by their receiver operating characteristics (ROC). When comparing asthma with control, COPD with control, and COPD with asthma, the respective areas under the curve (AUC) were 0.623, 0.875, and 0.880 in the Random Forest approach, demonstrating that it was COPD, which was recognized best.

Noteworthy enough, the variables identified as relevant in the Random Forest approach were also those relevant in the single decision trees. These trees had a maximum depth of 3 and clearly showed those combinations of values that were highly indicative of one of the diagnoses but also those combinations that were not informative as they did not correspond to marked changes compared to the a priori distribution of diagnoses. The overall diagnostic accuracy was neither impaired nor improved compared to the Random Forest approach. Moreover, the relationships found in the quantitative network diagram were consistent with the role of predictors in both the Random Forest and single tree approach.

These results indicate that capnovolumetry can not only be used for the diagnosis of airway obstruction, as shown in the first study, but also for the diagnosis of asthma and COPD, if it is combined with basic anamnestic questions. This combination can be depicted in an intuitive manner in form of decision trees. The algorithms proposed in the study might be helpful in those cases in which no reliable information was obtained by spirometry, while valid measurements of capnovolumetry could be achieved owing to its low demands regarding cooperation.

Author's contribution

Similar to the second study, the present analysis was also based on the measurements in 1400 patients, which the author had performed together with another medical doctoral student. In an analogous fashion, the responsibility for the establishment, completion and quality control of the data base was given for the present study. The author performed the statistical analyses using the SPSS and R statistical packages and was involved in all stages from the design of the study, interpretation of data, manuscript preparation and improvement, its submission and reviewing process, to the proofreading. Based on this, the position as leading author is appropriate.

5. Discussion

5.1. Synopsis of the three studies

The three studies that are part of the present doctoral dissertation had their focus on the diagnostic accuracy and clinical usefulness of capnovolumetry in the diagnosis of obstructive airway diseases. As capnovolumetry is not yet commonly used for clinical purposes, these questions have to be addressed as prerequisites of a potential implementation in clinical practice. This implementation seems worth to be considered, since capnovolumetry may be useful to circumvent some of the persistent difficulties arising from insufficient patients' cooperation in lung function measurements. In the following discussion, the main aspects are only recapitulated, as detailed considerations have already been integrated in the results section (see 4.).

The first study was designed as a confirmatory study to validate the results of a previous pilot study performed by Ponto et al. [5], who had proposed a specific value of the ratio s3/s2 (ratio between the slopes of phases 3 and 2) as cut-off criterion regarding the presence of airway obstruction. In the present study, the sensitivity of this ratio regarding airway obstruction was considerably lower and consequently their results could not be confirmed. This difference was probably due to the evaluation of different study populations and the fact that the present study was much larger and statistically reliable than the previous study. The results of Ponto et al. [5] have been obtained in selected patients, which favours an overestimation of diagnostic accuracy [77]. The unselected population investigated in our study, although from a specialists' practice, might be more representative of patients typically found in ambulatory care and thus provides a more realistic estimation of diagnostic accuracy. A further major reason for the decrease in sensitivity could have been that the commercially available device used by us utilized a modified computational algorithm compared to that used previously [5]. One cannot exclude that the diagnostic accuracy of the capnovolumetric device utilized in our study was affected by the modified algorithm. Therefore, it would be helpful to compare different ultrasound devices in diagnostic studies and to arrive at a consensus on optimal algorithms.

The present study also showed that sensitivity could be raised when using another cut-off value derived from the data by ROC analysis. Moreover, it revealed that it is of advantage not to use a single parameter but to employ a set of parameters from capnovolumetry in order to improve the detection of airway obstruction. The improvement was remarkable compared to the single parameter s3/s2, demonstrating the potential of capnovolumetry when describing the capnovolumetric curve by a set of parameters adapted to its specific features. This observation

was the basis of the further evaluation of the method in the two subsequent studies. Given the set of capnovolumetric parameters identified as statistically relevant, the first question was which physiological and clinical meaning these parameters had. This naturally led to the question in which way the capnovolumetric parameters were related to those of conventional lung function. As capnovolumetric parameters obviously depend on bronchial and alveolar volumes, this analysis should include spirometry and bodyplethysmography.

The second study addressed this problem and demonstrated a physiologically plausible mapping between four capnovolumetric and four conventional lung function parameters. This was achieved by a novel use of a sophisticated statistical technique, path analysis. Provided that the validity for the detection of airway obstruction as well as the physiological and clinical interpretation of parameters were guaranteed, the third question was, how capnovolumetry can be used for the diagnosis of asthma and COPD. When addressing this question, it would be reasonable to maintain the focus on practical usability and to answer it in a way that can be easily implemented into clinical practice.

The third study achieved this by the construction of decision trees on an empirical basis, either as random ensembles of trees that are associated with maximal statistical reliability (Random Forest), or as single trees that can be immediately used without the need for special software. The basis on which the trees were constructed, were four capnovolumetric parameters and seven simple anamnestic questions. The trees demonstrated how anamnestic information and capnovolumetric data could be interwoven in order to achieve maximally reliable diagnostic decisions from a small set of parameters and questions. The trees allowed to identify those patients in whom the achievement for diagnosis of either asthma or COPD was high, and those patients in whom the given set of parameters was insufficient to support one of the diagnosis; these patients would need additional investigation, for example by a specialist. Both aspects are relevant for clinical practice.

Taken together, the present work underlined the prospects of capnovolumetry as a lung function method with specific advantages and capabilities. To reveal this, a large dataset was collected and evaluated using a variety of statistical standard and advanced techniques, always focusing on the practical usefulness of the results. The three papers might help to extend the range of tools and capabilities in the diagnosis of obstructive airway diseases in particular for non-pulmonary specialists.

5.2. Limitations of the present work

The present study had the advantage of being performed prospectively and including a large number of participants. It was, however, a monocentric study in a pulmonary outpatient clinic. Its results cannot be necessarily extrapolated to other clinical settings, such as family medicine or general practitioners who might have patients with different pre-test probabilities. On the other hand, it is important to note that in Germany, outpatient clinics are organized as private practices of specialists in primary care, which can be visited by patients for diagnostic investigation and treatment without referral. Therefore, we think that we could determine the diagnostic accuracy with minor selection of patients under “real world” conditions. A further limitation is the fact that most patients were already treated with bronchodilators, thereby improving their lung function and probably reducing the diagnostic capability of capnovolumetry. This is again relevant for non-pulmonary specialists as among their patients the likelihood of a treatment prior to measurement may be different. It also cannot be excluded that technical differences between devices might have played a role. The differences mentioned might explain why the capnovolumetric target parameter showed a difference in cut-off values between this study and the previous pilot study [5]. Moreover, the present study used a specific capnovolumetric device and it is not clear to which extent the results apply to devices of other companies. This might be relevant for the definition of cut-off values in diagnostic algorithms, although it is unlikely that the relevance and rank order of capnovolumetric parameters is affected by this. These considerations and the fact that the previous study could not be confirmed, taken together with the promising results when extending the set of capnovolumetric parameters, underline the necessity of a further confirmatory study. This study ideally should use a device that is optimal as well as satisfying standards followed by different manufacturers. The limitations of the second and third study were based in the fact that these were secondary analyses of data already used in the first study. These findings also need to be confirmed in diagnostic studies. Irrespective of the limitations and further needs, the three studies of the present dissertation tried to utilize a large, comprehensive data set by different methodological approaches that explored the clinical and physiological potential of capnovolumetry as far as possible.

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7. Appendix

7.1. List of abbreviations

95%CI	95% confidence interval
AUC	area under the curve
AreaVol s3	ratio area to volume of capnovolumetric phase 3
CFI	comparative fit index
CO_2	carbon dioxide
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
CT	computer tomography
FEF_{25}	forced expiratory flow at 25% of vital capacity
FEF_{50}	forced expiratory flow at 50% of vital capacity
FeNO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
FRC	functional residual capacity
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICS	inhaled corticosteroid
LLN	lower limit of normal
Raw	airway resistance
RMSEA	root mean square error of approximation
ROC	receiver operating characteristic
RV	residual volume
s2	slope of capnovolumetric phase 2
s3	slope of capnovolumetric phase 3
sRaw	specific airway resistance
TLC	total lung capacity
volume s2	volume of capnovolumetric phase 2

7.2. List of publications

Kellerer C, Jankrift N, Jörres RA, Klütsch K, Wagenpfeil S, Linde K, et al. Diagnostic accuracy of capnovolumetry for the identification of airway obstruction–results of a diagnostic study in ambulatory care. Respiratory Research. 2019;20(1):92.

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7.4. Reprints of conducted studies

This section contains reprints of the three conducted studies that are part of this dissertation. Study 1 and 3 were published in open access journals, study 2 in a journal without open access. Therefore, the permission to reproduce the studies in this dissertation is adapted to these different situations.

Study 1 (*Kellerer C, Jankrift N, Jörres RA, Klütsch K, Wagenpfeil S, Linde K, et al. Diagnostic accuracy of capnovolumetry for the identification of airway obstruction–results of a diagnostic study in ambulatory care. Respiratory Research. 2019;20(1):92*) and study 3 *(Kellerer C, Klütsch K, Husemann K, Sorichter S, Jörres R, Schneider A. Capnovolumetry in combination with clinical history for the diagnosis of asthma and COPD. NPJ primary care respiratory medicine. 2020;30(1):1-9)* have been published under the Open Access Creative Commons Attribution License (CC-BY), which permits the use, distribution and reproduction of material from published articles, provided the original authors and sources are credited.

The permission to reprint study 2 *(Kellerer C, Schneider A, Klütsch K, Husemann K, Sorichter S, Jörres RA. Correspondence between Capnovolumetric and Conventional Lung Function Parameters in the Diagnosis of Obstructive Airway Diseases. Respiration. 2020;99(5):389-97)* in this dissertation was obtained by the journal (see e-mail below).

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Diagnostic accuracy of capnovolumetry for the identification of airway obstruction – results of a diagnostic study in ambulatory care

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Abstract

Background: One of the known weaknesses of spirometry is its dependence on patients' cooperation, which can only partially be alleviated by educational efforts. Therefore, procedures less dependent on cooperation might be of value in clinical practice. We investigated the diagnostic accuracy of ultrasound-based capnovolumetry for the identification of airway obstruction.

Methods: Consecutive patients from a pulmonary outpatient clinic were included in the diagnostic study. As reference standard, the presence of airway obstruction was evaluated via spirometry and bodyplethysmography. Capnovolumetry was performed as index test with an ultrasound spirometer providing a surrogate measure of exhaled carbon dioxide. Receiver operating characteristic (ROC) analysis was performed using the ratio of slopes of expiratory phases 3 and 2 (s3/s2) ≥ 0.10 as primary capnovolumetric parameter for the recognition of airway obstruction. Logistic regression was performed as secondary analysis to identify further useful capnovolumetric parameters. The diagnostic potential of capnovolumetry to identify more severe degrees of airway obstruction was evaluated additionally.

Results: Of 1400 patients recruited, 1287 patients were included into the analysis. Airway obstruction was present in 29% of patients. The area under the ROC-curve (AUC) of s3/s2 was 0.678 (95% CI 0.645, 0.710); sensitivity of s3/s2 ≥ 0.10 was 47.7 (95% CI 42.7, 52.8)%, specificity 79.0 (95% CI 76.3, 81.6)%. When combining this parameter with three other parameters derived from regression analysis (ratio area/volume phase 3, slope phase 3, volume phase 2) , an AUC of 0.772 (95% CI 0.743, 0.801) was obtained. For severe airway obstruction (FEV_1 ≤ 50% predicted) sensitivity of s3/s2 ≥ 0.10 was 75.9 (95% CI 67.1, 83.0)%, specificity 75.8 (95% CI 73.3, 78.1)%; for very severe airway obstruction (FEV_1 ≤ 30% predicted) sensitivity was 86.7 (95% CI 70.3, 94.7)%, specificity 72.8 (95% CI 70.3, 75.2)%. Sensitivities increased and specificities decreased considerably when the combined capnovolumetric score was used as index test.

Conclusions: Capnovolumetry by way of an ultrasound spirometer had a statistically significant albeit moderate potential for the recognition of airway obstruction in a heterogeneous population of patients typically found in clinical practice. Diagnostic accuracy of the capnovolumetric device increased with the severity of airway obstruction.

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Trial registration: The study is registered under DRKS00013935 at German Clinical Trials Register (DRKS).

Keywords: Capnovolumetry, Airway obstruction, Asthma, COPD, Diagnostic study, Sensitivity, Specificity, ROC analysis, Area under the curve (AUC)

Background

Asthma [1] and chronic obstructive pulmonary disease (COPD) [2] are frequent respiratory diseases associated with airway obstruction. Commonly, the diagnosis of these disorders is determined on the basis of clinical history and spirometry. Detailed guidelines and instructions for spirometry are widely available [3] and programs for improving the quality of assessments, particularly by the training of nurses, have been implemented. Despite this, the validity of spirometric results is not rarely insufficient in clinical practice [4, 5], most often due to difficulties of the patients to follow the instructions of forced maneuvers. Clinical experience shows that there are always patients not capable of performing correct breathing maneuvers even after repeated instruction. Therefore, methods requiring a low degree of cooperation could be helpful for establishing a diagnosis in these patients.

There are several methods with low demands regarding cooperation, such as the interrupter technique [6], impulse oscillometry (IOS) [7], and capnometry based on the measurement of the concentration of exhaled carbon dioxide (CO_2) [8]. Capnometry has been studied for about 70 years [9] but is still not integrated into clinical routine. Part of this might be due to the fact that additional equipment in form of CO_2 sensors was required. Meanwhile, however, techniques have been developed to estimate CO_2 from ultrasound signals used for spirometry solely by software algorithms, without the need for a CO_2 sensor [10]. This offers the possibility to perform capnographic measurements via suitable spirometers during a phase of quiet breathing prior to spirometry.

Capnographic measurements can be described by various parameters, and a number of investigations have addressed the question, which of these parameters are suited to assess the presence of airway obstruction (e.g. [8, 11, 12]). One study [10] suggested a high diagnostic accuracy especially for the ratio of slopes of phases 3 and 2 that are obtained when the expiratory CO_2 concentration is plotted against volume (capnovolumetry, see Fig. 1), thereby recommending this parameter for further evaluation. The clinical setting most promising for capnovolumetry might be primary care, in which the most basic diagnostic question refers to the presence of airway obstruction. Most of the available studies, however, investigated small, highly selected samples of patients which could lead to biased estimation [13]. Using the ratio of slopes in capnovolumetry as primary parameter, we therefore aimed to quantify the diagnostic accuracy of capnovolumetry for the recognition of airway obstruction in a large sample of unselected patients under ambulatory care conditions. For this purpose, we studied patients who visited a pulmonary outpatient clinic and were well characterized regarding their clinical and functional status.

Methods

Study design and sample

This prospective diagnostic study was performed between February and April 2018 in a pulmonary outpatient clinic led by six pneumologists in Augsburg (Germany). In Germany, outpatient clinics are organized as private practices of specialists in primary care, which can be visited by patients for diagnostic investigation and treatment without referral. We included 1400 consecutive patients attending the clinic for their first diagnostic work-up or follow-up evaluations and giving oral and written informed consent. Exclusion criteria were age less than 18 years and/or inability to understand the German language, without further requirements. Patients' diagnoses were based on the evaluation of all functional and clinical information available, including chest x-rays, bronchial provocation challenges and bronchodilator tests, as documented in the patients' files. All diagnoses including those of comorbidities were taken from these files. The specialists were blinded to the results of the capnographic measurements.

Based on previous studies, we expected a prevalence of airway obstruction of 20% [14]. In a pilot study using the ratio of slopes of phases 3 and 2 (s3/s2), the sensitivity was 90% and the specificity 86% for the detection of airway obstruction at the cut-off $s3/s2 \geq 0.10$ [15]. A power calculation based on these assumptions revealed that at least 1280 patients were needed to establish a sensitivity and specificity of 80% each with a 95% confidence interval of ±5% [16]. We expected incomplete data in about 10% of patients and therefore aimed to include 1400 patients. The study was approved by the Ethical Committee of the Technical University of Munich (TUM). The study protocol was registered in the German Clinical Trials Register (DRKS00013935).

Test methods

Capnovolumetric index test

Capnovolumetric measurements were based on ultrasound estimation of the expiratory carbon dioxide (CO_2) concentration using the device SpiroScout (Software LFX 1.8.0,

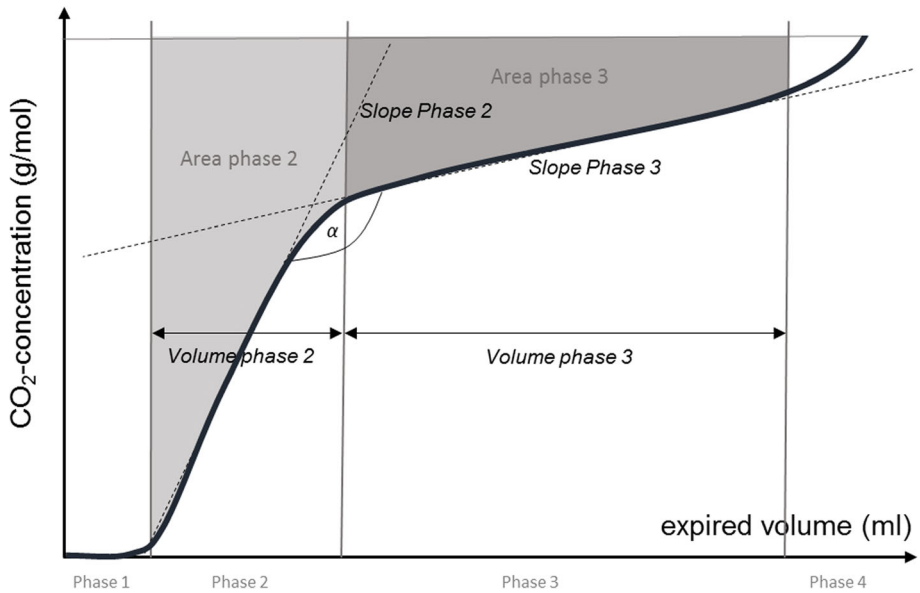

Fig. 1 Tracing of a volume-based capnogram during a single expiration. The capnogram is divided into four phases: phase 1, the CO_2-devoid volume of the dead space; phase 2, transition between airway and alveolar gas; phase 3, alveolar part; phase 4, final emptying of the lung (in tidal breathing normally absent or inconspicuous). (A) Parameters of capnographic measurement: s2 and s3 represent the slopes (concentration vs. volume) of the expiratory CO_2-curve in phase 2 and phase 3, respectively. The volume expired during phase 2 or phase 3 is termed 'volume phase 2' or 'volume phase 3'. In order to compute the parameters 'area phase 2' and 'area phase 3' a horizontal line at the end-tidal CO_2 concentration is drawn. The area above the CO_2 concentration curve bounded by the horizontal line in phase 2 and phase 3, respectively, represent the parameters 'area phase 2' and 'area phase 3'. These areas are complements of the areas under the curve. The angle alpha (α) is formed by the slopes of phases 2 and 3

Ganshorn, Niederlauer, Germany). The estimation was performed via molar mass measurement, as the ultrasound technology not only allows to detect relative changes in sound velocity that are proportional to flow rate but also the determination of absolute sound velocity which depends on air density and therefore CO_2 concentration. Patients performed quiet tidal breathing over at least 10 breathing cycles while sitting and wearing a noseclip. The verbal instruction given to them was only to avoid deep breaths or panting.

