

Chapter 1

Assessment of Airway Hyperresponsiveness: Comparison of Spirometry and Body Plethysmography

F. Nensa, N. Kotschy-Lang, H.-J. Smith, W. Marek, and R. Merget

Abstract While methacholine (MCH) testing is commonly used in the clinical diagnosis of asthma, the detection of airway narrowing often relies on either spirometry or body plethysmography, however comparative studies are rare. In this study we performed MCH testing in 37 patients with variable shortness of breath at work and in 37 patients with no history of airway disease. The inclusion criteria were: no acute respiratory infection within 6 weeks, no severe diseases, normal baseline specific airway resistance (sR_{aw}), normal baseline forced expiratory volume in 1 s (FEV_1), Tiffeneau index $>70\%$, no previous treatment with steroids within 14 days and no short acting bronchodilators within 24 h. Cumulative doses of 0.003, 0.014, 0.059, 0.239 and 0.959 mg MCH were inhaled by a dosimeter method. A FEV_1 decrease of $\geq 20\%$ from baseline and a 100% increase of sR_{aw} to ≥ 2.0 kPa/s was defined as end-of-test-criterion. Provocation doses were calculated by interpolation. Performance of lung function parameters was compared using receiver-operating-characteristic (ROC) analysis. ROC analysis resulted in an area under the ROC curve (AUC) of 0.74 for FEV_1 vs. 0.82 for sR_{aw} . The corresponding Youden Indices (J) were 0.46 for FEV_1 and 0.57 for sR_{aw} . The Youden Index of sR_{aw} was higher and sensitivity and specificity (73%/84%) were rather well-balanced, in contrast to FEV_1 (54%/92%). In conclusion, in cumulative MCH challenges sR_{aw} was found to be the overall most useful parameter for the detection of bronchial hyperresponsiveness. Body plethysmography yielded a balanced sensitivity-specificity ratio with higher sensitivity than spirometry, but comparable specificity.

Keywords Airway hyperresponsiveness • Asthma • Bronchodilation • Body plethysmography • Methacholine • Spirometry • Airway resistance

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1.1 Introduction

Airway hyperresponsiveness is defined as an exaggerated bronchoconstrictive response to a number of inhaled physical, chemical or pharmacologic stimuli that occurs in patients with asthma, but not or rarely in healthy subjects. As a distinctive characteristic of asthma it regularly appears earlier (at lower doses) and is more intensive in patients with asthma and therefore underlies the rationale for bronchial challenge testing (Crapo et al. 2000; Cockcroft et al. 1977; Juniper et al. 1981). Both the American Thoracic Society (ATS) (Crapo et al. 2000) and the European Respiratory Society (ERS) (Sterk et al. 1993) recommend challenge tests by inhalation of aerosolized methacholine (MCH).

Spirometry being technically simple, cheap and highly reliable is currently the most commonly used method of indirect airway narrowing detection. A fall of the forced expiratory volume in 1 s (FEV_1) of at least 20% from baseline following MCH inhalation is widely used to determine airway hyperresponsiveness. However, FEV_1 largely depends on the subject's cooperation, which especially has to be considered in the context of pediatric examinations and medical opinions. Furthermore, FEV_1 maneuvers require maximal inspiration that has been shown to reduce bronchoconstriction induced by histamine or methacholine (Cockcroft and Davis 2006; Nadel and Tierney 1961). Slats et al. (2007) showed that airways inflammation plays an essential role in the broncho-protective effects of deep inhalations in healthy subjects and patients with bronchial asthma. Bronchoprotection by deep inhalation may however be of only minor importance in patients with chronic obstructive pulmonary disease (COPD) and increased levels of airway resistance (Slats et al. 2007).

