ORIGINAL ARTICLE

Whole-Body Plethysmography in Suspected Asthma

A Prospective Study of Its Added Diagnostic Value in 302 Patients

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SUMMARY

Background: Whole-body plethysmography (WBP) with bronchial challenge testing to measure the (specific) airway resistance, $(s)R_{AW}$, is considered to be a more sensitive diagnostic procedure than spirometry, which can only measure the forced expiratory volume in one second (FEV_1). The evidence for the added diagnostic value of WBP is not yet conclusive.

Methods: In a prospective diagnostic study, we carried out WBP with bronchial challenge testing as well as a bronchodilation test in 400 patients with suspected asthma from June 2010 to October 2011. The bronchial provocation test was considered positive if the FEV_1 fell by at least 20% and/or the airway resistance doubled, with an increase of the sR_{AW} to at least $2.0 \text{ kPa} \times \text{s}$ and/or of the R_{AW} to $0.5 \text{ kPa} \times \text{s/L}$. Follow-up evaluation was performed one year later.

Results: The prevalence of asthma in the 302 patients who completed follow-up was 27.5%. The sensitivity of WBP with sR_{AW} measurement for asthma was 95.2% (95% confidence interval [CI] 88.3%–98.1%), and its specificity was 81.7% (95% CI 76.1%–86.3%). The sensitivity of FEV_1 was 44.6% (95% CI 34.4%–55.3%), and its specificity was 91.3% (95% CI 86.6%–94.4%). The negative predictive value (NPV) of WBP with sR_{AW} measurement was 97.8% (95% CI 94.5%–99.1%), while that of FEV_1 was 81.3% (95% CI 76.0%–85.7%). The positive predictive value (PPV) of WBP with sR_{AW} measurement was 66.4% (95% CI 57.5%–74.2%), while that of FEV_1 was 66.1% (95% CI 53.0%–77.1%).

Conclusion: With sR_{AW} measurement, asthma can be ruled out with high certainty. Improving the positive predictive value of testing for asthma remains a challenge, however, as sR_{AW} measurement does not yield any increase in specificity.

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Whole-body plethysmography (WBP) has been widely in use in Germany since the 1980s. It is available for everyday routine diagnostic evaluation not only in hospitals but also in every chest physician's practice. WBP provides more diagnostic information than spirometry; it measures intrathoracic gas volume, total lung capacity, functional residual capacity, and (specific) airway resistance R_{AW} (sR_{AW}), which requires no active cooperation of the patient to be captured (1). Especially sR_{AW} is regularly used in routine diagnostics, since it responds very sensitively to nonspecific bronchial provocation using methacholine or histamine. The provocation test is required to reach a guideline-conform diagnosis of bronchial asthma or rule this out, where spirometry results are normal—which is very often the case in mild asthma (2). The results of the bronchial challenge test are usually interpreted on the basis of the drop in FEV_1 and/or rise in R_{AW} or sR_{AW} .

The wide availability of WBP in Germany is in direct contrast to the available evidence for any additional diagnostic benefit compared with spirometry. One reason for this may be the fact that in earlier years, the need for systematic evaluations of diagnostic instruments was not seen as an issue (3). Accordingly, whole-body plethysmography is regarded as highly important in routine clinical practice for the diagnostic evaluation in asthma (4) and chronic obstructive pulmonary disease (COPD) (5), which is also reflected in German guidelines (6, 7), whereas it is barely mentioned in international guidelines. Renowned scientists in international pneumology keep casting doubt on its diagnostic usefulness (8). However, Decramer et al. showed recently on the basis of decision scenarios in focus groups that whole-body plethysmography contributed significantly to establishing the diagnosis (9). The specific role of WBP in the diagnosis of bronchial asthma has remained unclear, however, especially with regard of bronchial challenge testing. This is important because sR_{AW} is occasionally categorized as particularly sensitive to measuring artifacts (8). Some studies found that sR_{AW} may be superior to FEV_1 in assessing bronchial challenge, but the focus was either not on asthma (10) or the patients were preselected (11, 12),