The device measures airflow velocity via the delay and acceleration of ultrasound signals and at the same time the absolute velocity of signals which is related to the composition of air. Taking into account temperature and humidity by adequate models, the concentration of CO_2 can be derived from the measured molar mass of the exhaled air. Compared to conventional CO_2 measurement no additional hardware is needed, since the assessment is achieved by software from available signals.

The parameters describing the shape of the expiratory CO_2 curve against expired volume are explained in Fig. 1. Each parameter provided by the device represents a mean value of all recorded breathing cycles. The indices most important for the present study were the slopes of expiratory phases 2 (s2) and 3 (s3), as well as their ratio s3/s2. In addition, the expired volumes of the two phases and corresponding areas under the concentration-volume curve could be defined.

Reference standard

Spirometric and bodyplethysmographic measurements were routinely performed within the assessment of patients, following established criteria for spirometry [17] and bodyplethysmography [18, 19]. Whether airway obstruction was present, was decided on the basis of both spirometric and bodyplethysmographic results. Obstruction was assumed if the z-score of the ratio (FEV_1/FVC) of forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) was less than − 1.645 [20] or, in case of a normal ratio, either specific airway resistance (sRaw) or airway resistance (Raw) were above 1.2 kPa*s or 0.3 kPa*s/l, respectively [18]. Each patient with airway obstruction was reviewed by an expert team (RAJ, AS) to cross-check the diagnostic decision making.

Data analysis

Baseline data is presented descriptively. Regarding lung function and capnovolumetric parameters, differences between the groups of patients with and without airway obstruction were assessed via the Mann-Whitney U test. Categorical variables were compared using the Chi-square statistics. For the evaluation of capnovolumetry as index

test, the ratio (s3/s2) of slopes of phases 3 and 2 of the expiratory CO_2 concentration curve versus volume was chosen. Using this parameter, receiver operating characteristic (ROC) curves for the recognition of airway obstruction were constructed and quantified via the area under the curve (AUC), its standard error of mean (SEM) and the corresponding 95% confidence interval (95% CI). Two-by-two contingency tables of capnovolumetric values vs. bodyplethysmographic diagnosis of airway obstruction were prepared using different levels of s3/s2 as cut-off. Sensitivities and specificities were calculated for the previously identified cut-off of 0.10 [15] and for the Youden-Index (cut-off at the highest sum of sensitivity and specificity) [21]. 95% confidence intervals were calculated using Wilson's method [22].

In secondary analyses we addressed two questions, firstly the diagnostic accuracy (AUC, sensitivity, specificity) for the detection of airway obstruction in groups of patients with different degree of obstruction as quantified by FEV_1 being ≤80%, ≤50% or ≤ 30%, and secondly the role of capnovolumetric parameters in addition to the ratio of slopes of phases 3 and 2. The relative importance of capnographic parameters provided by the device was determined by stepwise multiple logistic regression analysis in the total population. To reduce problems arising from collinearity, the maximum number of parameters kept for prediction was limited to four. For the purpose of this analysis, the slope s3/s2 was log-transformed after addition of 0.05; this was done to account for zero values and to achieve a distribution as close to normal as possible. Similarly, the slope s3 was log-transformed after addition of 0.03. The score provided by the logistic regression analysis was then used for ROC analysis in analogy to s3/s2, and this was done in the total population as well as the groups of patients with different degrees of airway obstruction according to FEV_1.

Capnovolumetric parameters are known to be affected by anthropometric charcteristics and breathing pattern, especially tidal volume [23]. We thus addressed their dependence on tidal volume, age, height and gender in a sensitivity analysis, using standard multiple linear regression methods. Using the predicted values from these analyses, we then checked whether normalization of capnographic parameters improved the results regarding the recognition of airway obstruction.

All analyses were performed using the software package SPSS (Version 25, IBM, Armonk, NY, USA), and the level of statistical significance was assumed at $p = 0.05$.

Results

Study population

A total of 1287 patients could be included into the analysis, of whom 371 (29%) showed signs of airway obstruction according to spirometry and/or bodyplethysmography (Fig. 2). The characteristics of the participants are shown in Table 1, demonstrating that the group of patients with airway obstruction was significantly different from the group without obstruction in all measures except body mass index (BMI). The parameters assessed in capnovolumetry are explained in Fig. 1. Regarding the major capnovolumetric parameters (Table 2), the primary target parameter s3/s2 showed significantly higher values in patients with airway obstruction compared to those without. Similarly, all other parameters determined by capnovolumetry, except the expired volume of phase 2, showed significant differences between patients with and without airway obstruction.

ROC analysis

According to our primary study question, ROC analysis indicated a statistically significant ability of s3/s2 to detect the presence of airway obstruction (Fig. 3), as reflected in an AUC ± SEM of 0.678 ± 0.017 (95% CI 0.645, 0.710). The maximum Youden index was 0.277 and achieved for a cut-off value of 0.08. At this cut-off, sensitivity was 59.0% (95% CI 54.0, 63.9) and specificity 68.7% (95% CI 65.6, 71.6). When using the pre-defined cut-off value of 0.10 [15], sensitivity was 47.7% (95% CI 42.7, 52.8) and specificity 79.0% (95% CI 76.3, 81.6). More severe degrees of airway obstruction could be detected by s3/s2 at the pre-defined cut-off value of 0.10 with a higher diagnostic accuracy (Table 3).

Identification of other relevant capnovolumetric parameters

Stepwise multiple logistic regression analysis performed in the total study population identified the four parameters ratio area/volume of phase 3, log(s3/s2), log(s3) and volume of phase 2 as dominant ($p < 0.001$ each) predictors, in that order (Table 4); thus the ratio s3/s2 chosen for the primary analysis was contained in this parameter set. The ROC-curve based on the derived probability scores is shown in Fig. 3, with an AUC ± SEM of 0.772 ± 0.015 (95% CI 0.743, 0.801). The Youden index was 0.415 using a cut-off value of 0.26 for the probability score, with a sensitivity of 69.8% (95% CI 65.1, 74.7) and a specificity of 71.7% (95% CI 67.7, 73.7). Compared to s3/s2, a significant improvement was achieved as indicated by the fact that the confidence intervals did not overlap. Additionally, the diagnostic accuracy of the combined capnovolumetric score at the determined cut-off value of 0.26 increased for the detection of severe degrees of airway obstruction (Table 3).

Sensitivity analyses

In the capnovolumetric measurements, tidal volumes and breathing frequencies covered a broad range. According to multiple linear regression analyses, s3/s2 and

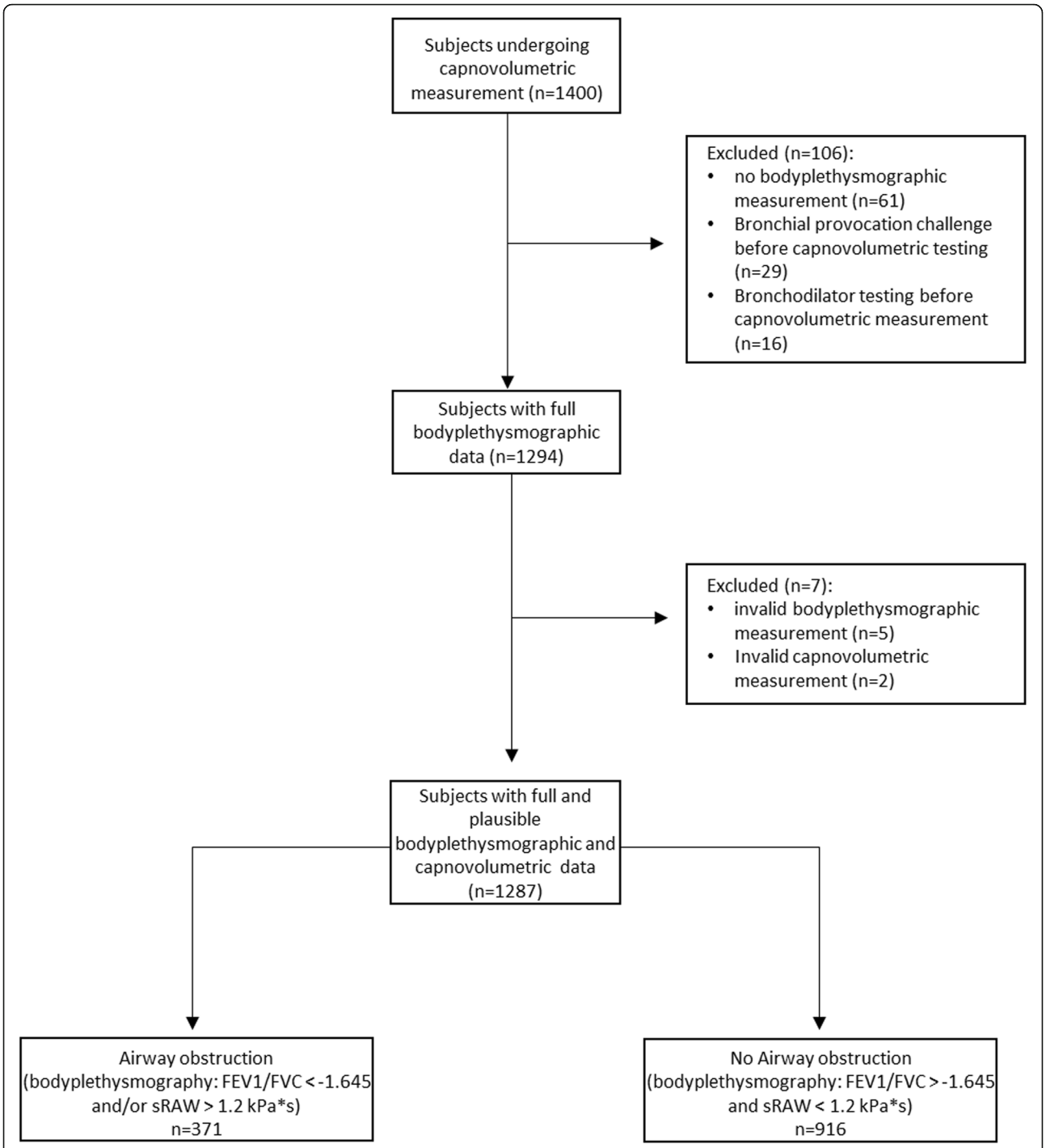

Fig. 2 Flow-chart of the selection process leading to the final population of 1287 patients. A total of consecutive 1400 patients underwent capnovolumetry. Patients who turned out to have had bronchial provocation challenges or bronchodilator testing prior to capnography due to organizational reasons were excluded from analysis ($n = 45$). Moreover, patients who did not undergo bodyplethysmographic and spirometric measurements ($n = 61$) were excluded. Five patients were excluded due to low quality of their bodyplethysmographic data, and two patients based on invalid capnovolumetric measurements

the other three capnovolumetric parameters identified as most informative for the recognition of airway obstruction (see above) significantly depended on tidal volume, height, age and gender ($p < 0.05$ each). This raised the question whether the recognition of obstruction could be improved when expressing the measured values of the four parameters as percent of the values predicted from the regression analyses. However, no improvement

Table 1 Baseline characteristics

Parameter		Presence of airway obstruction		
	All ($n = 1287$)	no ($n = 916$)	yes ($n = 371$)	Comparison between groups (p-value)
Gender (m/f)	589/698	385/531	204/167	< 0.001
BMI (kg/m^2)	26.9 (23.7; 31.1)	27.0 (23.9; 31.2)	26.7 (23.4; 35.3)	0.288
Age (y)	59.0 (47.0; 70.0)	56.0 (42.8; 77.0)	62.0 (53.0; 79.0)	< 0.001
FEV_1 z-Score	−0.92 (−1.98; − 0.05)	−0.47 (− 1.09; 0.24)	− 2.47 (− 3.16; − 1.65)	< 0.001
FEV_1/FVC	74.9 (66.2; 81.4)	78.6 (74.1; 83.8)	59.8 (48.9; 70.9)	< 0.001
FEV_1/FVC z-Score	− 0.63 (− 1.72; 0.25)	− 0.12 (− 0.74; 0.54)	−2.44 (− 3.3; − 1.77)	< 0.001
FVC z-Score	−0.58 (− 1.41; 0.20)	−0.37 (− 1.05; 0.38)	− 1.22 (− 2.02; − 0.33)	< 0.001
sRaw (kPa*s)	0.54 (0.27; 1.04)	0.39 (0.20; 0.62)	1.51 (0.85; 2.54)	< 0.001
Raw (kPa*s/l)	0.20 (0.10; 0.35)	0.14 (0.08; 0.23)	0.45 (0.28; 0.71)	< 0.001
FRC_{pleth} z-Score	−0.40 (− 1.16; 0.57)	− 0.66 (− 1.32; 0.08)	0.30 (− 0.56; 1.32)	< 0.001
Smoking status (current/ex/never)	253/485/536	154/303/447	99/182/89	< 0.001

The table shows absolute numbers in case of frequencies, median values and quartiles in case of continuous parameters. The groups were compared with each other using the Mann-Whitney-U-test, the categorical variables were compared using the Chi-square statistics. FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; sRaw, specific airway resistance (effective); FRC_{pleth}, functional residual capacity determined by bodyplethysmography. Z-Scores were computed using the respective prediction equations [20]. The groups were statistically significantly different from each other in all parameters except BMI. Among the 371 patients with airway obstruction, 108 (29%) had asthma, 223 (60%) COPD, 24 (7%) the diagnosis of other respiratory diseases (such as restrictive disorders, pneumonia or other infections, pleural diseases, lung tumor, bronchiectasis), while in 16 (4%) of these patients no respiratory disease was found. Among the 916 patients without airway obstruction, 325 (35%) had asthma verified by bronchial provocation, 243 (27%) suffered from other respiratory diseases (such as restrictive disorders, pneumonia or other infections, pleural diseases, lung tumor, bronchiectasis, chronic bronchitis), and 348 (38%) had no respiratory disease

could be achieved with this approach (AUC = 0.665 for s3/s2; AUC = 0.730 for the combination of the four capnovolumetric parameters).

Discussion

Based on the fact that ultrasound-based capnovolumetry requires only minimal cooperation from the patient, it appears to be a promising candidate for the determination of airway obstruction in clinical practice. To our knowledge, this is the first study evaluating its diagnostic accuracy for this purpose in unselected patients under ambulatory care conditions. When using the pre-defined cut-off s3/s2 ≥ 0.10, sensitivity was 47.7% and specificity 79.0%, with an area under the ROC-curve of 0.678, indicating a considerably lower sensitivity in the present study compared to previous data [10, 15]. The result could be improved by using s3/s2 ≥ 0.08 as a slightly different cut-off value, but markedly and significantly only by the combination with three other indices describing the complex relationship between CO_2 and volume. In patients with severe airway obstruction, its presence could be detected by s3/s2 and the combined capnovolumetric score with higher diagnostic accuracy. The s3/s2 ratio appears as an adequate measure at least of obstruction associated with ventilation

Table 2 Parameters of capnographic measurements

Parameter		Presence of airway obstruction		
	All ($n = 1287$)	No ($n = 916$)	yes ($n = 371$)	Comparison between groups (p-value)
Slope phase 2, s2 (g/mol*l)	2.89 (2.12; 3.81)	3.04 (2.23; 3.92)	2.59 (1.85; 3.43)	< 0.001
Slope phase 3, s3 (g/mol*l)	0.17 (0.10; 0.30)	0.16 (0.09; 0.27))	0.21 (0.12; 0.34)	0.001
log(s3)	−0.72 (−0.92; − 0.49)	−0.74 (− 0.96; − 0.54)	−0.64 (− 0.85; − 0.44)	< 0.001
Ratio s3/s2	0.06 (0.04; 0.10)	0.05 (0.03; 0.09)	0.09 (0.05; 0.14)	< 0.001
log(s3/s2)	−0.96 (−1.05; − 0.82)	− 1.00 (− 1.10; − 0.85)	− 0.85 (− 1.00; − 0.72)	< 0.001
alpha between s2 and s3 (°)	122.0 (116.0; 130.0)	120.5 (115.0; 127.0)	128.0 (119.0; 135.0)	< 0.001
Volume phase 2 (ml)	108.0 (91.0; 128.0)	109.0 (91.0; 129.0)	106.0 (89.0; 127.0)	0.134
Volume phase 3 (ml)	537.0 (392.0; 783.0)	522.5 (373.0; 751.8)	599.0 (432.0; 858.0)	0.002
Area/volume phase 2 (g/mol)	0.28 (0.24; 0.32)	0.27 (0.23; 0.31)	0.29 (0.25; 0.34)	< 0.001
Area/volume phase 3 (g/mol)	0.06 (0.05; 0.08)	0.05 (0.04; 0.07)	0.08 (0.06; 0.10)	< 0.001

The table shows median values and quartiles. The groups were compared with each other using the Mann-Whitney-U-test. For the explanation of parameters see Fig. 1. log(s3) is the logarithm (base 10) of the parameter s3, log(s3/s2) the logarithm (base 10) of the ratio s3/s2. Before taking the logarithm, the values of 0.03 and 0.05, respectively, were added to the parameter values in order to account for zero values and achieve a distribution being as close to normal as possible. The groups were statistically significantly different from each other in all parameters except volume phase 2

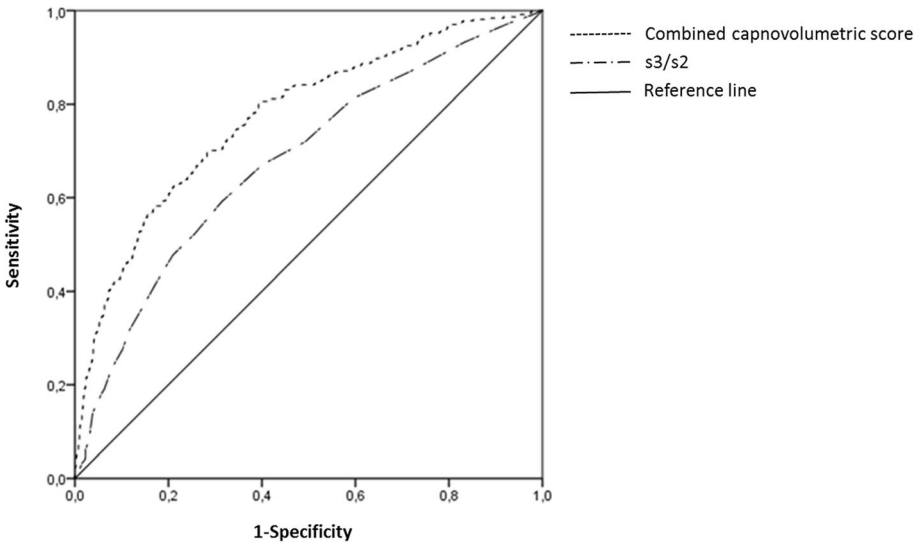

Fig. 3 ROC-curves for the recognition of airway obstruction. The AUC for the ratio of slopes s3 and s2 (s3/s2) was 0.678 (95% CI 0.645, 0.710). The AUC for the combined capnovolumetric score derived from the area-to-volume ratio of phase 3, the logarithm of the slopes of phase 3, the volume of phase 2, and the logarithm of the ratio of slopes of phases 3 and 2 was 0.772 (95% CI 0.743, 0.801)

inhomogeneity, as inhomogeneity should be associated with a steepening of the slope of phase 3 (unequal alveolar ventilation) and a flattening of the slope of phase 2 (mixing within bronchial compartment).