In contrast, body plethysmographic measurements of specific airway resistance (sR_{aw}) are performed under tidal breathing conditions, requiring only a minimum of the subject's cooperation. A $\geq 100\%$ increase of sR_{aw} from baseline to a minimum absolute value of 2.0 kPa/s is a commonly used threshold to determine airway hyperresponsiveness (Baur et al. 2005; Cri e et al. 2011). Comparative studies between spirometry and body plethysmography as effect parameters are rare. Hence both methods were compared in order to evaluate the concordance of spirometry and body plethysmography concerning their clinical value during MCH testing.

1.2 Methods

1.2.1 Subjects

MCH testing was performed in 74 patients (Table 1.1) during their stay at Berufsgenossenschaftliche Klinik f r Berufskrankheiten, Falkenstein, Germany. Subjects were assigned to two groups. The asthma group consisted of 37 (20 males) patients who reported variable shortness of breath at work in recent years. Subjects with isocyanate exposure and subjects with COPD-like disease were excluded. The control group consisted of 37 (22 males) patients with unrelated diagnoses that are not known to cause airway hyperresponsiveness, but no history of airway diseases.

All subjects met the following criteria: no acute respiratory infection or exacerbation within the preceding 6 weeks; no severe accompanying diseases; normal baseline sR_{aw} and FEV_1 , $FEV_1/FVC > 70\%$, no previous treatment with oral or inhaled steroids within 14 days, and no short acting bronchodilators within 24 h before MCH testing. Also patients were asked to refrain from using caffeine containing beverages. A paradoxical increase in $FEV_1 > 5\%$ of baseline during methacholine testing was regarded as a sign of unstable breathing control and those tests ($n = 8$) were subsequently excluded from the study for quality assurance. All patients were over 18 years

Table 1.1 Demographic and pulmonary baseline data of subjects included in the study

Group	N (males)	Age (year)	Weight (kg)	Height (cm)	sR _{aw} (kPa/s)	FVC (L)	FEV ₁ (L)	FEV ₁ /FVC (%)
Normal	37 (20)	48 ± 13	78 ± 15	171 ± 9	0.70 ± 0.2	4.1 ± 0.9	3.3 ± 0.8	82 ± 6
Asthmatic	37 (22)	47 ± 14	83 ± 18	170 ± 10	0.85 ± 0.2	4.2 ± 0.9	3.4 ± 0.7	82 ± 5

Table 1.2 Methacholine testing protocol

Step	Concentration	Dose (mg)	Cumulative dose (mg)	Substance	Procedure
B	0.9%	0.072	0.072	Saline	8 breaths
1	3.3 mg/mL	0.003	0.003	Methacholine	1 breath
2	16.5 mg/mL	0.011	0.014	Methacholine	1 breath
3	16.5 mg/mL	0.045	0.059	Methacholine	3 breaths
4	16.5 mg/mL	0.180	0.239	Methacholine	10 breaths
5	16.5 mg/mL	0.720	0.959	Methacholine	16.36 s inspiration

of age (range 22–74, average 47 years) and informed written consent was obtained from each subject. The study protocol was approved by a local Ethics Committee.

1.2.2 Methacholine Testing

An ATS-adapted dosimeter method was used, with minor modifications as described recently (Merget et al. 2009). Briefly, methacholine chloride (Provokit, Lindopharm, Hilden, Germany) was dissolved in sterile water supplied with the product to a concentration of 3.3 mg/mL for the first very low dose provocation step and 16.5 mg/mL for all following steps (Table 1.2). After measuring baseline values and an initial inhalation of aerosolized isotonic saline, MCH was administered in up to five steps (0.003, 0.011, 0.045, 0.180, and 0.720 mg) aerosolized by a MedicAid nebulizer (mass median aerodynamic diameter of particles of 3.2 µm) and dosimetrically applied by the APS provocation system (CareFusion, Höchberg, Germany).

The cumulative inhaled doses after each step of inhalation (0.003, 0.014, 0.059, 0.239, and 0.959 mg MCH) were obtained by taking one breath (3.3 mg/mL) at step one, one breath (16.5 mg/mL) at step two, three breaths (16.5 mg/mL) at step three and ten breaths (16.5 mg/mL) at step four. At step five patients took multiple breaths until a total inspiration time of 16.36 s was accumulated.