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TABLE 1

Characteristics of patients at baseline (study inclusion) (t0)

	Asthma n (%)	COPD n (%)	No obstructive respiratory disease n (%)
n	154 (39.2)	5 (1.3)	234 (59.5)
Female sex	91 (59.1)	2 (40.0)	142 (60.7)
Are you experiencing dyspnea? (yes)	98 (63.6)	5 (100.0)	123 (52.6)
During the past 12 months, have you noticed a wheezing in your chest while breathing? (yes)	97 (63.0)	5 (100.0)	79 (33.8)
Do you often have a cough? (yes)	65 (42.2)	3 (60.0)	112 (47.9)
Do you often cough up sputum? (yes)	44 (28.6)	3 (60.0)	58 (24.8)
In the past 12 months, have you woken up at night with a sensation of tightness around your chest? (yes)	54 (35.1)	1 (20.0)	59 (25.2)
In the past 12 months, have you woken up because of dyspnea attacks? (yes)	35 (22.7)	1 (20.0)	28 (12.0)
Do you often have allergic rhinitis (for example, hay fever)? (yes)	76 (49.4)	0 (0)	47 (20.1)
Do you smoke? (yes)	19 (12.3)	0 (0)	20 (8.5)
Have you smoked in the past? (yes)	56 (36.4)	4 (80.0)	79 (33.8)
	MV [SD]	MV [SD]	MV [SD]
Age	40.5 [15.4]	60.8 [17.0]	44.6 [16.5]
FEV ₁ in liters	3.3 [0.9]	2.0 [1.1]	3.4 [1.0]
FEV ₁ as % of expected	101.3 [17.0]	74.1 [12.3]	107.7 [16.3]
FEV ₁ /VC as %	81.8 [8.4]	66.8 [9.8]	85.6 [7.3]
How much do you smoke/did you smoke? (In pack years)	10.1 [10.7]	42.5 [3.5]	12.9 [15.8]

COPD, chronic obstructive pulmonary disease; MV, mean value; SD, standard deviation

which may lead to bias in assessing diagnostic accuracy (13). The present study aimed to determine the added-diagnostic value of sR_{AW} in bronchial challenge testing in patients who presented to a specialist chest physician for the first time for the purpose of routine diagnostic evaluation of suspected bronchial asthma.

Methods

Study design

The prospective data collection in the sense of a delayed-type diagnostic study (14) was undertaken between June 2010 and October 2011 in a private practice of chest physicians in Augsburg (15, 16). The present analysis aimed to determine the added diagnostic-prognostic value of WBP and sR_{AW} in the diagnostic evaluation of bronchial asthma.

Population

400 patients were entered into the study consecutively, who presented with suspected bronchial asthma to a specialist chest physician for the first time (indicated population [3]). Our inclusion criteria were the description of typical symptoms, such as dyspnea and a productive cough lasting longer than two months, which raised suspicion of the presence of a respiratory disease and required extensive examination including WBP. Our exclusion criteria were: infections of the respiratory tract within the preceding six weeks and contraindications to bronchial challenge testing—such as pregnancy, cardiac arrhythmias, or coronary heart disease. The study was approved by the ethics committee of the Medical Faculty of the University Hospital Klinikum rechts der Isar/Technische Universität München. Information on participants' medical histories were documented using a structured questionnaire (Table 1).