In the present study the sensitivity of s3/s2 regarding airway obstruction was considerably lower than reported previously [10, 15]. One reason might be found in differences between the study populations since the results by Ponto et al. [15] have been obtained in selected patients, which favours an overestimation of diagnostic accuracy [13]. The unselected population investigated in our study, although from a specialists' practice, might be more representative of patients typically found in ambulatory care and thus provides a more realistic estimation of diagnostic accuracy. Differences in the study population appear to be particularly relevant when including patients with controlled asthma and a type of airway obstruction less associated with ventilation inhomogeneity than typical for COPD. A further reason for the decrease in sensitivity could have been that the commercially available device used by us utilized a modified computational algorithm compared to that used previously [15]. This might be relevant, as the derivation of a CO_2 signal from the molar mass signal requires a number of non-trivial assumptions and computations, e.g. regarding the time course of temperature and humidity. Ultrasound spirometers have the benefit that no CO_2 sensor is required, and thus no additional investment and risk of sensor instability over time. In case of a practical implementation it would be helpful to compare different ultrasound devices in diagnostic studies and to arrive at a consensus on optimal algorithms. Our study probably provides a realistic lower limit of the diagnostic accuracy that can be achieved

Table 3 ROC Analyses of s3/s2 and the combined capnovolumetric score for different stages of airway obstruction

Airway obstruction (AO)	s3/s2				Combined capnovolumetric score			
	cut-off	sensitivity (%)	specificity (%)	AUC ± SEM (95% CI)	cut-off	sensitivity (%)	specificity (%)	AUC ± SEM (95% CI)
AO in spirometry / bodyplethysmography*	0.10	47.7 (42.7;52.8)	79.0 (76.3; 81.6)	0.678 ± 0.017 (0.645; 0.710)	0.26	69.8 (65.1; 74.7)	71.7 (67.7; 73.7)	0.772 ± 0.015 (0.743; 0.801)
$FEV_1 \leq 80$	0.10	46.2 (41.7; 50.8)	81.0 (78.2; 83.6)	0.699 ± 0.015 (0.669; 0.729)	0.26	64.8 (60.5; 69.3)	72.7 (69.0; 75.1)	0.743 ± 0.015 (0.713; 0.772)
$FEV_1 \leq 50$	0.10	75.9 (67.1; 83.0)	75.8 (73.3; 78.1)	0.851 ± 0.016 (0.820; 0.883)	0.26	88.9 (80.5; 92.8)	62.6 (60.6; 66.1)	0.854 ± 0.019 (0.818; 0.890)
$FEV_1 \leq 30$	0.10	86.7 (70.3; 94.7)	72.8 (70.3; 75.2)	0.887 ± 0.025 (0.838; 0.935)	0.26	93.3 (78.7; 98.2)	60.3 (57.6; 63.0)	0.860 ± 0.025 (0.810; 0.909)

The table shows the results of ROC analyses with s3/s2 and the combined capnovolumetric score for the recognition of different degrees of airway obstructions defined by restrictions in FEV_1. FEV_1, forced expiratory volume in one second; *AO* Airway obstruction, *AUC* area under the curve, *SEM* standard error mean, *95% CI* 95% confidence interval. (* z-Score $FEV_1/FVC < -1.645$ and / or sRAW > 1.2 kPa*s)

Table 4 Logistic regression analysis

Logistic regression analysis, dependent variable: airway obstruction ($n = 1287$)

Predictor	Regression coefficient	Standard error	95% Confidence interval	
			Lower limit	Upper limit
Area/Volume phase 3 (g/mol)	31.805	3.290	25.3566	38.2534
log (s3/s2)	6.665	0.843	5.01272	8.31728
log(s3)	−4.092	0.542	−5.15432	−3.02968
Volume phase 2 (mL)	−0.019	0.003	−0.02488	−0.01312
Constant	2.328	0.795	0.7698	3.8862

The table shows the results of logistic regression analysis for the identification of relevant capnovolumetric parameters regarding the presence of airway obstruction. Only the four most relevant parameters were accepted; further parameters did not improve the result in a relevant manner. For the explanation of parameters see Fig. 1. The ratio of slopes of phases 3 and 2 (s3/s2) and the slope of phase 3 were logarithmically transformed prior to analysis in order to approximate normal distributions, and values of 0.03 and 0.05, respectively, were added before taking the logarithm in order to account for zero values. The predicted probability (P) of airway obstruction for each individual patient can be calculated as usual from the equation:

$P = \frac{e^L}{1+e^L}$

in which L = constant + 31.805 * Area/Volume phase 3 + 6.665 * logs3s2 + (− 4.092) * logs3 + (− 0.019) * Volume phase 2. These predicted scores were used in the ROC analysis shown in Fig. 3

under the conditions of clinical routine with current technology. This accuracy is encouraging at least for patients with more severe airway obstruction, given the problems arising from insufficient spirometric maneuvers.

Among the indices characterizing the CO_2-volume curve, the ratio s3/s2 has the advantage to be easily interpretable in terms of ventilation inhomogeneity. If inhomogeneity is present, different regions of the lung show different CO_2 concentrations, thus the concentration of exhaled CO_2 in the alveolar phase 3 rises more steeply, i.e. the slope increases, when these regions are consecutively emptied. In parallel to the increase in the slope of phase 3, the slope of the bronchial phase 2 decreases, again as a result of inhomogeneous ventilation that smears out the concentration profile related to the airways; further details on capnovolumetry can be found in the literature [24]. Mismatches in the ratio of ventilation to perfusion may additionally contribute to changes in the slope particularly of phase 3. As a result, the ideal expiratory CO_2 profile which is characterized by a very steep increase in the bronchial phase and a very flat curve in the alveolar phase, is distorted in two opposite ways, thereby explaining the superiority of the ratio s3/s2 compared to other parameters, as reported previously [10].

Accuracy could be considerably increased by using information beyond the ratio s3/s2, via inclusion of three further indices describing the shape of the expiratory CO_2-curve (ratio area/volume of phase 3, slope of phase 3, volume of phase 2). This resulted in an area under the ROC-curve of 0.772, with sensitivity of 69.8% and specificity of 71.7%. The three additional parameters are also plausible from the pathophysiological point of view. As discussed above, the slope of phase 3 is closely related to the inhomogeneity of ventilation, which is linked to obstruction particularly in COPD [25, 26]. The same applied to the ratio of area to volume in phase 3, since, by definition, the area obtained by integrating the CO_2 concentration over volume represents a total amount of exhaled CO_2 due to inhomogeneity and thus the ratio to volume an average CO_2 concentration change due to inhomogeneity. This was increased in obstructive patients, reflecting the concomitant deterioration of gas exchange and ventilation.

Of specific interest seemed the volume of phase 2 which was included in the logistic regression model, even though, in univariate analysis, it did not show a significant difference between the total groups of patients with and without airway obstruction. According to the algorithm by which this parameter is computed, its values should change in parallel to those of the classical Fowler dead space [27], provided that the threshold deadspace does not significantly change; this was the case in our study. Olsson et al. found that patients with mild airway obstruction not showing inhomogeneity of ventilation (e.g. with stable asthma) can exhibit a reduction of their bronchial space and thus of Fowler dead space [28]. To understand this issue we checked our data by stratification according to diagnoses, which indeed revealed the volume of phase 2 to be reduced in asthma, thereby contributing to the recognition of airway obstruction. In the present analysis, however, we focused on the basic clinical question of airway obstruction, without extension to differential diagnoses which would require information on clinical history and thus render a decision algorithm more complicated.

Limitations and strength

The device used in the present study derived CO_2 concentrations via the molar mass of exhaled air taking into account humidity and temperature. We cannot exclude slight deviations from the true CO_2 concentration, as measurable, e.g., via a fast infrared sensor. At least in principle, a dependency of the temperature profile of exhaled air from airway obstruction [29] could affect the estimated values but this would not necessarily reduce their diagnostic usefulness. The parameter s3/s2 allows an intuitive interpretation reflecting the bend in the concentration-volume curve which separates phases 2 and 3. It was, however, inferior to the combined capnovolumetric score comprising the information from four

parameters, whereby the critical cut-off point of the combined score was derived by secondary analysis. Therefore, this finding needs to be confirmed by a further diagnostic study. Such a study might also comprise different computational algorithms beyond the algorithm available in the commercial device in order to identify the most suited one.

A strength of the study was that we included a large group of patients consecutively within a large private practice of pneumologists. By reason of free access to health care, also regarding specialists, we think that this enabled us to determine the diagnostic accuracy with minor selection of patients under ´real world´ conditions. However, not all patients were included into the analysis, due to interventions performed prior to capnovolumetry. As this occurred in only few patients, it renders this selection secondary. As a major strength we consider the requirement that lung function was assessed via both spirometry and bodyplethysmography at about the same time as capnographic measurements.

Conclusions

The results obtained in a large, unselected population from a pulmonary outpatient clinic indicate that capnovolumetry has a certain, but limited potential to indicate the presence of airway obstruction, at least if the previously recommended capnographic parameter s3/s2 and the currently available technology is used. However, by a combined score comprising four parameters diagnostic accuracy could be markedly improved. It is important to note that the diagnostic accuracy of the capnovolumetric device increased with the severity of airway obstruction. This diagnostic benefit should be considered in view of the low demands regarding the patients' cooperation. There might be room for improvement by optimization of the computational algorithms, and the comparison of different devices/algorithms within further diagnostic studies would be necessary to enhance the efficiency of capnovolumetry.

Abbreviations

95% CI: 95% confidence interval; AUC: Area under the curve; BMI: Body mass index; CO_2: Carbon dioxide; COPD: Chronic obstructive pulmonary disease; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; IOS: Impulse oscillometry; Raw: Airway resistance; ROC-curve: Receiver operating characteristic curve; s2: Slope of expiratory phase 2; s3: Slope of expiratory phase 3; s3/s2: Ratio of slopes of expiratory phases 3 and 2; SEM: Standard error of mean; sRaw: Specific airway resistance

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Availability of data and materials

The dataset analysed during the current study is available from the corresponding author on reasonable request.

Authors' contributions

C.K. and N.J. recruited the patients and were involved in the analysis of data. C.K. prepared the final manuscript and is responsible for the content. R.A.J. performed the data analysis and was involved in the preparation of the manuscript. K.K., K.L. and S.W. helped with analysis, reviewed the manuscript and commented on drafts of the final manuscript. A.S. had the project idea, developed the design of the study and was involved in data analysis and manuscript preparation. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethical Committee of the Technical University of Munich (TUM). The study protocol was registered in the German Clinical Trials Register (DRKS00013935).

Consent for publication

Not applicable.

Competing interests

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Publisher's Note

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Correspondence between Capnovolumetric and Conventional Lung Function Parameters in the Diagnosis of Obstructive Airway Diseases

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Keywords
Capnovolumetry · Asthma · Chronic obstructive pulmonary disease · Airway obstruction · Spirometry · Body plethysmography · Path analysis

Abstract
Background: Capnovolumetry is of interest as a method for the diagnosis of obstructive airway diseases, requiring little cooperation from the patient. ***Objective:*** To help in the interpretation of capnovolumetric parameters, we aimed to identify their correspondence to conventional lung function indices. ***Methods:*** We studied 978 patients from a diagnostic study with complete functional data and the clinical diagnosis of asthma, chronic obstructive pulmonary disease (COPD), or no respiratory disease. Using path analysis, four capnovolumetric parameters (slope of expiratory phase 3, ratio of slopes of phases 3 and 2, volume of phase 2, and the ratio area/volume of phase 3) previously identified as predictors of airway obstruction in terms of spirometry and body plethysmography, were analyzed regarding their relationship to each other and the diagnostic categories of asthma or COPD versus control, or obstruction versus no obstruction. We then identified four lung function parameters showing relationships as much as possible isomorphic to those between capnovolumetric parameters. ***Results:*** The four capnovolumetric parameters were related to COPD and obstruction via both direct and indirect influences, but only two of them to asthma. Regarding the correspondence to lung function parameters, the slope of expiratory phase 3 corresponded best to the ratio of residual volume to total lung capacity, the ratio of slopes of phases 3 and 2 to forced expiratory volume in 1 s, the volume of phase 2 to forced expired flow at 50% of vital capacity, and the ratio area/volume of phase 3 to forced vital capacity. ***Conclusions:*** Our results indicated an intricate relationship of capnovolumetric parameters to each other and to airway obstruction, asthma, or COPD. The correspondence to conventional lung function measures seemed to reflect the entities lung hyperinflation, overall ventilatory impairment, bronchoconstriction, and ventilated lung volume, in that order. These findings might be helpful for clinicians in the interpretation of capnovolumetry.

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Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are common respiratory diseases [1, 2] which in clinical practice are diagnosed by signs and symptom, as well as the results of lung function testing, in particular spirometry. Unfortunately, the quality of spirometric measurements can be insufficient, often due to difficulties arising from the patient's cooperation [3, 4]. Other potential problems, especially those arising from the use of different equipment, seem to be less important and can be tackled in an efficient way [5].

As one of the methods to assess lung function with low cooperation requirements, capnovolumetry has been proposed, whereby the concentration of carbon dioxide (CO_2) is plotted as a function of expired volume [6]. The resulting curve can be described by a set of parameters that can be evaluated for diagnostic purposes. In a previous study [7], we performed capnovolumetry in a large sample of unselected patients from a pulmonary outpatient clinic, aiming at the detection of airway obstruction as judged from spirometry and body plethysmography. The slope of expiratory phase 3 (s3), its ratio to the slope of phase 2 (s3/s2), the volume of phase 2 (Vol s2), and the ratio area/volume of phase 3 (AreaVol s3) were the four most relevant parameters; for their definition see Figure 1 in Kellerer et al. [7]. Compared to conventional lung function, however, the capnovolumetric parameters are not well known to most clinicians, which might hamper their interpretation. To better understand their meaning, a systematic analysis of their mutual relationships and especially a comparison with conventional lung function parameters could be helpful; this kind of mapping has not been undertaken until now.

Based on this, the first aim of the present analysis was to describe the relationship of capnovolumetric parameters to each other and to the diagnoses of airway obstruction, asthma, and COPD; for this purpose, the four parameters previously identified as most important [7] were used. The second aim was to find four parameters from spirometry and body plethysmography that showed relationships to each other and the diagnoses similar to those of the capnovolumetric measures.

Methods

Study Population

The analysis was based on the data of a prospective diagnostic study performed in a pulmonary outpatient clinic in Augsburg, Germany, from February 2018 to April 2018, that had the aim to assess the diagnostic accuracy of capnovolumetry for the detection of airway obstruction [7]. Patients were consecutively enrolled if the inclusion criteria of age ≥18 years and the ability to understand the German language were met. Out of 1,400 patients recruited [7], only those with complete data of capnographic, spirometric, and body plethysmographic measurements and without prior bronchial provocation challenge or bronchodilator testing were included. The present analysis was further restricted to patients with a clinical diagnosis of asthma and/or COPD or control subjects, the latter group comprising all subjects without any respiratory disease. The diagnoses were taken from the patients' files and based on the evaluation of all functional and clinical information available, including bronchial provocation challenges and bronchodilator tests, as documented in the files. These requirements resulted in a final set of 978 participants.