1.2.3 Lung Function Measurements

sR_{aw} and intrathoracic gas volume (FRCpleth) were recorded by body plethysmography (MasterScreen, CareFusion, Höchberg, Germany). Spirometry was performed after sR_{aw} tidal breathing analysis and linked to FRCpleth in the sitting position. Body plethysmography and forced spirometric maneuvers were performed at rest and 2 min after inhalation of saline and each MCH dose, with the measurements of sR_{aw}, FRCpleth, and FEV₁.

A fall of FEV₁ ≥20% from baseline together with an sR_{aw} increase of ≥100% from baseline to ≥2 kPa/s or application of the maximum MCH dose was defined as end-of-test-criterion. Because most thresholds in MCH testing are defined relative to the baseline values and therefore the accuracy of these are critical to the whole test, baseline measurements without any prior inhalation were repeated several times. From three spirometric measurements that fulfilled acceptability criteria the best was identified by the maximal sum of FEV₁ and forced vital capacity (FVC). Calculating the median of

five airway resistance and three FRCpleth measurements reduced artifacts in body plethysmographic baseline values. While body plethysmography was performed in an identical way after each intermediate MCH inhalation step, spirometry was done only once. After the end-of-test-criterion was reached measurements were performed as during baseline measurements.

1.2.4 Data Analysis

It was the aim of this study to compare body plethysmographic and spirometric parameters not only regarding the dose response at discrete steps of provocation levels, but to perform statistical data analysis over a continuous dose interval. Using regression analysis of the recorded lung function parameters with the applied MCH doses as the covariates the corresponding MCH provocation doses or concentrations (PD or PC) at arbitrary thresholds could be estimated by interpolation. An interpolated MCH dose that was needed to cause a fall of FEV_1 of 20% (10%) from baseline was called $PD_{20}FEV_1$ ($PD_{10}FEV_1$). $PD_{100}sR_{aw}$ was defined as the interpolated MCH dose needed to cause an increase in sR_{aw} of 100% from baseline, $PD_{+100}sR_{aw}$ with the additional increase of sR_{aw} to ≥ 2 kPa/s.

Performance of lung function parameters in binary classification of patients into asthmatic and non-asthmatic groups was compared using receiver-operating-characteristic (ROC) analysis taking the MCH dose as the varying discrimination threshold. For comparison of the ROC curves the area-under-the-ROC-curve (AUC), a robust measure for the overall quality of a classifier, was calculated. In contrast to the AUC being a summary statistic for test comparison the maximum test performance was quantified by estimating the Youden Index $J = \max(sensitivity + specificity - 1)$ (Schisterman et al. 2005), which also provides a criterion for choosing an ‘optimal’ threshold value (Greiner et al. 2000).

To investigate the impact of the definition of the reactive thresholds on the tests’ ability to discriminate subjects with and without asthma, ROC analysis was performed iteratively over broad intervals of reasonable threshold definitions and summarized by plotting these thresholds against their corresponding AUC values (Fig. 1.2). According to O’Connor et al. (1987), the dynamics of the dose–response curves were summarized by a measure defined as the slope of a line extending from baseline to the last data point obtained from provocation. FEV_1 and sR_{aw} were again compared by ROC analysis using this alternative approach.

All calculations were done using an Oracle© 10 g XE database, custom Java© code (Java Development Kit 1.6) and the R software environment for statistical computing (Ihaka and Gentleman 1996). ROC analysis was facilitated by the ROCR (Sing et al. 2005) package.

1.3 Results

Normal and asthmatic subjects were comparable in terms of demographic and pulmonary baseline characteristics (Table 1.1). Baseline sR_{aw} was significantly ($p < 0.05$) higher in the asthmatics group but still within normal limits due to inclusion criteria used.