Diagnostic examination using whole-body plethysmography

Patients were instructed not to smoke on the day of their examination (t0). They were asked to stop taking anti-obstructive medication that they may previously have been prescribed, 12 hours before the examination. Lung function tests were undertaken according to a standardized protocol, adjusted for sex, age, and body height (17). In case of FEV₁/VC (=vital capacity) <0.70 and/or FEV₁<80% of predicted, patients underwent a bronchodilation test using the short-acting beta-sympathomimetic agonist salbutamol. Airway obstruction was diagnosed according to international guidelines in patients with a pathological Tiffeneau index (FEV₁/VC <0.70). In patients whose FEV₁ improved by at least 12% and 200 mL, a diagnosis of bronchial asthma was made, when FEV₁ reached the target value after inhalation of salbutamol (18). A diagnosis of COPD was made in patients with a negative bronchodilation test, when FEV₁ was <12% or <200 mL and the test results were consistent with the patient's history (Figure 1).

Participants without airway obstruction were subjected to a bronchial challenge test using methacholine,

FIGURE 1

Diagnostic work-up when patients were included in the study. BDT, bronchodilation test; COPD, chronic-obstructive pulmonary disease

according to the 1-concentration-4-step dosimeter protocol (19). This protocol is of comparable accuracy as the multiconcentration protocol of the American Thoracic Society (ATS) (20), but its advantages in routine clinical practice include the fact that it can be conducted much more rapidly and simply. The challenge tests were evaluated on the basis of the challenge test concentrations; this refers to the concentrations of methacholine, which is inhaled in increasing dosages, in which a defined change of the lung function parameter occurs. The test was considered to be positive in the sense of bronchial hyperreactivity if FEV₁ fell by at least 20% after inhalation of up to a maximum methacholine concentration of 16 mg/mL (PC₂₀FEV₁<16 mg/mL) and/or if specific airway resistance (sR_{AW}) increased by at least 100% and simultaneously to at least 2.0 kPa*s (PC₁₀₀sR_{AW}<16 mg/mL), and/or an increase in airway resistance R_{AW} by at least 100% and simultaneously to 0.5 kPa*s/L (1). The diagnosis was made by a specialist chest physician, taking into consideration all relevant elements: medical history, clinical symptoms, and results on whole-body plethysmography, possibly under conditions of bronchial challenge.

Follow-up

Twelve months (t1) after the initial diagnosis, patients were contacted by telephone and underwent a structured interview asking for clinical signs and symptoms relating to bronchial asthma or COPD (the questionnaire can be viewed as an *eSupplement* [in German]).

Questions included were whether participants were still experiencing symptoms of an obstructive respiratory disease or still felt well, respectively. Furthermore they were asked if they were still taking antiobstructive medications and if so, which ones. At t1, their primary care physicians and chest physicians were also contacted and asked whether in their view, the patient still had asthma/COPD, whether they still issued prescriptions for anti-asthma drugs, and how often which medications had been prescribed in the preceding 12 months. Only those patients were included in the follow-up survey whose data, including the interview with their primary care physician, were completed. The chest physicians were reached in every case. An expert panel (AS, RAJ, JS) discussed patients' and doctors' responses and classified these diagnostically; the panel were blinded vis-à-vis the test parameters FEV₁ and sR_{AW} at t0. If patients, chest physicians, and primary care physicians agreed that no asthma symptoms were present and no medication was taken, the assumption was that the participant did not have asthma. If a patient reported that s/he experienced symptoms or took relevant medications, a follow-up diagnosis of asthma was documented.

Statistical analysis

For the purposes of evaluation, FEV₁ at t0 was compared with total specific airway resistance (sR_{AW}) at t0, which is regarded as more sensitive than the effective specific resistance (1); furthermore, sR_{AW} was selected

Diagnostic classification in follow-up analysis after 12 months (BDT = bronchodilation test)