Table 1. Distribution of the study population over the three diagnostic groups

Functional diagnostic groups	Clinical diagnostic groups		
	control	asthma	COPD
Airway obstruction	15	104	223
No airway obstruction	303	297	36
Total	318	401	259

The table shows absolute numbers. For the definition of airway obstruction using the results of body plethysmography and spirometry, see Methods. Airway obstruction was judged from FEV_1/FVC being below or equal to the lower limit of normal in 7, 84, and 198 patients of the control, asthma, and COPD groups, respectively. In the other patients it was based on airway resistance and/or specific airway resistance [7]. COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Assessments

As described previously [7], spirometric and body plethysmographic measurements were performed following established criteria [8, 9]. The parameters used were forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), their ratio (FEV_1/FVC), forced expired flow at 50 and 25% of vital capacity (FEF_{50}, FEF_{25}), residual volume (RV), and the ratio of RV to total lung capacity (RV/TLC), as well as specific airway resistance (sRaw) and airway resistance (Raw), both as effective values. Capnovolumetric measurements were based on the ultrasound estimation of CO_2 concentration (SpiroScout, LFX 1.8.0; Ganshorn Medizin Electronic GmbH, Niederlauer, Germany). Patients performed quiet tidal breathing over at least 10 breathing cycles in a sitting position while wearing a nose clip. The only instruction given to them was the advice to avoid deep breaths or panting. Each parameter provided by the device represents a mean value of the last five recorded breathing cycles [7].

Information on the clinical diagnosis of asthma or COPD was taken from the patients' files, while the presence of airway obstruction was determined from spirometric and body plethysmographic results at the time of the visit. Obstruction was assumed if the *z*

Table 2. Baseline characteristics

Parameters	Clinical diagnostic groups			Comparison between the three groups
	control	asthma	COPD	*p* value
Sex, m/f	158/160	146/255	163/96	<0.001
Body mass index	27.0 (23.8–31.0)	26.9 (24.1–31.1)	26.6 (22.8–30.6)	0.221
Age, years	55 (41–67)	53 (39–63)	66 (57–75)	<0.001
FEV_1 *z* score	–0.19 (–0.90 to 0.49)	–0.82 (–1.62 to –0.22)	–2.56 (–3.36 to –1.79)	<0.001
FVC *z* score	–0.22 (–0.95 to 0.43)	–0.38 (–1.15 to 0.33)	–1.34 (–2.19 to –0.60)	<0.001
RV/TLC *z* score	–0.60 (–1.41 to 0.36)	0.13 (–0.81 to 0.88)	1.58 (0.35 to 2.74)	<0.001
FEF_{50} *z* score	–0.40 (–1.02 to 0.32)	–1.29 (–1.82 to –0.60)	–2.37 (–2.68 to –2.05)	<0.001
s3, g/mol/L	0.15 (0.08 to 0.26)	0.15 (0.09 to 0.27)	0.24 (0.16 to 0.38)	<0.001
Log(s3)	–0.74 (–0.96 to –0.54)	–0.74 (–0.92 to –0.52)	–0.57 (–0.72 to –0.39)	<0.001
s3/s2	0.05 (0.03 to 0.09)	0.05 (0.03 to 0.08)	0.11 (0.07 to 0.18)	<0.001
Log(s3/s2)	–1.00 (–1.10 to –0.85)	–1.00 (–1.10 to –0.89)	–0.80 (–0.92 to –0.64)	<0.001
Vol s2, mL	111.0 (92.8 to 131.3)	103.0 (86.0 to 123.0)	111.0 (95.0 to 131.0)	<0.001
AreaVol s3, g/mol	0.05 (0.04 to 0.07)	0.06 (0.04 to 0.07)	0.08 (0.06 to 0.10)	<0.001

The table shows absolute numbers in case of frequencies and median values, and quartiles in case of continuous parameters. The three diagnostic groups were compared with each other using the Kruskal-Wallis test and the categorical variables using χ^2 statistics. For the definition of diagnostic groups see Methods. For the explanation of parameters see our previous publication [7]. Before taking the logarithm, the values of 0.03 and 0.05, respectively, were added in order to account for zero values and to achieve a distribution as close to normal as possible. AreaVol s3, ratio area/volume of phase 3; COPD, chronic obstructive pulmonary disease; FEF_{50}, forced expired flow at 50% of vital capacity; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; Log, logarithm (base 10); RV, residual volume; s3, slope of expiratory phase 3; s3/s2, ratio of slopes of phases 3 and 2; TLC, total lung capacity; Vol s2, volume of phase 2.

score of the ratio of FEV_1 to FVC was <–1.645 [10] or, in case of normal FEV_1/FVC, sRaw or Raw were elevated according to established cutoff values [9].

Statistical Analysis

For the description of patient characteristics, median values and quartiles are shown. Comparisons between the three diagnostic groups (asthma, COPD, control) were performed by the Kruskal-Wallis test or by χ^2 statistics in case of categorical variables.

The four selected capnovolumetric parameters (s3/s2, s3, Vol s2, AreaVol s3) had been identified previously via logistic regression analysis for the detection of airway obstruction, as defined above, irrespective of diagnosis [7]. Their meaning can be seen in online supplementary Figure S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000507098). To understand their relationship to the clinical diagnoses of asthma and COPD, we performed analogous logistic regression analyses with these diagnoses as dependent variable. Moreover, the mutual relationship of capnovolumetric parameters was elucidated via multiple linear regression analyses. In all these computations, the slope s3/s2 was log-transformed after addition of 0.05, and the slope s3 was log-transformed after addition of 0.03 in order to account for zero values and to achieve a distribution as close to normal as possible, as done previously [7].

The results of these analyses were the starting point for a path analysis model. The capnovolumetric parameters were taken as measured values, since their dependence on anthropometric characteristics was weak and there are no generally accepted predicted values. The goodness of fit was described by a χ^2 value that quantifies the deviation of the data from the model, implying that *p* values >0.05 indicate a good fit. Moreover, the comparative fit index (CFI) and the root mean square error of approximation (RMSEA) were used, with required values of >0.95 and <0.05, respectively. We took these measures of fit as primary criteria, as in large data sets the χ^2 statistics can be oversensitive to deviations.

To identify the conventional lung function measures showing the best correspondence to capnovolumetric parameters, the following strategy was followed. For each capnovolumetric parameter we first defined sets of lung function parameters that could be related to them based on pathophysiological considerations and the results of regression analyses: slope s3 (RV/TLC, RV, FEV_1), s3/s2 (RV/TLC, RV, FEV_1), Vol s2 (FEF_{50}, FEF_{25}, FEV_1), and AreaVol s3 (RV/TLC, FVC, FEV_1). Choosing from these sets, we replaced the capnovolumetric parameters within the given path structure and identified those lung function measures that at the same time yielded a good fit and preserved the path structure as far as possible, i.e., required to add and discard as few links as possible. This approach was superior to multiple or logistic regression analyses, as it took into account the fact that the sets of parameters showed multiple relationships within each other, raising the problem of collinearity. The superiority was reflected by the fact that we found a statistically robust and consistent mapping, whereas all regression analyses were plagued with problems arising from collinearity. To account for the known dependence of lung function parameters on anthropometric characteristics, *z* scores were used

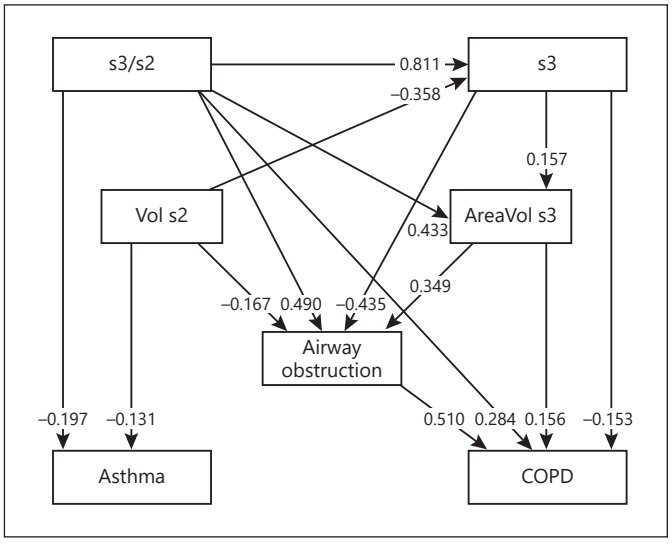

Fig. 1. Path analysis model of capnovolumetric parameters (continuous variables) and the binary variables asthma, COPD, and airway obstruction. For the explanation of parameters see our previous publication [7]. Arrows indicate directed relationships in terms of linear regression coefficients. Error terms that are required for each dependent variable for mathematical reasons were omitted for the sake of clarity. Moreover, a correlation coefficient between asthma and COPD that reflects the to a large extent mutually exclusive presence of these entities was omitted. Only coefficients that were statistically significant are shown. The numbers next to the arrows indicate the standardized regression coefficients of the respective arrows. The model was estimated using the generalized least squares method but was robust against using other estimation methods such as maximum likelihood. AreaVol s3, ratio area/volume of phase 3; COPD, chronic obstructive pulmonary disease; s3, slope of expiratory phase 3; s3/s2, ratio of slopes of phases 3 and 2; Vol s2, volume of phase 2.

based on the predicted values of the GLI [10] or ECCS [11] publications.

For path analysis, AMOS version 25 (IBM Corp., Armonk, NY, USA) and the generalized least squares estimation criterion were used. All other statistical analyses were performed with SPSS version 25 (IBM Corp.). Statistical significance was assumed at $p < 0.05$.

Results

Study Population

Regarding airway obstruction, the distribution of the study population over the three diagnostic groups is shown in Table 1. Patient characteristics, lung function, and capnovolumetric values are shown in Table 2, again stratified according to the three diagnostic groups. As indicated in the table, the results of the three groups were significantly different from each other in all measures except for body mass index.

Relationship between Capnographic Parameters and Their Relation to Diagnoses

The path analysis model for capnovolumetric parameters is shown in Figure 1, with standardized regression coefficients referring to standardized variables at each arrow; the unstandardized coefficients are given in online supplementary Table S1. The χ^2 statistics was 13.95 with six degrees of freedom ($p = 0.030$), the CFI 0.99, and the RMSEA 0.037, indicating an acceptable fit. Most capnovolumetric parameters were either directly or indirectly related to the diagnoses of obstruction and COPD. The clinical diagnosis of asthma was not linked to the functional diagnosis of obstruction, reflecting the fact that patients were well controlled. It was, however, related to Vol s2. The ratio of slopes s3/s2 was linked to both asthma and COPD. This model was parsimonious in the sense that no additional statistically significant arrows (regression coefficients) could be added and that there was no improvement in χ^2 statistics corresponding to a likelihood ratio test.

Relationship between Conventional Lung Function Parameters and Their Relation to Diagnoses

The correspondence of conventional lung function to capnovolumetric parameters that was optimal according to the criteria described above is illustrated in Figure 2, again with standardized regression coefficients; for unstandardized coefficients see online supplementary Table S2. The goodness of fit was similar to that of the capnovolumetric model, with a χ^2 statistics of 13.77 at six degrees of freedom ($p = 0.032$); the CFI was 0.99 and the RMSEA was 0.036, again indicating an acceptable fit. The relationships between the chosen parameters were identical to those of capnovolumetric parameters, except for FEF_{50} that replaced Vol s2. Only this replacement yielded a specific relationship to asthma even in well-controlled patients and achieved a good fit; such a fit was not obtained with FEF_{25} or FEV_1. Moreover, the results for $FEF_{25–75}$ were similar to those for FEF_{50}, but with a lower degree of fitting. For an optimal fit, additional associations of FEF_{50} with FEV_1 and FVC had to be introduced, corresponding to the known correlations within the flow volume curve. Conversely, there was no direct association between FEF_{50} and RV/TLC. Noteworthy enough, when alternatively introducing intrathoracic gas volume, sRaw, and Raw as measures replacing capnovolumetric param-

eters, all of them turned out to be inferior to the lung function parameters given above.

Sensitivity Analyses

Following the selection strategy described above, the path analysis model of Figure 2 was the only one achieving a good fit and maintaining the structure of the capnovolumetric model as far as possible. When choosing different lung function measures, or interchanging measures, or introducing additional relationships (arrows), or reversing relationships (arrows), it always turned out that the resulting structure showed an inferior fit. We further analyzed the robustness of capnovolumetric and lung function path analysis models by omitting either the diagnostic category of airway obstruction keeping those of asthma and COPD, or by omitting the two categories asthma and COPD while keeping airway obstruction. In all cases, the relationships between parameters were maintained, and the magnitudes of the regression coefficients were virtually unchanged. Moreover, we studied whether the relationships differed between patients with asthma and COPD by omitting one of the two groups of patients. This led to nonsignificance of the relationship between FEV_1 and asthma as well as between s3/s2 and asthma, i.e., a parallel change in the networks. In COPD, only the relationship between s3 and AreaVol s3 changed, while that between RV/TLC and FVC was maintained. When omitting the 36 patients with a diagnosis of COPD but without airway obstruction according to spirometry and body plethysmography (Table 1), the pattern of significant regression coefficients was also maintained. Taken together, these results indicated that the mapping of capnovolumetric onto conventional lung function parameters was statistically robust.

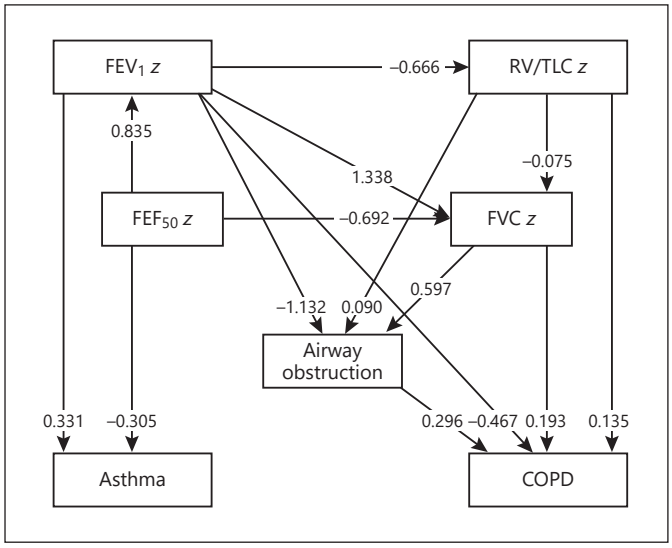

Fig. 2. Path analysis model of conventional lung function parameters (continuous variables) and the binary variables asthma, COPD, and airway obstruction. All values are expressed as *z* scores, either according to GLI [10] or ECCS [11]. Error terms of dependent variables and the correlation coefficient between asthma and COPD were omitted for the sake of clarity. Only coefficients that were statistically significant are shown. All further explanations are as in Figure 1. Please note that the changes regarding the replacement of associations (arrows) refer only to the parameter FEF_{50} (see Discussion) and leave the remaining structure of relationships intact. This underlines the analogy between the parameters shown in this figure and those shown in Figure 1. s3 versus RV/TLC might reflect lung hyperinflation, s3/s2 versus FEV_1 overall ventilatory impairment, Vol s2 versus FEF_{50} bronchial obstruction, and AreaVol s3 versus FVC the ventilated lung volume. AreaVol s3, ratio area/volume of phase 3; COPD, chronic obstructive pulmonary disease; FEF_{50}, forced expired flow at 50% of vital capacity; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; RV, residual volume; s3, slope of expiratory phase 3; s3/s2, ratio of slopes of phases 3 and 2; TLC, total lung capacity; Vol s2, volume of phase 2.

Discussion

Spirometry is the basic tool for the assessment of lung function and has been shown to be valuable in numerous studies. It depends, however, on cooperation and is therefore susceptible to weaknesses on the patient's side, e.g., due to language or coordination problems. These problems cannot be fully tackled by the skills of the personnel and their training [12]. Thus, lung function assessments requiring a low or different degree of patient cooperation could improve the diagnostic setup under the conditions of clinical practice. Among these is capnovolumetry, which could partially alleviate these difficulties, if capable of indicating airway disease with sufficient reliability. Recent findings support this assumption regarding obstructive disorders [7, 13]. The parameters of capnovolumetry are, however, not well known and appear rather abstract compared to conventional lung function, which might impede their clinical interpretation. A deeper understanding of their relationship to conventional parameters might improve this situation. We tried to achieve this goal by delineating the relationship of four major capnovolumetric to common, well-understood lung function indices, as well as to the diagnoses of airway obstruction, asthma, and COPD.

For this purpose, we used a mapping based on path analysis. This method is an extension of conventional re-

gression analysis and is suitable for combining statistical results and pathophysiological or clinical information [14–17]. It allows to treat variables as dependent and independent simultaneously and to describe direct and indirect effects within a hierarchy of relationships [18]. In using the method, we aimed at a parsimonious model, i.e., one that fitted well while incorporating only essential relationships. This was also motivated by the fact that a very complex model is not helpful for understanding. The correspondences that we identified by our approach are discussed in the following paragraphs.

Slope of Expiratory Phase 3

This slope has been shown to reflect the inhomogeneity of alveolar ventilation, with increased values indicative of increased inhomogeneity [19, 20]. Among the indices from body plethysmography and spirometry, it corresponded best to the ratio RV/TLC, a well-known measure of lung hyperinflation. Outside the conditions of artificial ventilation and in particular in COPD patients, hyperinflation is usually associated with inhomogeneous ventilation, therefore the correspondence appears reasonable. RV/TLC was special in the sense that it could not be replaced by RV or FEV_1 without loss of statistically significant associations and deterioration of the overall fit. This probably reflects the fact that even a perfectly performed spirometry is relatively insensitive regarding the detection of small airway dysfunction [21]. The flow rates at low lung volumes are considered as informative but in practice prone to errors due to insufficient cooperation; in our study they were not relevant. In contrast, the inhomogeneous ventilation as indicated by s3 is likely to be a measure of small airway dysfunction. In asthma, there are also alterations in small airway function [22], but these were probably much more difficult to detect in our study population, as patients were well controlled.

Ratio of Slopes of Phases 3 and 2

This parameter additionally takes into account alterations occurring in phase 2 of the capnogram, thereby involving the bronchial compartment. As the best analog of s3/s2 we identified FEV_1, not RV or RV/TLC. FEV_1 is an integrative measure depending on both the degree of airway obstruction and the volume supplied from the alveolar region. This volume is influenced by airway collapse, the degree of which is related to the inhomogeneity of ventilation. Following this line of argument, s3/s2 and FEV_1 can be considered as integrative measures of lung function, and the correspondence between these overall measures of impairment appears plausible.