1.3.1 ROC Analysis

When applying $PD_{20}FEV_1$ for spirometry and $PD_{+100}sR_{aw}$ including an absolute threshold of ≥ 2.0 kPa/s for body plethysmography (Fig. 1.1), ROC analysis resulted in AUC of 0.74 for FEV_1 vs. 0.82 for

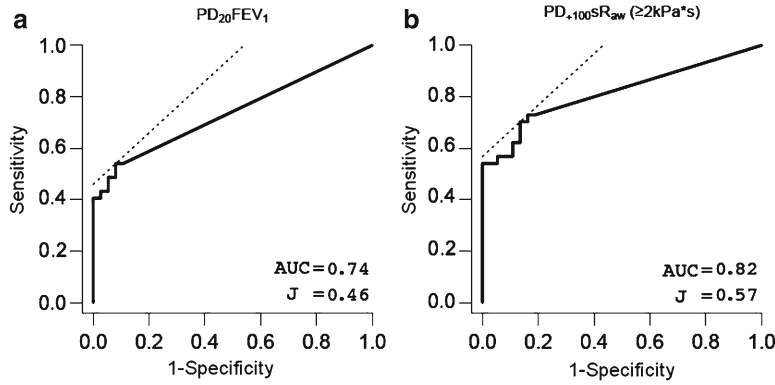


Fig. 1.1 Comparison of FEV_1 and sR_{aw} using ROC analysis. The intersections of the *dashed* line with the ROC curves represent the Youden Indices (J). *AUC* area under the curve

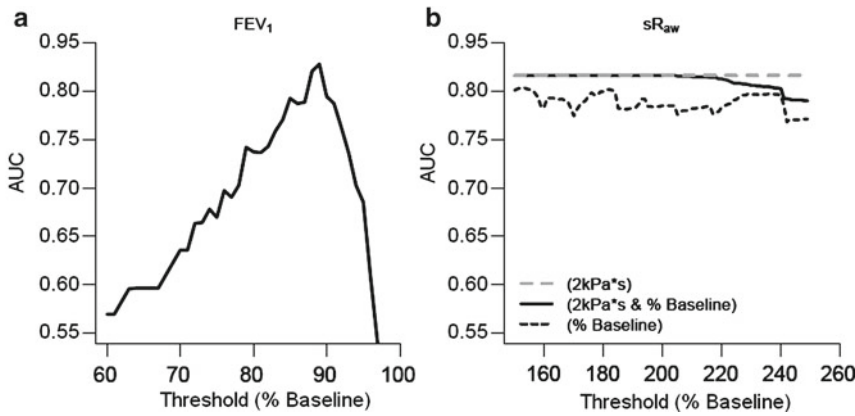


Fig. 1.2 Effect of the definition of reactive thresholds on test performances measured as areas under the curves (AUC)

sR_{aw} . The corresponding Youden Indices (J) were 0.46 for FEV_1 and 0.57 for sR_{aw} . The Youden Index in sR_{aw} was not only higher, but sensitivity and specificity (73%/84%) were rather well-balanced, in contrast to FEV_1 (54%/92%).

1.3.2 Threshold Optimization

By iterative threshold variation, FEV_1 -based MCH testing was found to perform best at thresholds near 90% ($PD_{10}FEV_1$) of baseline value (Fig. 1.2, left part) being significantly better than that at 80% ($PD_{20}FEV_1$). Evaluating threshold definitions for body plethysmography was more complex because two synergistic thresholds, relative increase (% baseline) and 2.0 kPa/s absolute value, and their logical “AND” combination had to be analyzed. The performance of sR_{aw} based MCH testing was completely determined by the absolute threshold of 2.0 kPa/s. Variation of the relative threshold did not improve the performance of the test but instead resulted in a test performance decline for thresholds $\geq 200\%$ (Fig. 1.2, right part).