FIGURE 2

instead of R_{AW} for the purpose of standardization. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of PC_{20} of FEV_1 (t0) and PC_{100} of sR_{AW} (t0) were calculated by using a 2 x 2 contingency table, with the diagnosis at t1 as the reference standard. A sensitivity analysis was also undertaken, in which a drop in FEV_1 by only 15% ($PC_{15}FEV_1 < 16$ mg/mL) was set, because an increase in sensitivity by a smaller extent of the required change in FEV_1 might ultimately have the same effect as measuring sR_{AW} , which is generally regarded as more sensitive. Previous studies suggested such relationships (21). We calculated 95% confidence intervals by using the method developed by Wilson (22). The power calculation showed that a sample size of at least 302 patients was needed in order to determine an estimated minimum sensitivity of 32% and specificity of 93% (16) with a 95% confidence interval of $\pm 9\%$, which

was deemed sufficient (22). In order to describe the patients, means and standard deviations (SD) were used. We chose a significance level of $\alpha < 0.05$. We used SPSS 22 for Windows for all our statistical analyses.

Results

A total of 400 patients participated in the study. Seven patients were not included in the evaluation because their documentation was incomplete (Figure 1). At the time of inclusion in the study (t0), bronchial asthma was diagnosed in 154 patients (39.2%), COPD in 5 patients (1.3%), and no obstructive respiratory disease in 234 patients (59.5%) (Table 1).

The latter group had the following diagnoses:

- 13 had restrictive lung disease
- 10 had chronic bronchitis without obstruction
- 30 had bronchial hyperreactivity subsequent to bronchopulmonary infection

TABLE 2

Distribution of diagnostic variables at 12-month follow-up (t1)

Index test: Test results at baseline (t0)	Reference standard: Diagnosis after 12 months (t1)		Total
	Asthma n (%)	No asthma n (%)	
$PC_{20}FEV_1$ positive & $PC_{100}sR_{AW}$ negative	10 (12.0)	11 (5.0)	21
$PC_{20}FEV_1$ positive & $PC_{100}sR_{AW}$ positive	22 (26.5)	8 (3.7)	30
$PC_{20}FEV_1$ negative & $PC_{100}sR_{AW}$ positive	42 (50.6)	21 (9.6)	63
BDT FEV_1 positive	5 (6.0)	0 (0)	5
$PC_{20}FEV_1$ negative & $PC_{100}sR_{AW}$ negative	4 (20.8)	179 (81.7)	183
Total	83 (100)	219 (100)	302

$PC_{20}FEV_1$ = reaction of forced expiratory capacity at 1 second (FEV_1) on bronchial challenge test using methacholine

$PC_{100}sR_{AW}$ = reaction of specific airway resistance (sR_{AW}) on bronchial challenge test

BDT = bronchodilation test (undertaken when $FEV_1 < 80\%$; no bronchial challenge test is undertaken in this setting)

TABLE 3

2 x 2 contingency table of diagnostic parameters of whole-body plethysmography for prognostic diagnostic evaluation of bronchial asthma after 12 months

Only FEV ₁ evaluated	Asthma (t1)	No asthma (t1)	Total	FEV ₁ and sR _{AW} evaluated	Asthma (t1)	No asthma (t1)	Total
(t0) Spirometry parameter: PC ₂₀ FEV ₁ positive or BDT FEV ₁ positive	37	19	56	(t0) WBP: PC ₁₀₀ sR _{AW} and/or PC ₂₀ FEV ₁ or BDT FEV ₁ positive	79	40	119
(t0) Spirometry parameter: PC ₂₀ FEV ₁ negative	46	200	246	(t0) WBP: PC ₁₀₀ sR _{AW} and PC ₂₀ FEV ₁ negative	4	179	183
	83	219	302		83	219	302
Sensitivity	44.6% (95% CI: 34.4 to 55.3)			Sensitivity	95.2% (95% CI: 88.3 to 98.1)		
Specificity	91.3% (95% CI: 86.8 to 94.4)			Specificity	81.7% (95% CI: 76.1 to 86.3)		
PPV	66.1% (95% CI: 53.0 to 77.1)			PPV	66.4% (95% CI: 57.5 to 74.2)		
NPV	81.3% (95% CI: 76.0 to 85.7)			NPV	97.8% (95% CI: 94.5 to 99.1)		