Volume of Phase 2

This parameter corresponded best to FEF_{50} and not to FEF_{25} or FEV_1. In our previous analysis [7], we observed that patients with controlled asthma showed a slightly reduced Vol s2, possibly as a sign of residual bronchoconstriction [23]. FEF_{50}, or similarly $FEF_{25–75}$, is commonly considered a sensitive measure particularly of bronchial obstruction [24]. In accordance with this it showed a direct relationship to the clinical diagnosis of asthma, although the majority of patients was well controlled, as reflected by the fact that only about 25% had airway obstruction (Table 1). There were only indirect effects of FEF_{50} on the diagnoses of airway obstruction and COPD, mediated via the other three lung function parameters. This may be explained by the fact that in our study COPD patients, in whom s3 and s3/s2 played the major role, dominated the diagnosis of obstruction. Considering these arguments, the analogy between FEF_{50} and the capnographic Vol s2 appears reasonable as a measure of bronchial obstruction. It should be noted that Vol s2 and s2, which have been evaluated in other studies and have been shown to be sensitive to bronchoconstriction, are inversely related to each other, as confirmed in our data. In the present and the previous analysis [7], however, the volume turned out to be statistically superior to the slope. Both parameters depend on the end-tidal lung volume, which may vary during breathing, but the fact that we found a systematically lower Vol s2 in patients with asthma indicates that variability did not abolish the differences between groups. Whether Vol s2 is relevant for the diagnosis or the monitoring of asthma remains to be explored. For other methods capable of differentiating between central and peripheral airway characteristics, such as the forced oscillation technique, the clinical value in asthma has been recently demonstrated [25].

Ratio Area/Volume of Phase 3

This parameter is computed by dividing the area (integral of concentration over volume, i.e., amount of CO_2) above the curve by the volume of this phase, formally resulting in a measure of the average CO_2 concentration difference within phase 3. This appears difficult to interpret, but certainly should depend on ventilation inhomogeneity and the volume available for ventilation. Although the measure is not based on arterial CO_2 concentration, it appears to be closely related to alveolar dead space [26], which influences the lung volume accessible for gas exchange. Therefore, lung hyperinflation should play a role, and this was reflected by the fact that the parameter was linked to s3/s2 and s3. The analogous links in the lung function path

analysis structure were those with RV/TLC, FEV_1, and FEF_{50}. Interestingly, the only lung function measure that matched AreaVol s3 was FVC, whereas FEV_1 and RV/TLC resulted in a loss of significant relationships.

This seems reasonable insofar as FVC is a measure of ventilated lung volume and dependent on both hyperinflation and obstruction, which have an effect on dead space volumes. This was reflected in the intermediate positions which FVC and AreaVol s3 took within their respective networks (Fig. 1, 2) and supported by an overall negative correlation between FVC and AreaVol s3. None of these two parameters was informative for asthma, in accordance with the assumed normal status of alveolar ventilation in this disease. It might be that AreaVol s3 is also related to the total gas exchange capacity of the lung, in addition to alveolar dead space, and carries relevant information beyond lung mechanics. Noteworthy enough, according to a previous analysis involving mathematical modelling [27], AreaVol s3 is linked to alveolar cross-sectional area which is related to FVC. Our findings are consistent with this, although derived on a purely empirical basis. It might be of interest that there are multiple other uses of capnography beyond diagnostic applications, particularly in anesthesiology and bronchoscopic interventions [28], in which the end-tidal CO_2 concentration plays a major role. We did not evaluate this parameter, but it might well be related to AreaVol s3, which we used for diagnostic purposes.

Clinical Interpretation

The considerations given above can be summarized in terms of functional alterations predominantly reflected by these parameters. Table 3 lists the four capnovolumetric parameters, the corresponding lung function parameters, and the functional entities that appear to be primarily represented. Tentatively, these entities might be termed "hyperinflation/inhomogeneity," "overall ventilatory impairment," "bronchial obstruction," and "ventilated lung volume." The rather nonspecific term "overall ventilatory impairment" emphasizes the multiple causes of alterations of FEV_1, not only in patients with obstruction but also in patients with restrictive lung disorders, and preliminary data seem to support this interpretation. In extension of Table 3, the meaning of the capnovolumetric parameters is schematically shown in online supplementary Figure S1.

The roles of capnographic parameters in different respiratory diseases have already been described previously [6, 29, 30], and in our first study [7] we identified the four most important parameters regarding airway obstruction. In the present study, these parameters were used to provide a map of the associations between capnovolumetric indices themselves as well as to the additional diagnostic categories of asthma and COPD. The clinical diagnosis of COPD was dependent on the functional diagnosis of airway obstruction, which in turn was dependent on all four capnovolumetric parameters, but the three parameters involving phase 3 showed additional specific links to the diagnosis of COPD. The fact that some patients with COPD had no airway obstruction according to conventional lung function, or the inclusion or exclusion of the various diagnostic categories, did not affect the results. In contrast to COPD, the diagnosis of asthma in the well-controlled patients of our study was related only to parameters involving phase 2, possibly indicating effects of residual bronchial obstruction. The mapping between capnovolumetric and lung function parameters appeared physiologically meaningful and provided an approximate translation between both sets of indices, at least regarding obstructive airway diseases.

Table 3. Correspondence between capnovolumetric and conventional lung function measures

Capnovolumetry	Lung function	Pathophysiological entity
s3	RV/TLC	hyperinflation/inhomogeneity
s3/s2	FEV_1	overall ventilatory impairment
Vol s2	FEF_{50}	bronchial obstruction
AreaVol s3	FVC	ventilated lung volume

Correspondence between capnovolumetric and conventional lung function measures as depicted in Figures 1 and 2, and the hypothetical pathophysiological correlate reflected by these. AreaVol s3, ratio area/volume of phase 3; FEF_{50}, forced expired flow at 50% of vital capacity; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; RV, residual volume; s3, slope of expiratory phase 3; s3/s2, ratio of slopes of phases 3 and 2; TLC, total lung capacity; Vol s2, volume of phase 2.

Limitations

Although capnovolumetry does not require the coordination efforts of forced maneuvers, it still requires regular breathing at tidal volumes through the mouthpiece. There are single patients not being capable or willing to perform such breathing. Therefore, capnovolumetry can only be one of the supplementary techniques in lung function assessment. To avoid transient effects from taking the mouthpiece, we evaluated only the last five out of ten

breathing cycles. Another limitation of our study results from the fact that it was based on a secondary analysis of a diagnostic study performed in a specific population [7]. Therefore, our findings need to be validated and potentially refined in further studies. It would also be of interest to reveal whether the correspondence between capnovolumetric and lung function measures is maintained or modified within bronchodilator testings and bronchial provocation tests. Moreover, it might be of interest to identify parameters or combinations of parameters that could help in the phenotyping of COPD patients, especially the detection of lung emphysema. Possibly, this will require reference to gas exchange parameters, including the amount and peak values of exhaled CO_2.

Conclusion

The four capnovolumetric parameters identified as most important for the recognition of airway obstruction were linked to the clinical diagnoses of COPD or asthma within a robust network of relationships. This pattern corresponded to a very similar network of four common lung function indices obtained from spirometry and body plethysmography, whereby the pairs of parameters appeared to reflect the entities "lung hyperinflation," "overall ventilatory impairment," "bronchial obstruction," and "ventilated lung volume." The mapping identified by us might be helpful in the clinical interpretation of capnovolumetric parameters.

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Statement of Ethics

The study was approved by the Ethics Committee of the Technical University of Munich, and all patients gave their written informed consent. The study protocol was registered in the German Clinical Trials Register (DRKS00013935).

Disclosure Statement

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Author Contributions

C. Kellerer prepared the final manuscript, was involved in the statistical analysis and interpretation of data, and agreed to be accountable for all aspects of the work. A. Schneider developed the design of the study and was involved in data analysis and manuscript preparation. K. Klütsch, K. Husemann, and S. Sorichter reviewed the manuscript and commented on drafts of the final manuscript. R.A. Jörres provided the idea of the statistical analysis strategy, performed the data analysis, and participated in the preparation of the manuscript.

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Supplement

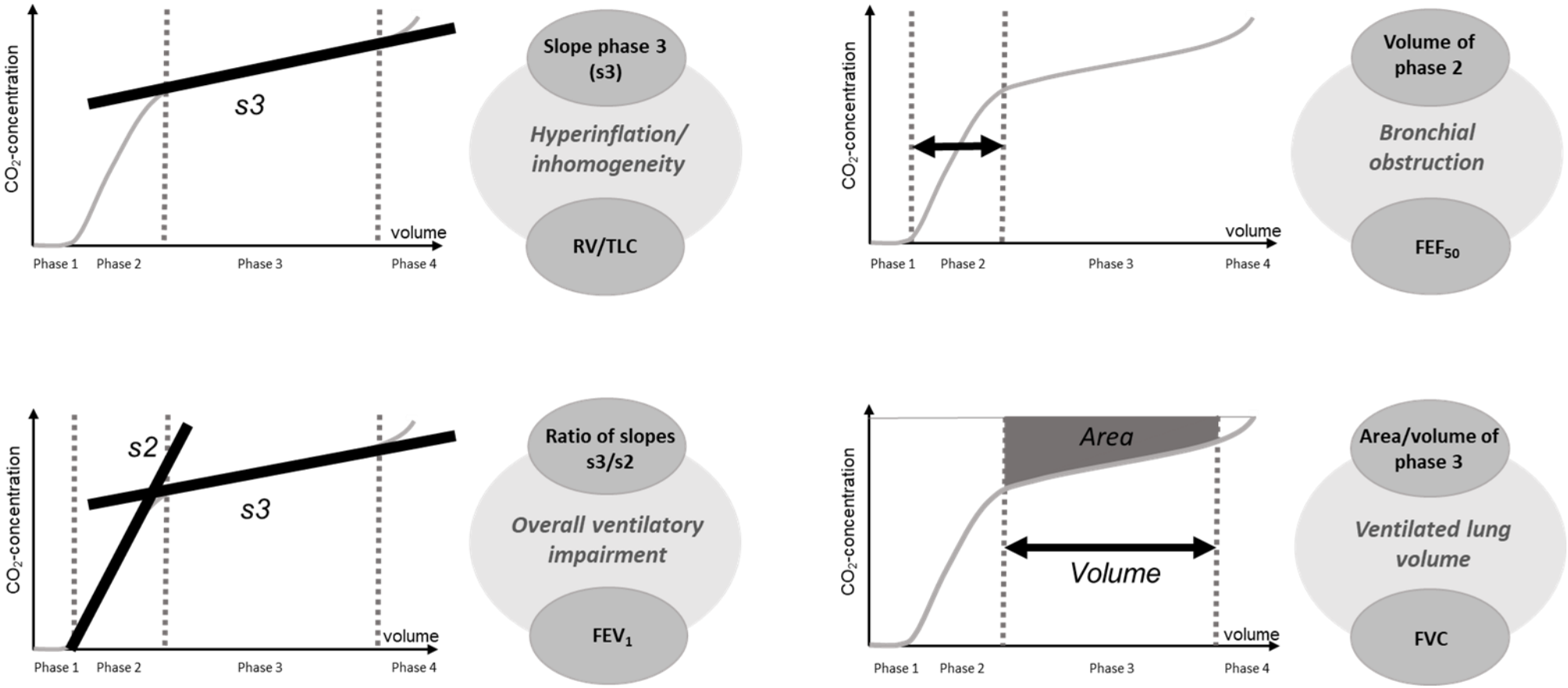

Figure S1. Illustration of the correspondences shown in table 3. Each of the four panels shows the correspondence on the right side and the meaning of the respective capnovolumetric parameters within the CO_2-volume-curves on the left side. On the right side, the upper ellipse shows the capnovolumetric parameter and the lower ellipse the conventional lung function parameter that was found to be best corresponding to the capnovolumetric parameter. The middle ellipse

shows the respective pathophysiological entity. Of course, these entities have additional indicators beyond those shown, for example derived from the forced oscillation technique, but the present analysis had the topic of capnovolumetry. FEV_1 = forced expiratory volume in 1 s, FVC = forced vital capacity, FEF_{50} = forced expiratory flow at 50% of the forced vital capacity, RV/TLC = ratio of residual volume to total lung capacity as determined by bodyplethysmography.

Tables

Table S1: Regression weights for the model given in figure 1.

Relationship			Estimate	S.E.	p-value
COPD	←	Airway obstruction	0.467	0.022	<0.001
Airway obstruction	←	Ratio s3/s2	1.207	0.144	<0.001
Asthma	←	Ratio s3/s2	-0.499	0.080	<0.001
COPD	←	Ratio s3/s2	0.642	0.093	<0.001
Slope s3	←	Ratio s3/s2	1.296	0.024	<0.001
AreaVol s3	←	Ratio s3/s2	0.061	0.006	<0.001
Airway obstruction	←	Slope s3	-0.671	0.095	<0.001
COPD	←	Slope s3	-0.216	0.055	<0.001
AreaVol s3	←	Slope s3	0.014	0.004	<0.001
Airway obstruction	←	Volume s2	-0.003	0.001	<0.001
Asthma	←	Volume s2	-0.002	0.001	<0.001
Slope s3	←	Volume s2	-0.004	0.000	<0.001
Airway obstruction	←	AreaVol s3	6.105	0.601	<0.001
COPD	←	AreaVol s3	2.505	0.441	<0.001

The table describes the unstandardized regression coefficients of the path analysis model comprising the capnovolumetric parameters (continuous variables) and the binary variables asthma, COPD and airway obstruction. The first column shows the dependent and independent variables, the next two the non-standardized estimate and its standard error (S.E.), and the last one the corresponding p value. The standardized regression coefficients corresponding to the non-standardized estimates are indicated in figure 1. Ratio s3/s2 = ratio between slopes of phases 3 and 2, Slope s3 = slope of expiratory phase 3, Volume s2 = volume of phase 2, AreaVol s3 = ratio between the area of phase 3 and the volume of phase 3.

Table S2: Regression weights for the model given in figure 2.

Relationship			Estimate	S.E.	p-value
COPD	←	Airway Obstruction	0.272	0.031	<0.001
Airway obstruction	←	FEV_1	-0.367	0.012	<0.001
COPD	←	FEV_1	-0.139	0.017	<0.001
Asthma	←	FEV_1	0.111	0.018	<0.001
RV/TLC	←	FEV_1	-0.784	0.028	<0.001
FVC	←	FEV_1	1.090	0.023	<0.001
Airway obstruction	←	FVC	0.238	0.014	<0.001
COPD	←	FVC	0.071	0.016	<0.001
Airway obstruction	←	RV/TLC	0.025	0.007	<0.001
COPD	←	RV/TLC	0.034	0.007	<0.001
FVC	←	RV/TLC	-0.052	0.013	<0.001
Asthma	←	FEF_{50}	-0.131	0.023	<0.001
FEV_1	←	FEF_{50}	1.067	0.023	<0.001
FVC	←	FEF_{50}	-0.720	0.027	<0.001

The table describes the unstandardized regression coefficients of the path analysis model of conventional lung function parameters (continuous variables) and the binary variables asthma, COPD and airway obstruction. The first column shows the dependent and independent variables, the next two the non-standardized estimate and its standard error (S.E.), and the last one the corresponding p value. The standardized regression coefficients corresponding to the non-standardized estimates are indicated in figure 2. FEV_1 = forced expiratory volume in 1 s, FVC = forced vital capacity, FEF_{50} = forced expiratory flow at 50% of the forced vital capacity, RV/TLC = ratio of residual volume to total lung capacity as determined by bodyplethysmography.

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Capnovolumetry in combination with clinical history for the diagnosis of asthma and COPD

C. Kellerer[1,2]✉, K. Klütsch[2], K. Husemann[3], S. Sorichter[4], R. A. Jörres[2] and A. Schneider[1]

Capnovolumetry performed during resting ventilation is an easily applicable diagnostic tool sensitive to airway obstruction. In the present analysis, we investigated in which way capnovolumetric parameters can be combined with basic anamnestic information to support the diagnosis of asthma and COPD. Among 1400 patients of a previous diagnostic study, we selected 1057 patients with a diagnosis of asthma ($n = 433$), COPD ($n = 260$), or without respiratory disease ($n = 364$). Besides performing capnovolumetry, patients answered questions on symptoms and smoking status. Logistic regression analysis, single decision trees (CHAID), and ensembles of trees (random forest) were used to identify diagnostic patterns of asthma and COPD. In the random forest approach, area/volume of phase 3, dyspnea upon strong exertion, s3/s2, and current smoking were identified as relevant parameters for COPD vs control. For asthma vs control, they were wheezing, volume of phase 2, current smoking, and dyspnea at strong exertion. For COPD vs asthma, s3/s2 was the primary criterion, followed by current smoking and smoking history. These parameters were also identified as relevant in single decision trees. Regarding the diagnosis of asthma vs control, COPD vs control, and COPD vs asthma, the area under the curve was 0.623, 0.875, and 0.880, respectively, in the random forest approach. Our results indicate that for the diagnosis of asthma and COPD capnovolumetry can be combined with basic anamnestic information in a simple, intuitive, and efficient manner. As capnovolumetry requires less cooperation from the patient than spirometry, this approach might be helpful for clinical practice.

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INTRODUCTION

Capnovolumetry has been proposed as a method to obtain information on the functional state of patients with obstructive airway diseases[1–4]. Capnovolumetric measurements are not time consuming and relatively easy to perform since the patient only needs to perform quiet tidal breathing over about 10 breathing cycles. Thus it is a technical method with low demands regarding cooperation. A further advantage of capnovolumetry is that the technique is already integrated in some of the commercially available spirometers without additional costs. The CO_2 concentration in the exhaled air can be estimated from ultrasound signals by software algorithms without the need for an additional CO_2 sensor, and ultrasound spirometers do not need to be calibrated. In contrast to spirometry, there is no need to give detailed instructions for forced breathing maneuvers by the technical personnel. Therefore, it is of special interest in conditions where spirometry is unreliable due to insufficient cooperation by the patients[5] or lack of experience of the personnel in guiding the maneuvers or even concerns regarding the accuracy of spirometers[6]. Previous studies have shown a moderate diagnostic accuracy of this method regarding airway obstruction[1] and an acceptability of spirograms for clinical use in only about 60% of patients in a primary care setting[6]. However, the establishment of a clinical diagnosis also includes clinical history, signs, and symptoms, which can be covered by a set of standard questions. Capnovolumetry might be combined with this information in the diagnostic set-up of obstructive airway diseases to increase diagnostic discrimination, similar to biomarkers that are effective in the diagnosis of specific conditions, including asthma[7–9]. There are several methods to achieve this integration, one of them being the construction of decision trees following objective statistical criteria. Such trees are well suited for clinical purposes[10] and have been used, e.g., for the recognition of malignant lesions in magnetic resonance mammography[11] or the identification of patients at risk from heart failure[12]. Decision trees also seem promising in the diagnosis of asthma and chronic obstructive pulmonary disease (COPD)[13]. Single decision trees computed by established techniques illustrate the structure of the decision process; however, as such trees are prone to overfitting, systematically constructed sets of independent trees (e.g., random forest) can be used to check the validity of the results.