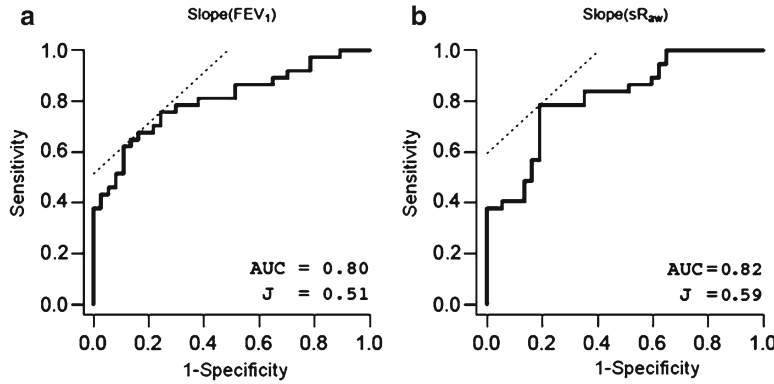


Fig. 1.3 ROC analysis of dose-response curve slopes. The intersections of the *dashed line* with the ROC curves represent the Youden Indices (J). *AUC* area under the curve

1.3.3 Slopes as Alternative Measures

The discrimination between both groups based on slopes of both FEV_1 and sR_{aw} were comparable. ROC analysis of sR_{aw} slopes resulted in a slightly higher AUC (0.82 sR_{aw} vs. 0.80 FEV_1) and a higher Youden Index (0.59 sR_{aw} vs. 0.51 FEV_1), but FEV_1 slopes produced a more uniform and stable ROC curve with several alternative maxima suitable as Youden Indices (Fig. 1.3). Both parameters provide well balanced sensitivity and specificity ratios (78%/81% sR_{aw} vs. 76%/76% FEV_1).

1.4 Discussion

It was the aim of the present study to assess the diagnostic value of spirometry and body plethysmography in MCH testing. We chose a case-control design, which has also been used for the same purpose by Cockcroft and Berscheid (1983) almost 30 years ago. In that study the authors compared $PC_{20}FEV_1$ and $PC_{35}sG_{aw}$ (provocation dose at a 35% fall of specific airway conductance from baseline) in 16 asthmatic and 27 normal subjects. The major result of that study was that $PC_{20}FEV_1$ was about fourfold larger than $PC_{35}sG_{aw}$, but the authors recommended to use FEV_1 because of better separation of both groups. The study was criticized some years later by Popa and Singleton (1988) because of the ceiling method that was used to define the cut-offs. The ceiling method selects the highest provocation dose in the asthmatic group as the cut-off value consequently leading to poor specificity if provocation doses overlap between normal and asthmatic groups, which appears to be the situation in the general population (Cockcroft et al. 1983; Hendrick et al. 1986; Tiffeneau 1957; van der Lende et al. 1973; Woolcock et al. 1987). There was very little overlap between groups in Cockcroft and Berscheid's (1983) study, possibly due to selection of the subjects. In the study by Popa and Singleton (1988), $PD_{20}FEV_1$ was about threefold higher than $PD_{40}sG_{aw}$ and the authors recommended using $PD_{20}FEV_1$ because this parameter produced lower misclassification rates due to lower variability of the endpoint. However, as it was obviously not the primary goal of that study to compare spirometry and body plethysmography and no threshold variations of sG_{aw} besides the $PD_{40}sG_{aw}$ (40% fall without an additional absolute threshold) were considered, this result is threading on thin ice.

Whereas both studies considered only one, Khalid et al. (2009) compared $PC_{20}FEV_1$ with three different body plethysmographic parameter variations (45%, 52%, and 56% fall). That study was

performed retrospectively in subjects with suspected asthma. However, because $PD_{20}FEV_1$ was used as the gold standard for ROC analysis, it could not answer the question whether one method was superior to the other and thus the authors could not explain the high number of subjects with significant responsiveness in sG_{aw} without reaching the spirometric criterion. All available studies had used the spirometric end-of-test-criterion because of the much lower threshold doses of body plethysmography. Although it is a plausible assumption that subjects with a 20% fall of FEV_1 will all show a significant fall in sG_{aw} , this has never been demonstrated by using two combined end-of-test-criteria, i.e., to terminate the test when both end-of-test criteria are reached.