WBP = whole-body plethysmography

PC₂₀FEV₁ = reaction of forced expiratory volume at 1 second capacity (FEV₁) on bronchial challenge test using methacholine

PC₁₀₀sR_{AW} = reaction of specific airway resistance (sR_{AW}) on bronchial challenge test

BDT = bronchodilation test (undertaken when FEV₁ <80%; no bronchial challenge test is undertaken in this setting)

PPV = positive predictive value; NPV = negative predictive value

95% CI= 95% confidence interval

- 28 had acute bronchitis
- 18 had gastro-esophageal reflux disease
- 6 had vocal cord dysfunction
- 1 had a bronchial carcinoma
- 5 had chronic cough because of long-term use of an ACE inhibitor.

In the remaining 123 patients, no respiratory disease was detected. A diagnosis of asthma was made in 145 patients (94.2%) because of a positive result in the bronchial challenge test and in 9 patients (5.8%) because of a positive bronchodilation test.

At 12 months' follow-up (t1), 344 patients and the primary care physicians of 335 patients were successfully contacted by telephone; complete data were obtained for 302 patients (Figure 2). In 33 cases (10.9%) with an initial diagnosis of bronchial asthma, the patients and their primary care physicians were in agreement that 12 months later, no symptoms of a respiratory disease remained. In four cases (1.3%), primary care physicians and patients agreed that bronchial asthma was present, although the challenge test had been negative. These patients continued to use asthma inhalers. At t1, 83 patients (27.5%) still had a diagnosis of bronchial asthma; 50 (60.2%) of these were female. At t0, responders had a mean FEV₁ of 3.3 (SD 0.9) liters and 105.5 (16.3) % target value, as well as a Tiffeneau index (FEV₁/VC) of 84.1 (7.7) %. The 91 patients who were not included in the follow-up analysis (non-responders) were significantly younger than responders (39.4 years v 44.5 years; p = 0.006 in the t test); no significant differences were seen regarding sex distribution, asthma frequency, and lung function values.

In 42 (50.6%) of the 83 patients who still had a diagnosis of bronchial asthma at t1, the diagnosis was made

only on the basis of a change in sR_{AW} of at least 100% during the bronchial challenge test (Table 2). Conversely, in 21 (9.6%) of cases, the mere reaction of sR_{AW} on bronchial challenge was false-positive in this regard. In 32 patients (38.6%), FEV₁ dropped by 20% during the bronchial challenge test and in 5 (6.0%) a sufficiently strong reaction developed during the bronchial dilation test. In these patients, charting the flow-volume curve while measuring FEV₁ and VC by using spirometry would have been sufficient to make a diagnosis. In 19 patients (8.7%), the reaction of FEV₁ was false-positive. The respective 2 x 2 contingency tables (Table 3) show that the sensitivity notably increased when sR_{AW} was included, whereas the specificity slightly decreased. Correspondingly, the negative predictive value (NPV) of whole-body plethysmography was very high when PC₁₀₀sR_{AW} was included—97.8% (95% CI 94.5% to 99.1%), whereas the NPV of PC₂₀FEV₁ alone—which could as well have been measured by using spirometry—was notably lower, at 81.3% (95% CI 76.0% to 85.7%) (Table 3). The positive predictive value (PPV) of the WBP was only slightly higher when PC₁₀₀sR_{AW} was used (66.4%; 95% CI 57.7% to 74.2%) than when only PC₂₀FEV₁ was used (66.1%; 95% CI 53.0% to 77.1%). The sensitivity analysis regarding PC₁₅FEV₁ <16 mg/mL found a sensitivity of 60.2% (95% CI 49.5% to 70.1%) and a specificity of 83.1% (95% CI 76% to 87.5%). Accordingly, NPV was 84.7% (95% CI 79.2% to 88.9%) and PPV 57.5% (95% CI 47.0% to 67.3%).