Based on these arguments, we examined in which way questions regarding clinical history, signs, and symptoms could be best combined with capnovolumetric parameters in the diagnostic work-up of asthma and COPD. For this purpose, we used a large data set from a diagnostic study[1] in which we had addressed the ability of capnovolumetry for the detection of airway obstruction without reference to the underlying diagnosis.

RESULTS

Baseline characteristics

A total of 1400 consecutive patients underwent capnovolumetry. Patients who turned out to have had bronchial provocation challenges or bronchodilator testing prior to capnovolumetry due to organizational reasons were excluded ($n = 45$). Moreover, patients who did not undergo bodyplethysmographic and spirometric measurements ($n = 61$) were excluded. Five patients were excluded due to low quality of their bodyplethysmographic measurement data and two patients based on invalid

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Table 1. Baseline characteristics.

Parameter	Diagnostic groups			Comparison between groups
	Control	Asthma	COPD	*p* value
Gender (M/F)	172/192	155/278	163/97	<0.001
Age (years)	55 (41; 67)	53 (38; 63)	66 (57; 75)	<0.001
BMI (kg/m^2)	26.9 (23.9; 30.9)	26.9 (24.1; 31.1)	26.6 (22.8; 30.5)	0.239
FEV_1 *Z*-score	−0.13 (−0.88; 0.53)	−0.82 (−1.53; −0.07)	−2.56 (−3.35; −1.78)	<0.001
FEV_1/FVC *Z*-score	0.10 (−0.51; 0.76)	−0.68 (−1.36; 0.10)	−2.58 (−3.56; −1.67)	<0.001
FVC *Z*-score	−0.21 (−0.92; 0.45)	−0.38 (−1.14; 0.35)	−1.32 (−2.19; −0.60)	<0.001
Log_{10}(s3)	−0.72 (−0.96; −0.52)	−0.72 (−0.92; −0.52)	−0.57 (−0.72; −0.39)	<0.001
Log_{10}(s3/s2)	−1.00 (−1.10; −0.85)	−1.00 (−1.10; −0.89)	−0.80 (−0.92; −0.64)	<0.001
Area/volume phase 3 (g/mol)	0.05 (0.04; 0.07)	0.06 (0.04; 0.07)	0.08 (0.06; 0.10)	<0.001
Volume phase 2 (ml)	110.0 (92.0; 130.0)	102.0 (86.3; 121.8)	111.0 (95.0; 131.0)	<0.001
Current smoking	19.3% positive	11.6% positive	36.3% positive	<0.001
Ex-smoking	32.0% positive	34.8% positive	57.1% positive	<0.001
Wheezing in the past 12 months	40.5% positive	63.2% positive	56.3% positive	<0.001
Frequent cough	34.5% positive	43.1% positive	36.7% positive	0.040
Frequent phlegm	25.9% positive	31.5% positive	43.0% positive	<0.001
Dyspnea upon strong exertion	50.9% positive	67.9% positive	89.3% positive	<0.001
Dyspnea upon weak exertion	18.6% positive	20.6% positive	49.0% positive	<0.001

The table shows absolute numbers or percentages in case of frequencies and median values and quartiles in case of continuous parameters. The categorical variables were compared between the diagnostic groups using the chi-square statistics, while continuous parameters were compared using Kruskal–Wallis test. For the explanation of parameters, see ref. [1]. Log_{10}(s3/s2) is the logarithm of the ratio s3/s2, log_{10}(s3) the logarithm of slope of phase 3. Before taking the logarithm, the values of 0.05 and 0.03, respectively, were added to account for zero values and achieve a distribution being as close to normal as possible.

capnovolumetric measurements. For the present analysis, patients were selected who had a diagnosis of COPD or asthma (or potentially overlap) or did not show any respiratory disease (control subjects). Two hundred and thirty patients with the diagnosis of other respiratory diseases (such as restrictive disorders, pneumonia or other infections, pleural diseases, lung tumor, bronchiectasis) were excluded (see Supplementary Fig. S1). Therefore, 1057 patients were analyzed, 567 (53.6%) were female and mean age was 56 years. Four hundred and thirty-three (41.0%) patients had a diagnosis of asthma, 260 (24.6%) COPD, and 364 (34.4%) were control patients (Table 1). Based on the lung function criteria used in our previous analysis[1], 347 patients had airway obstruction. Of these, 108 (31%) had asthma, 223 (64%) had COPD, and 16 (5%) belonged to the control group. Thus 37 patients received a COPD diagnosis by pneumologists without actual airway obstruction.

Logistic regression analyses

The comparison of COPD vs controls revealed dyspnea upon strong exertion, current smoking, a history of previous smoking, phlegm, the ratio of slopes of phases 3 and 2 (s3/s2), the slope of phase 3 (s3), and the ratio of area to volume of phase 3 (area/volume phase 3) as significant predictors ($p < 0.05$ each). Regarding asthma vs controls, wheezing, dyspnea upon strong exertion, current smoking, and the volume of phase 2 were predictors ($p < 0.05$ each). Regarding COPD vs asthma, wheezing, dyspnea upon both strong or mild exertion, cough, current smoking, a history of previous smoking, the ratio s3/s2, the s3, and the area/volume phase 3 were predictors ($p < 0.05$ each). The results of stepwise logistic regression analyses in terms of statistically significant odds ratios (ORs) are summarized in Supplementary Table S1. Histograms of the ratio s3/s2 for COPD vs control and of volume of phase 2 for asthma vs control are shown in Fig. 1, illustrating the significant, though small differences between the respective groups.

Network analysis

When constructing the network diagram (Fig. 2), we used a predefined cut-off value of 0.10[1,4] for s3/s2, and for the volume of phase 2 a cut-off value identified as optimal by receiver operator curve (ROC) analysis in the detection of asthma. The ratio s3/s2 was strongly linked to COPD and the volume of phase 2, although much weaker, to asthma. As expected, breathlessness at strong exertion was related to COPD and wheezing to asthma. Cough was related to asthma, phlegm to COPD, and smoking to both, but with opposite signs. The group of control patients was implicit in this analysis, as it served as the reference for the computation of phi-coefficients. The numerical values of the phi-coefficients are depicted in Supplementary Table S2; the frequencies of positive answers to anamnestic questions are shown in Supplementary Table S3.

Random forest decision trees

The area under the curve (AUC) was 0.623 for the comparison of asthma vs control, corresponding to a sensitivity of 68.1% (95% confidence interval (CI) 63.5, 72.5%) and specificity of 50.3% (45.0, 55.5%). Wheezing, the volume of phase 2, dyspnea upon strong exertion, and current smoking were identified as the four most important variables. For COPD vs control, the AUC was 0.875, with sensitivity of 75.0 (69.3, 80.1%) and specificity of 83.0% (78.7, 86.7%). Area/volume of phase 3, s3/s2, dyspnea upon strong exertion, and current smoking were the four most important variables. For COPD vs asthma, the AUC was 0.880, with sensitivity and specificity of 71.2% (65.2, 76.6%) and 89.4% (86.1, 92.1%), respectively. Current smoking, s3/s2, area/volume of phase 3, and smoking history were the four most important variables.

The initial choices of the numbers of trees and variables within each tree (approximate square root of the total number of variables) were based on the default settings of the R procedure. In the next step, the parameters were tuned to establish the robustness of results. The prediction accuracy showed a plateau

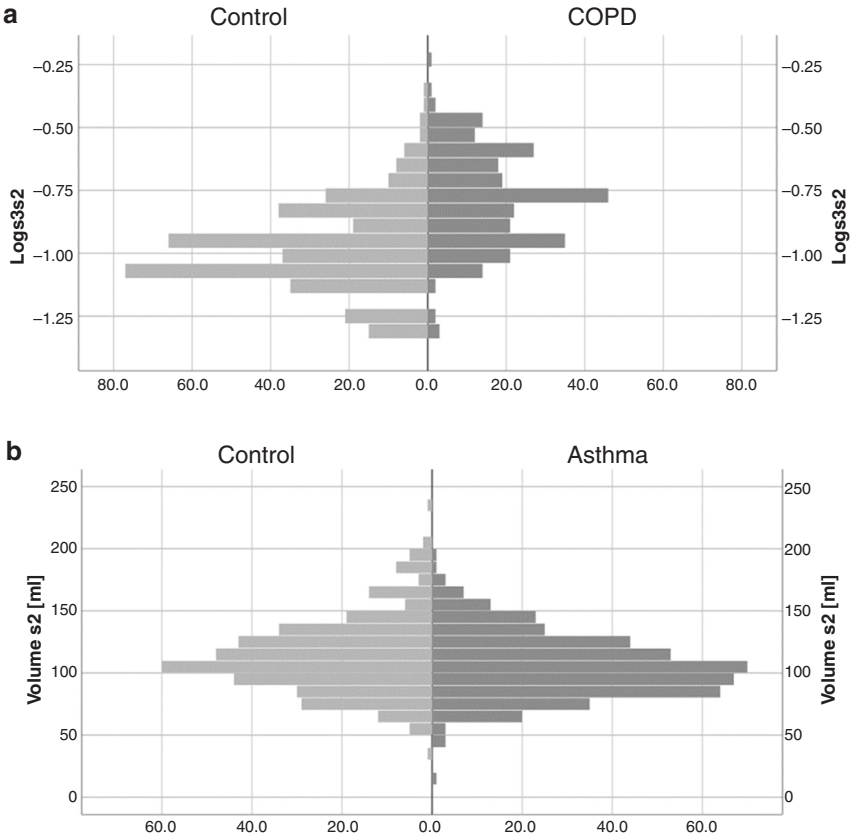

Fig. 1 Frequency distributions of capnovolumetric parameters. Frequency distributions of the ratio s3/s2 for COPD vs control, shown as logarithm to base 10 (**a**) and of the volume of phase 2 for asthma vs control (**b**). Before taking the logarithm of the ratio s3/s2, the value of 0.05 was added to account for zero values and achieve a distribution as closely to normal as possible.

for a number of trees of about ≥300, thus the number of trees chosen was sufficient. Moreover, the search for the optimal number of variables used for each tree node showed that the best accuracy was obtained for three variables. Based on this, the three ensembles of trees and the sets of variables selected as important can be considered as optimal.

Single classification and decision trees

Three single decision trees were constructed as an addition to the three ensembles, with the aim to illustrate the role of variables in single trees. To avoid small sample sizes and instability, the trees were limited to at most three generations of branches. All questions and all capnovolumetric parameters were offered to the CHAID search algorithm.

In the decision tree for COPD vs control (Fig. 3), the four variables identified as relevant were the same as those identified in the random forest as most important. The first criterion was area/volume phase 3. If this was low, dyspnea upon strong exertion became relevant. If this was absent, COPD became very unlikely. If it was present, the ratio s3/s2 became important, whereby patients with a smaller ratio had less likely COPD. If the area/volume phase 3 was high, again dyspnea upon strong exertion was relevant. If this was present, the prevalence of COPD markedly increased, while on the next level a further increase occurred if the patient was a current smoker. Under these conditions, the prevalence of COPD increased from a baseline value of 41.7% to a final value of 88.7%. Conversely, it was as low as 6% in patients showing a low area/volume phase 3 value in the absence of dyspnea upon strong exertion. Overall, the decision tree allowed a correct classification of 77.9% of patients, with sensitivity of 76.5% (95% CI 70.9%, 81.6%) and specificity of 78.8% (74.3, 82.9%).

For asthma vs control, the decision tree is shown in Fig. 4. Again, the four variables identified as important were those identified in the random forest as most important. Wheezing in the past 12 months turned out to be the dominant criterion. If answered positive, asthma was probable and the volume of phase 2 was selected as second criterion, leading to a further, though small, increase in the prevalence of asthma from a baseline value of 54.3% to a final value of 72.9%. If no wheezing was reported, the next important question was that of smoking status. If the patient was a smoker, asthma was much less likely. If the patient was a non-smoker, dyspnea at strong exertion was next informative, rendering the absence of asthma more likely in the absence of dyspnea. Overall, 62.6% of patients were correctly classified, with sensitivity of 82.6% (95% CI 78.8%, 86.1%) and specificity of 38.7% (33.7, 44.0%).

Regarding the comparison between asthma and COPD, the decision tree is shown in Fig. 5. The three variables involved in the decision tree were among the four most important variables of the random forest. The first important variable was the ratio s3/s2. If this was low, the prevalence of asthma increased. It further increased on the next two levels if the patient was a never smoker. Under these conditions, the prevalence of COPD dropped from 37.5 to 2.6%. Conversely, if the ratio s3/s2 was high, the prevalence of COPD increased to 82.6%, if the patient was a current smoker. If the patient did not smoke, being an ex-smoker was associated with a higher prevalence of COPD and never smoking with a high likelihood for asthma. The results demonstrated that beyond s3/s2 the smoking status was important for further differentiation. Overall, 79.5% of patients were correctly

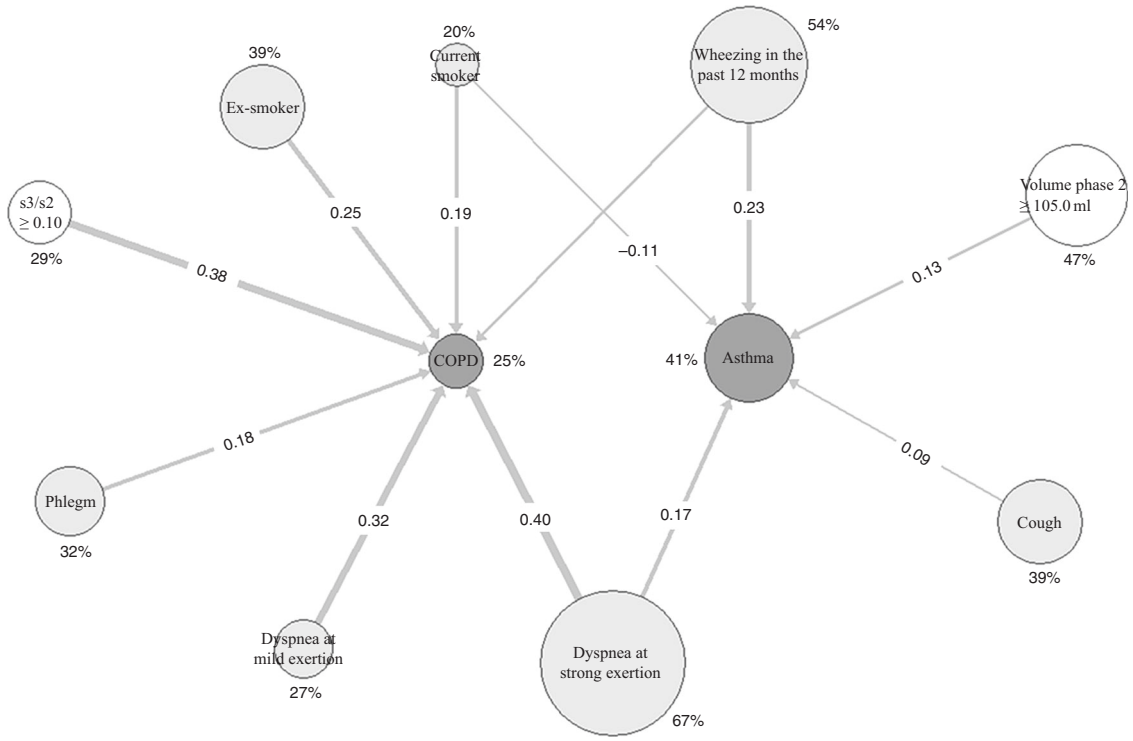

Fig. 2 Multiple relationships of capnovolumetric parameters and clinical signs and symptoms. Quantitative network diagram comprising two capnovolumetric parameters and patients' clinical history and symptoms. The area of the circles indicates the frequency of positive answers or positive conditions of capnovolumetric parameters compared to the cut-off values (see text). The thickness of the arrows is proportional to the respective phi-coefficients as measures of the strength of association, ranging in absolute values from 0.09 (thin line) to 0.40 (thick line) if significantly different from zero. The numerical values of phi-coefficients are given in Supplementary Table S2; the frequency of positive answers to anamnestic questions or positive capnovolumetric conditions in Supplementary Table S3. Both are indicated in the diagram.

classified, with sensitivity of 74.6% (95% CI 68.9%, 79.8%) and specificity of 82.4% (78.5, 85.9%).

Taken together, in the comparisons of COPD vs control, asthma vs control, and asthma vs COPD the random forest approach categorized 79.6, 60.0, and 82.5%, respectively, of subjects correctly, and the single decision tree 77.9, 62.6, and 79.5%, respectively.

DISCUSSION

The present analysis aimed at the integration of capnovolumetric parameters with symptoms and clinical history in the diagnosis of asthma and COPD. The parameters were those identified previously as relevant for the recognition of airway obstruction[1]. In a network analysis, we found the ratio s3/s2 to be related to COPD, and the volume of phase 2 to asthma, consistent with the results of logistic regression analyses and previous findings[1]. Dyspnea upon exertion, wheezing, smoking status, and phlegm were linked to COPD, while in asthma wheezing and the absence of smoking were more important, matching the expectations from clinical experience. We therefore felt justified to use our data for the development of decision trees, using the random forest approach as one of the machine learning methods, which has already been used in clinical studies[11–13]. The random forest approach was supplemented by the construction of single decision trees in order to illustrate their structure by specific examples. The results of both approaches were in very good agreement. While the single trees were more amenable to interpretation, the random forest was statistically slightly superior as judged from positive predictive values (PPVs). All trees were consistent with the network diagram and the results of our previous analysis[1], underlining the role of the capnovolumetric parameters area/volume phase 3, ratio of slopes of phases 3 and 2 (s3/s2), and volume of phase 2; the latter is similar to the Fowler deadspace[1,14] and inversely related to the slope of phase 2.