When we designed this study, firstly, we wanted to avoid limitations of earlier studies by comparing spirometry and body plethysmography over continuous threshold intervals. Secondly, our study was designed as a systematic comparison of FEV_1 and sR_{aw} with both spirometric and body plethysmographic parameters as end-of-test criteria without the need for extrapolation to missing values. Third, we wanted to test a second body plethysmographic criterion that is widely used in Germany. As it may not be relevant to produce a relative change within reference limits, it is plausible to add an absolute criterion of a clinically relevant airway obstruction (at a sR_{aw} of about 2 kPa/s subjects experience dyspnea).

It is essential for case control studies to clearly define cases and controls. In this study we used subjects with suspected occupational asthma, i.e., variable shortness of breath at work. This may be considered as a weakness of the present study explaining its relatively low sensitivities (e.g., with the 20% fall of FEV_1 criterion merely 20 asthmatics were considered hyperresponsive). However, low sensitivities within a similar range as in our study were reported in a recent cohort study (Anderson et al. 2009). In order to avoid misclassification in future studies, further information should be included in the case definition.

The main conclusion of our study is that sR_{aw} is the overall most useful parameter for the detection of airway hyperresponsiveness. sR_{aw} yielded a more balanced sensitivity-specificity ratio with higher sensitivity than FEV_1 , but comparable specificity. With a threshold at 80% of baseline the FEV_1 -based test may not be tuned to produce optimal results. Optimization of reactive thresholds showed a distinct absolute peak near 90% of baseline ($PD_{10}FEV_1$) for FEV_1 that indicates that the often-used $PD_{20}FEV_1$ might not always be ideal, particularly as lower thresholds (closer to baseline) decrease false negative test rates. It must be considered though, that our study group was assembled to meet criteria like normal baseline FEV_1 as well as Tiffeneau index $>70\%$, which subsequently reduced variance in airway obstruction and therefore shifted optimal thresholds closer to the baseline. Furthermore, by not including those patients in the study that showed mild airway obstruction at baseline, and consecutively in most cases a strong airway response to MCH, the sensitivity of both FEV_1 and sR_{aw} was artificially reduced. FEV_1 tends to be more specific than sensitive and therefore yields more false negative test results, which is not a desirable feature of early screening tests. In fact MCH testing should be adjusted to provide low false negative rates, which of course requires high sensitivities.

Threshold optimization of sR_{aw} showed the test performance to be completely determined by the absolute 2.0 kPa/s threshold, which might as well be attributed to our concrete study group that did not include patients with non-asthmatic obstructive pulmonary diseases. Relative thresholds avoid the misclassification of subjects with those diseases, such as silicosis. These obstructive diseases are characterized by high absolute baseline resistance and therefore might cross the 2.0 kPa/s boundary prematurely without originating in airway hyperresponsiveness.

Apart from describing hyperresponsiveness with static absolute or relative thresholds there are alternative approaches that focus on the dynamics of the dose–response curve. Lötvall et al. (1998) proposed different pathophysiological mechanisms that lead to differently shaped curves. The authors separated hypersensitivity characterized by a general left-shift from hyperreactivity characterized by a steeper slope of the dose–response curve. The slope of the dose–response curve provides additional valuable information that prospectively should be integrated into the diagnosis of airway hyperresponsiveness. The slope-based test performances were comparable to those of the threshold-based

analyses, which suggests that the dynamics of the dose–response curve may be regarded as an alternative or additional measure to effectively separate asthmatics from normal subjects.

In summary, this study indicates that body plethysmography adds valuable information to the question whether a subject has airway hyperresponsiveness. Its most important advantage is the reduction of false negative tests which may occur with spirometry. This is important especially in the diagnosis and compensation of occupational asthma. While we are still waiting for optimal threshold definitions based on credible normative data and reliable statistical methods, a combination of both, spirometry and body plethysmography, should offer the best information.

Conflicts of Interest: The authors declared no conflicts of interest in relation to this article.

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