In the comparison of COPD with controls, the most important variable was area/volume phase 3. Given this, dyspnea upon strong exertion, the ratio s3/s2, and current smoking were relevant for the exclusion or inclusion of COPD, which seems plausible. To account for the fact that a different set of parameters was relevant, the comparison of asthma vs controls was performed separately. Noteworthy enough, the volume of phase 2 became important only when wheezing was confirmed, a low volume favoring the diagnosis of asthma, whereas in the absence of wheezing current smoking markedly decreased the likelihood of asthma. Accordingly, in the comparison of COPD with asthma current smoking, smoking history, the ratio s3/s2, and the area/volume phase 3 were most important. In the single tree, the finding that the ratio s3/s2 was the primary parameter reflected the fact that asthma patients had a low degree of airway obstruction and were similar to controls. All subsequent decisions regarding the comparison asthma vs COPD involved the current and previous smoking status, suggesting that the ratio s3/s2 comprised most of the information regarding the differential diagnosis between asthma and COPD. The cut-off values of s3/s2 within the trees were those identified as optimal for the diagnostic decisions regarding COPD, whereas the previously used[1] value of 0.10 was pre-determined[4] aiming at the detection of airway obstruction.

The three single trees were also valuable in demonstrating that some combinations of values were associated with marked changes in disease probability and others not. Regarding asthma vs control, for example, the absence of wheezing plus current smoking, or its presence plus low volume of phase 2, resulted in large changes. Conversely, the combination of non-smoking with

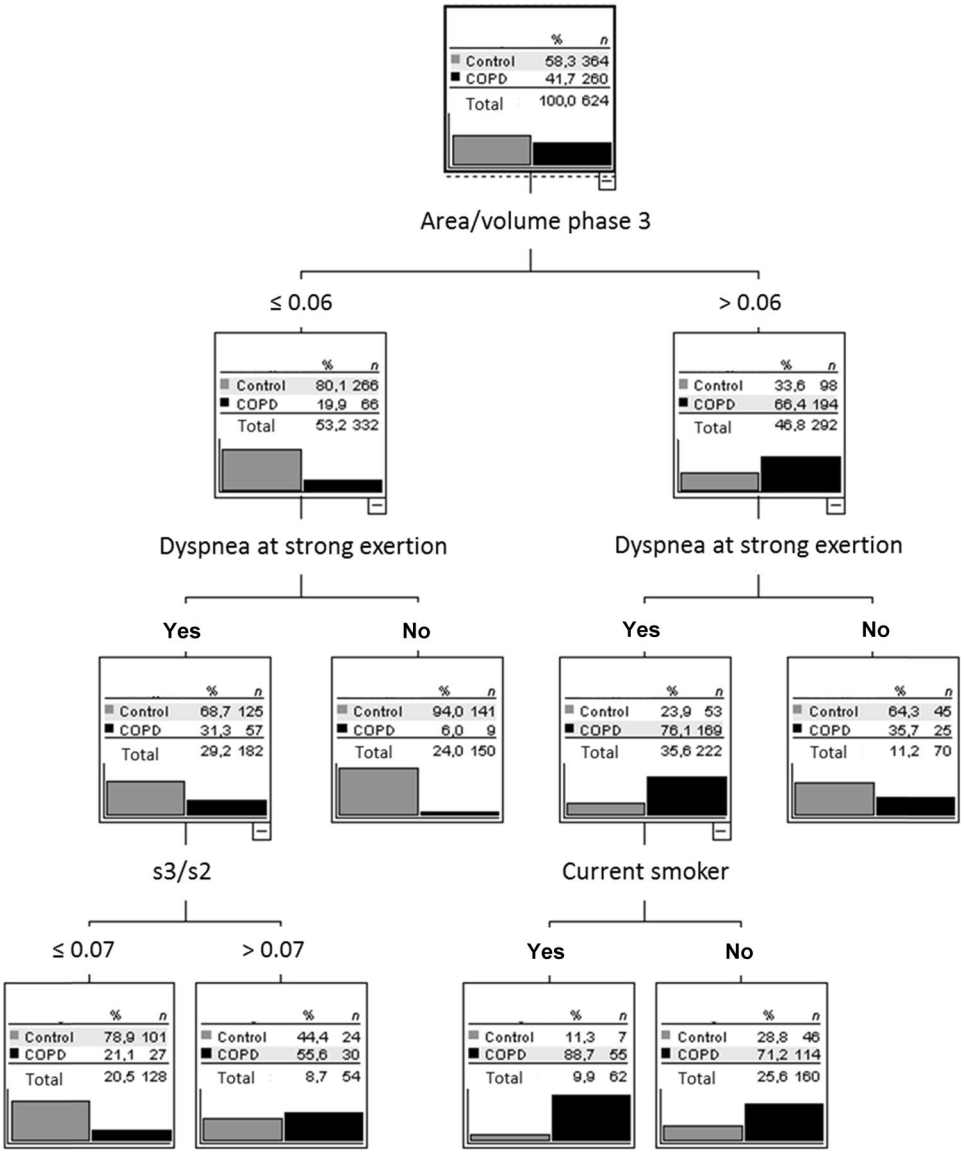

Fig. 3 Decision tree for the comparison of COPD with control. Only patients with COPD and the control group were included. Anamnestic questions (wheezing in the past 12 months, dyspnea at strong or mild exertion, cough, phlegm, current smoker, ex-smoker) and capnovolumetric parameters (s3/s2, volume phase 2, area/volume phase 3, slope of phase 3) were offered to the algorithm (CHAID), which selected the optimal criteria. The figure shows the average result of a tenfold cross-validation.

dyspnea upon strong exertion, or of wheezing with a high volume of phase 2, did not markedly change the probability for asthma.

Taken together, we found that all decision trees involved at least one capnovolumetric parameter, suggesting that capnovolumetry bears relevant information in addition to clinical signs and symptoms in the clinical diagnosis of asthma and COPD. Noteworthy enough, the maximal probability to suffer from COPD as illustrated in the decision tree of Fig. 3 was similar to the PPV of spirometry to detect COPD in a general practice population[5], while the maximal probability of asthma (Fig. 4) was equal to the PPV of bronchial provocation[15,16]. Although capnovolumetry is no substitute for spirometry, as the latter method allows to describe the severity of airway obstruction according to established criteria, our results underline its potential if no valid spirometry is available. Future studies may also combine capnovolumetry with other easily available diagnostic information to establish decision algorithms optimally combining efficiency with simplicity. According to our observation, that different sets of parameters were best for different suspected diagnoses, this probably requires separate decision algorithms, supporting the view that medical expert knowledge in terms of prior diagnostic suspicions remains indispensable.

Regarding the limitations of the study, it has to be mentioned that the present study was a secondary analysis based on previous results[1]. It included information not previously used and followed a different methodological path focusing on decision algorithms. Decision trees offer high flexibility, as different criteria can apply at each node, a complexity that in conventional regression analyses can be realized only via difficult-to-understand higher-order interaction terms. Trees suffer from overfitting, thus we used the well-known random forest ensemble approach to achieve robust and reliable results. This approach has, however, the disadvantage that the final algorithm cannot be easily depicted. To visualize the major results in a comprehensible manner, we went back to single

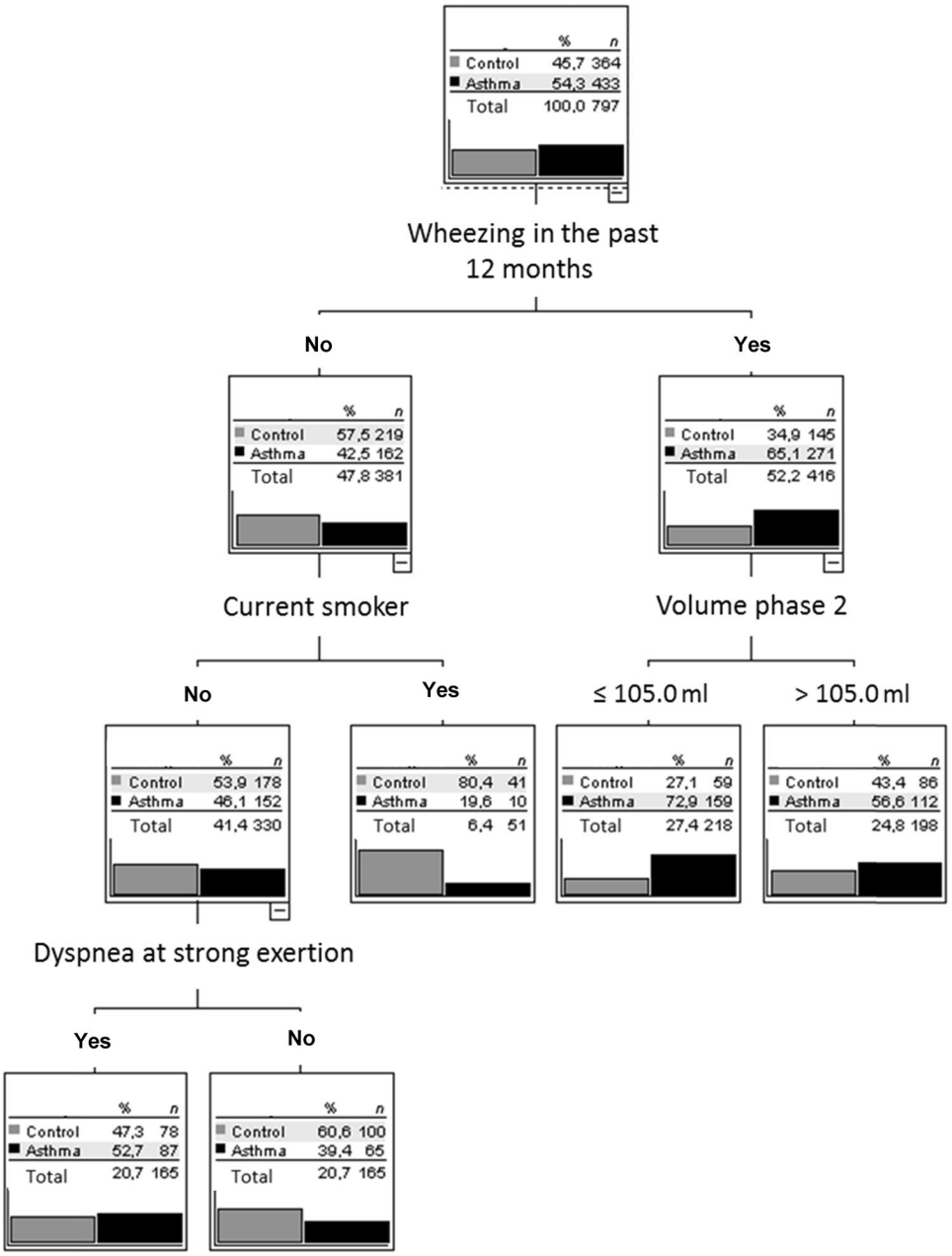

Fig. 4 Decision tree for the comparison of asthma with control. Only patients with asthma and the control group were included. Anamnestic questions (wheezing in the past 12 months, dyspnea at strong or mild exertion, cough, phlegm, current smoker, ex-smoker) and capnovolumetric parameters (s3/s2, volume phase 2, area/volume phase 3, slope of phase 3) were offered to the algorithm (CHAID), which selected the optimal criteria. The figure shows the average result of a tenfold cross-validation.

decision trees, which were, naturally, inferior to the ensemble approach. It also should be kept in mind that especially the patients with asthma who were included in the study had been previously diagnosed using the full repertoire of diagnostic methods including bronchodilator and bronchoprovocation testing. Therefore, the diagnosis could be considered as reliable, while of course a categorization solely based on capnovolumetry cannot be more than a diagnostic hint that must be evaluated by further procedures including the response to therapy.

For an implementation of the random forest approach into clinical practice, further studies in a variety of study populations would be needed. It also would be helpful to supplement our findings by inclusion of other biomarkers, such as exhaled nitric oxide, that can be easily obtained even in primary care conditions. Unfortunately, only few ultrasound capnovolumetric devices are currently commercially available. If the method should be used in clinical practice on a broader scale, technical comparisons will also be needed. The diagnostic decision-making process might be another limitation. Thirty-seven patients received the COPD diagnosis despite showing no signs of airway obstruction. The diagnoses relied on a comprehensive assessment of the patients' files and lung function data and had been established by a pneumologist previous to the study visit in nearly all cases. Some pneumologists might retain to the old classification COPD 0 (as a risk factor). Beyond that, in clinical practice it might occur that patients suffering from a mild form of COPD, with typical signs

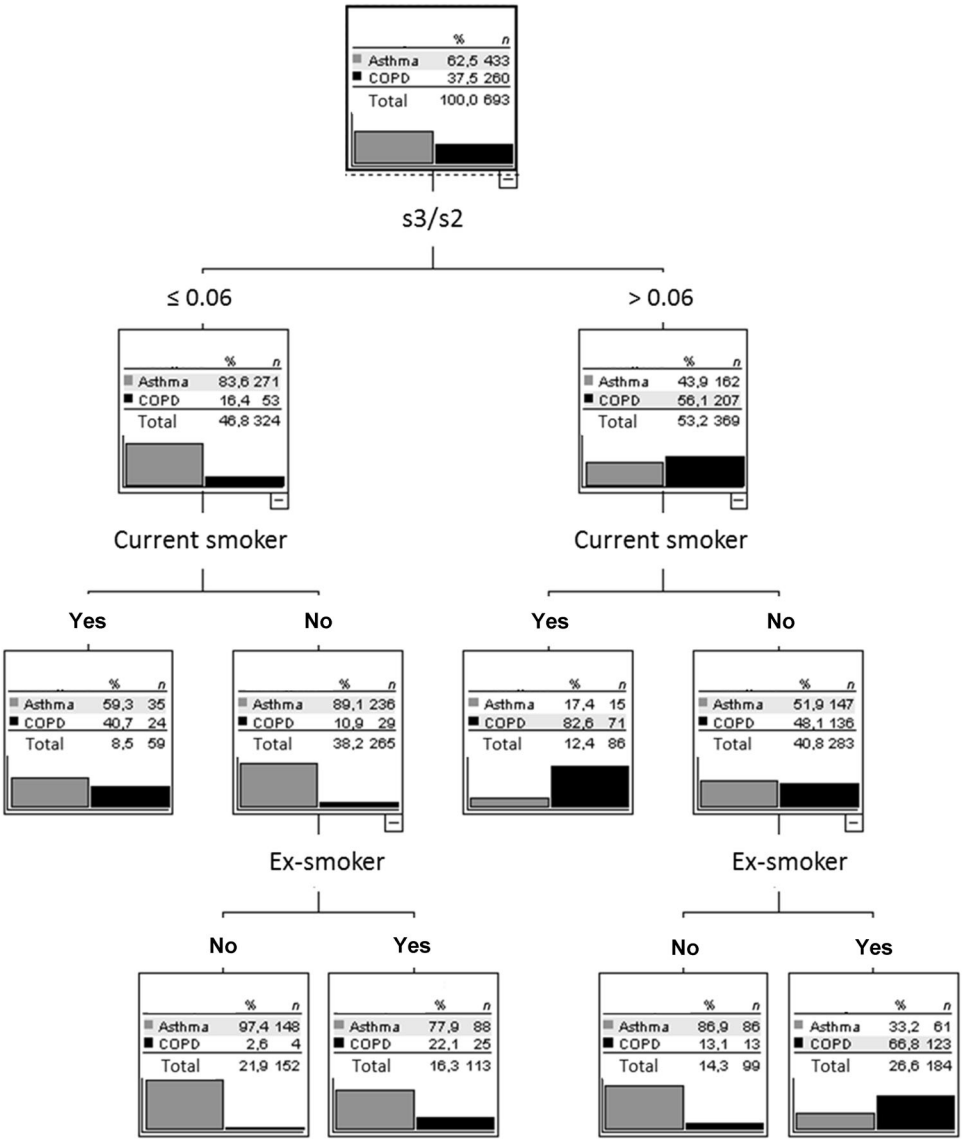

Fig. 5 Decision tree for the comparison of asthma with COPD. Only patients with asthma or COPD were included. Anamnestic questions (wheezing in the past 12 months, dyspnea at strong or mild exertion, cough, phlegm, current smoker, ex-smoker) and capnovolumetric parameters (s3/s2, volume phase 2, area/volume phase 3, slope of phase 3) were offered to the algorithm (CHAID), which selected the optimal criteria. The figure shows the average result of a tenfold cross-validation.

and symptoms, from time to time show no airway obstruction in lung function tests, using, for example, the established cut-off value of 0.7 for forced expiratory volume in 1 s/forced vital capacity; at one visit, the value may be 0.71, at another visit 0.69. Therefore, we performed a sensitivity analysis with classification of all patients without airway obstruction as "healthy controls" and found that 78.2% of patients were still correctly categorized (compared to 77.9%).

Taken together, capnovolumetry has low demands on patients' cooperation and may be applicable in those in whom spirometry fails. Using a large diagnostic data set, we analyzed in which way capnovolumetric parameters could be combined with basic information on clinical history, signs, and symptoms to support the diagnosis and differential diagnosis of asthma and COPD. Using the approach of either single decision trees or randomized ensembles of such trees, three capnovolumetric parameters, as well as wheezing, dyspnea upon strong exertion, and smoking history, turned out to be most relevant. Our findings underline the usefulness of capnovolumetry as an additional tool in the diagnostic assessment of asthma and COPD.

METHODS

Patients

The analysis used data from a previous study performed in a private clinical practice in Augsburg, Germany, in which capnovolumetry was performed as index test, while the presence or absence of airway obstruction was evaluated via spirometry and bodyplethysmography as a reference standard[1]. The physician-based diagnoses relied on a comprehensive assessment of the patients' files and lung function data. No other inclusion or exclusion criteria were used. Patients with COPD and the comorbidity asthma ($n = 34$) were assigned to the COPD group, as this disease dominated the functional alterations. The study had been approved by the Ethical Committee of the Medical Faculty of the Technical University of Munich, and all patients gave their written, informed consent. The original study is registered under DRKS00013935 at German Clinical Trials Register (DRKS) where the study protocol can be accessed.

Assessments

Capnovolumetry was performed during tidal breathing over at least ten breathing cycles, with the only instruction to avoid deep breaths or panting, and the last five cycles were evaluated as mean values. The time course of expiratory CO_2 was determined via ultrasound via determination of the molar mass (SpiroScout, software LFX 1.8.0, Ganshorn, Niederlauer, Germany), whereby the parameters describing the capnovolumetric curves were computed by the built-in software. The four parameters previously identified as most relevant for the detection of airway obstruction were the s3, s3/s2, the volume of phase 2, and area/volume phase 3[1]. The capnovolumetric parameters describe the form of the expiratory CO_2 curve plotted against expiratory volume. The initial phase 1 comprises the dead space and is characterized by a CO_2 concentration near zero. It is followed by a steep rise of CO_2 concentration (with slope s2) in phase 2, as a result of the mixing of CO_2-free air with alveolar gas within the bronchial volume. Phase 2 is followed by phase 3 that represents the alveolar compartment and shows a slope of CO_2 concentration (s3) that is less than the slope of phase 2. In the presence of emphysema, slope 3 increases and slope 2 decreases, both primarily due to inhomogeneity of ventilation, thereby leading to a marked increase in the ratio s3/s2. In asthma, there is at least a tendency for a reduction of slope 2 and the volume of phase 2, both of which are indicative of (residual) bronchial obstruction. Area/volume phase 3 is closely related to alveolar ventilation, especially alveolar dead space, and therefore valuable particularly for the recognition of COPD.

For the comprehensive assessment of clinical history, signs, and symptoms, a questionnaire covering seven questions regarding dyspnea upon mild or strong exertion, cough, phlegm, wheezing, and smoking status (current, ex-smoker) was used (see Supplementary Methods for the questions).

Statistical analysis

As we aimed at the evaluation of capnovolumetry, only functional data from this measurement were used. Median values and quartiles were computed for patients' description, and binary logistic regression analyses were performed for the comparison of the COPD with the control group, asthma with control, and COPD with asthma. We relied on these binary distinctions, as the sets of relevant parameters turned out to be different and ternary comparisons resulted in complicated and non-robust predictive models.

In a next step, a quantitative network diagram describing the multiple relationships between parameters was constructed, using an adjacency matrix based on the strength of associations (phi-coefficients; control group as reference). This diagram comprised the anamnestic information as binary variables; moreover, binary categorizations of the ratio of slopes s3/s2 and the volume of phase 2 could be correlated with the binary results of the questions. These two parameters were chosen among the parameters of capnovolumetry in order to limit the complexity of the diagram. In the diagram, the area of the circles indicates the frequency of positive answers or capnovolumetric conditions, respectively, and the thickness of the arrows indicates the strength of association (phi-coefficient). For construction, the statistical software R was used[17].

While illustrating different associations for asthma and COPD, the network did not provide a decision algorithm. This was achieved by systematic generation of ensembles of binary classification and decision trees using the random forest approach and taking the majority vote of trees as outcome. Separate ensembles were constructed for COPD vs control, asthma vs control, and COPD vs asthma. Consistent with the fact that the sets of relevant predictors for these three comparisons were different (see above), comparisons comprising all three groups resulted in non-robust, difficult-to-interpret results and were thus not further evaluated. Following established procedures[18], the trees were constructed from the data by random selection of patients' subsets ($n = 500$) and sets of variables at each node (mtry = 3). All seven questions and all four continuous capnovolumetric parameters (without pre-defined cut-off values) were offered to the search algorithm. The patients not included in a specific tree (out of bag) allowed the evaluation of accuracy in terms of 2×2 confusion matrices and ROCs, yielding sensitivity, specificity, and AUC. The relative importance of parameters was described by the computed mean decrease in accuracy as well as the GINI criterion[18].

While random forests have the advantage of reducing problems arising from overfitting, they have the disadvantage that the ensembles of trees can be described only statistically. Therefore, a parallel construction of single trees by a classical procedure might be helpful for illustration and interpretation, in particular if the single trees comprise most or all of the variables identified as important in the ensembles. For this purpose, we used the CHAID method as implemented in SPSS[10], including Bonferroni correction and tenfold cross-validation. Again, separate trees were constructed for COPD vs control, asthma vs control, and COPD vs asthma.

A more detailed description of the statistical methods can be found in Supplementary Methods. All statistical analyses were performed with SPSS (Version 25, IBM Corp., Armonk, NY, USA) and the module "randomForest" from the software package R[19]. The level of significance was assumed at $p < 0.05$.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

DATA AVAILABILITY

The data set analyzed during the current study is available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

C.K. prepared the final manuscript, was involved in the statistical analysis and interpretation of data, and agreed to be accountable for all aspects of the work. R.A.J. provided the idea of the statistical analysis strategy, performed the data analysis, and participated in the preparation of the manuscript. K.K., K.H., and S.R. reviewed the manuscript and commented on drafts of the final manuscript. A.S. had the project idea, developed the design of the study, and was involved in data analysis and manuscript preparation.

COMPETING INTERESTS

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ADDITIONAL INFORMATION

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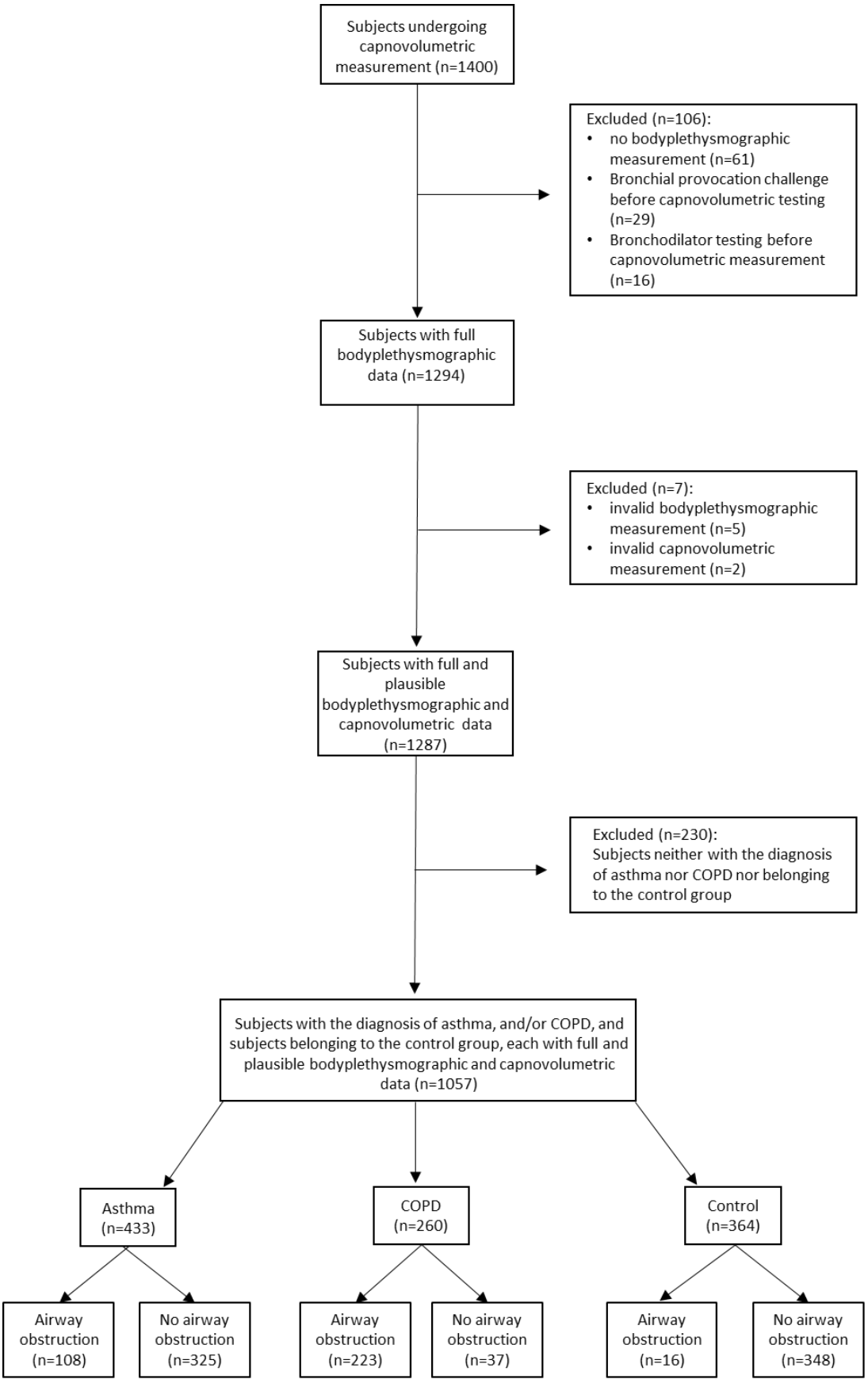
SUPPLEMENT


Subjects undergoing capnovolumetric measurement (n=1400)
Excluded (n=106):
• no bodyplethysmographic measurement (n=61)
• Bronchial provocation challenge before capnovolumetric testing (n=29)
• Bronchodilator testing before capnovolumetric measurement (n=16)
Subjects with full bodyplethysmographic data (n=1294)
Excluded (n=7):
• invalid bodyplethysmographic measurement (n=5)
• invalid capnovolumetric measurement (n=2)
Subjects with full and plausible bodyplethysmographic and capnovolumetric data (n=1287)
Excluded (n=230):
Subjects neither with the diagnosis of asthma nor COPD nor belonging to the control group
Subjects with the diagnosis of asthma, and/or COPD, and subjects belonging to the control group, each with full and plausible bodyplethysmographic and capnovolumetric data (n=1057)
Asthma (n=433)
COPD (n=260)
Control (n=364)
Airway obstruction (n=108)
No airway obstruction (n=325)
Airway obstruction (n=223)
No airway obstruction (n=37)
Airway obstruction (n=16)
No airway obstruction (n=348)

Supplement

Supplementary Figure S1. Flow-chart of the selection process leading to a subset of 1057 patients included into the present analysis. A total of 1400 consecutive patients underwent capnovolumetry. Patients who turned out to have had bronchial provocation challenges or bronchodilator testing prior to capnovolumetry due to organizational reasons were excluded (n=45). Moreover, patients who did not undergo bodyplethysmographic and spirometric measurements (n=61) were excluded. Five patients were excluded due to low quality of their bodyplethysmographic measurement data, and two patients based on invalid capnovolumetric measurements. For the present analysis patients were selected who had a diagnosis of COPD or asthma (potentially both), or did not show any respiratory disease (control subjects). Those with the diagnosis of other respiratory diseases (such as restrictive disorders, pneumonia or other infections, pleural diseases, lung tumor, bronchiectasis) were excluded (n=230), leading to a final subset of 1057 patients.

Supplementary table S1

The table shows the results of stepwise logistic regression analyses in terms of the statistically significant odds ratios (OR). The OR refer to the first versus second condition for the three comparisons of diagnoses shown. In case of answers to questions, a positive answer is associated with the OR given. In case of continuous variables from capnovolumetry, the OR for an interquartile change in the study population (COPD, asthma, control) is shown to ensure the comparability within the table. Values that were not statistically significant are indicated by a hyphen.

	COPD vs Control	**Asthma vs Control**	**COPD vs Asthma**
Phase 3 (s3)	0.566	-	1.618
s3/s2	2.285	-	2.151
Area/volume phase 3	3.212	-	2.507
Volume phase 2	-	0.775	-
Current smoker	12.773	0.488	30.857
Ex-smoker	7.988	-	7.868
Frequent cough	-	-	0.605
Frequent phlegm	1.748	-	-
Wheezing in the last 12 months	-	2.378	0.426
Dyspnea at strong exertion	7.037	1.440	3.063
Dyspnea at mild exertion	-	-	2.696

Supplementary Table S2

Phi-coefficients as measures of association for two binary variables. Binary results (yes/no) of anamnestic questions or capnovolumetric conditions were analyzed for their relationship to asthma or COPD, taking the control group as reference. For the ratio of s3/s2 a predefined cut-off value (0.10) was used. The cut-off value of 105.0 ml for the volume of phase 2 was identified by ROC analysis of asthma vs control as optimal, using this parameter as a single predictor. Only significant phi-coefficients are listed. The phi-coefficients were used for the construction of a quantitative network diagram (figure 2). n.s. = not significant.

Asthma - Control	
Questions (binary results (yes/no))	**Phi-coefficient**
Wheezing in the last 12 months?	0.23
Dyspnea at mild exertion?	n.s.
Dyspnea at strong exertion?	0.17
Current smoker?	-0.11
Ex-smoker?	n.s.
Frequently coughing?	0.09
Increased phlegm?	n.s.
Ratio s3/s2 ≥ 0.10	n.s.
Volume of phase 2 ≤ 105.0ml	0.13
COPD - Control	
Questions (binary results (yes/no))	**Phi-coefficient**
Wheezing in the last 12 months?	0.16
Dyspnea at mild exertion?	0.32
Dyspnea at strong exertion?	0.40
Current smoker?	0.19
Ex-smoker?	0.25
Frequently coughing?	n.s.
Increased phlegm?	0.18
Ratio s3/s2 ≥ 0.10	0.38
Volume of phase 2 ≤ 105.0ml	n.s.

Supplementary Table S3.

Frequency of positive answers to anamnestic questions or capnovolumetric conditions. In addition, the prevalence of the diagnoses of asthma and COPD in the study population is indicated. For the ratio of s3/s2 a predefined cut-off value (0.10) was used. The cut-off value of 105.0 ml for the volume of phase 2 was identified by ROC analysis (see legend table S1). The values were used in the quantitative network diagram shown in figure 2.

Anamnestic questions/ capnovolumetric conditions/ diagnoses	Frequency of positive answers (%)
Wheezing in the last 12 months?	53.7
Dyspnea at mild exertion?	26.9
Dyspnea at strong exertion?	67.4
Current smoker?	20.3
Ex smoker?	39.4
Frequently coughing?	38.6
Increased phlegm?	32.4
Ratio s3/s2 ≥ 0.10	28.9
Volume of phase 2 ≤ 105.0ml	47.4
Asthma	41.0
COPD	24.6

Supplementary Methods

Short description of the statistical methods

Logistic regression analysis

This is a modification of the well-known linear regression analysis in the sense that the dependence of an outcome variable of a number or predictor variables is determined. The predictor variables can be continuous or categorical, especially binary. The difference to linear regression analysis is that the outcome variable is categorical, usually binary. A typical binary comparison is that between two diagnoses, a typical binary predictor “smoking Yes/No”, and a typical continuous predictor a lung function measure. The dependence on the predictors is determined simultaneously, i.e. not separately for each of them. The degree of dependence can be expressed through a coefficient in analogy to linear regression. However, as this occurs in an exponential function, it is commonly expressed as odds ratio giving the relative chance of one of the outcomes relative to the other for a change in one unit of the predictors. The latter may be a Yes/No change in case of a binary predictor. The practical use is to multiply the respective odds ratios if their conditions are met and thus to derive an estimate for the likelihood of one diagnosis over the alternative, provided the model is correct.

Supplement

Network analysis

This is a way to depict relationships and their strength among a set of binary variables, such as Yes/No answers. Continuous variables are dichotomized using a pre-defined cut-off value and can thereby be included. Essentially, the relationship between variables is determined in 2x2 contingency tables and expressed as phi-coefficient that can be interpreted as correlation coefficient. The frequency of each condition is commonly indicated by the size of circles representing the variables, and the strength of each relationship by the thickness of the respective line. This approach provides a convenient visualization of the overall findings, however without a deeper analysis in terms of multiple simultaneous relationships or the prediction of diagnoses.

Decision trees

We assume that we aim at a decision between two diagnoses based on a set of variables. The first step is to identify the most relevant variable for decision, i.e. the variable yielding the best separation between individuals regarding their categorization into two groups. The criterion for this is either fixed, e.g. Yes/No, or, for continuous variables, identified via the optimal cut-off value. This results in a categorization of individuals into two groups, one comprising those in which the criterion is met, the other those in whom it is not met. Each of the two groups is then analyzed in exactly the same way, the resulting groups again, and so on, until an end criterion is met, e.g. the size of the groups is smaller than some value. Thus, a decision is made at each node, which results in a branching. In our approach, we allowed only for two branches to keep the model simple. It is important to note that in each of parallel branches different variables may be relevant, a fact which allows for a great flexibility of decision trees. The commonly used algorithms differ by technical details, for example in the way, which variables are selected, whether variables can be used repeatedly throughout a branch or are “used up” if they occurred once in a branch. The CHAID algorithm used by us is based on a chi-square statistics computed at each node and does not use a variable again in a branch if it had already been used. This reduces the risk of overfitting in the sense that trees tend to fit the data from which they are constructed very well but are less reliable when applied to new data. The advantage of the decision tree is that it can be used directly by inserting a patient’s values at each node and looking for the final result of the decision sequence.

Random forest

Decision trees are easy to visualize, understand and use, but known to be susceptible to errors resulting from overfitting. To increase the robustness, an ensemble of trees can be constructed that work in parallel, using their majority vote for decision. The construction of each tree can be based on a subset of the data which is sampled by a random procedure from the total data set, typically with

the possibility to draw each individual's data set repeatedly. Moreover, at each branch, a random subset of variables is offered to the algorithm searching for the optimal variable (and possibly optimal cut-off value for continuous variables); the algorithms typically work as described above for decision trees. This approach has been shown to be remarkably statistically robust and safe against overfitting, while at the same time in many cases yielding better results than a single tree. The disadvantage is that the ensemble of trees that are constructed (typically of the size 500-1000) cannot be visualized, naturally, and also cannot be listed in a compact form that is directly useful for a reader. It can only be realized as software algorithm, and the characteristics of the trees can only be described statistically in terms of the distributions of variables and nodes. This was the reason why we additionally identified a single optimal tree. The fact that this tree contained just the variables that had been identified as most important in the random forest approach and that the reliability in the recognition of diagnoses was only slightly less, underlined the consistency of our data set and analyses.