Discussion

The present study showed for the first time the added diagnostic value in routine practice of chest physicians

of measuring specific airway resistance (sR_{AW}) by using whole-body plethysmography in patients with suspected asthma. The sensitivity of sR_{AW} during non-specific bronchial provocation was high. This yielded a high negative predictive value and therefore made it possible to exclude bronchial asthma with high certainty.

Our data underline the legitimacy of making sR_{AW} during bronchial challenge tests a central component for excluding asthma on the basis of the high negative predictive value; the method has been widely in use in Germany but has thus far not been sufficiently scientifically supported. For the diagnostic procedure this means that primary care physicians should refer patients with suspected asthma and normal results on spirometry—which is common in mild asthma (2)—to specialist chest physicians for the purpose of bronchial challenge testing with analysis in the whole-body plethysmograph. In case of a negative result, the patient is unlikely to have bronchial asthma. Some guidelines suggest measuring peak flow variability in order to improve diagnostic certainty (6, 18), but Germany's national asthma guideline emphasized its low validity compared with the bronchial challenge test (6).

KEY MESSAGES

- Whole-body plethysmography (WBP) has been widely implemented in Germany from the 1980s onwards. During bronchial challenge tests it is considered to be a more sensitive procedure than spirometry; the evidence for its added diagnostic value is, however, unclear to date.
- The change in the specific airway resistance sR_{AW} during bronchial challenge testing is captured by whole-body plethysmography. Including sR_{AW} in the interpretation of the bronchial challenge test makes it possible to exclude bronchial asthma with high certainty (negative predictive value [NPV] = 97.8%; 95% CI 94.5% to 99.1%) while sensitivity is substantially increased, at 95.2% (95% CI 88.3% to 98.1%).
- The change in FEV_1 alone—which can also be measured by using spirometry—shows a clearly lower certainty for the purpose of excluding the disorder (NPV = 81.3%; 95% CI 76.0 to 85.7). The sensitivity was 44.6% (95% CI 34.4% to 55.3%).
- Improving the positive predictive value of the diagnostic evaluation in suspected bronchial asthma remains a challenge because even including sR_{AW} in the diagnostic analysis of WBP has not improved specificity.
- The added diagnostic value of whole-body plethysmography in suspected bronchial asthma was confirmed for routine clinical practice for the first time. For the diagnostic procedure this means that primary care physicians should refer patients with suspected asthma and normal results on spirometry to specialist chest physicians for the purpose of bronchial challenge testing and analysis in the whole-body plethysmograph.

It is well known that an increase of 100% in R_{AW} corresponds with a smaller decrease in FEV_1 of less than 20%; this decrease has been reported to be 16% and is similar for sR_{AW} (21). The sensitivity analysis, however, still shows clear inferiority compared with $PC_{100}sR_{AW}$. Accordingly, the reaction during whole-body plethysmography seems to be more closely linked to asthma than is the case for the reaction on spirometry. However, the positive predictive value for the bronchial challenge test did not increase as a result of including sR_{AW} . The explanation is the lower specificity of sR_{AW} compared with FEV_1 . False positive diagnoses may result from post-infectious or generally present bronchial hyperreactivity, gastro-esophageal reflux, and vocal cord dysfunction. According to Bayes' theorem (23), the positive predictive value of the bronchial challenge test using $PC_{20}FEV_1$ as the evaluation criterion is 70% if the pretest probability of asthma is 30% (20). Nensa et al. also found in a diagnostic experimental study including 74 preselected patients that determining sR_{AW} did not result in improved specificity (11). Improving the positive predictive value in bronchial asthma therefore remains a challenge.

One limitation of our study is the fact that no complete follow-up data were obtained for 91 patients. These patients were on average younger and more of them had bronchial asthma, but this difference did not reach significance. In principle, responders' resultant lower pretest probability may have resulted in an overestimate of the negative predictive value. Furthermore, patients were not invited for a follow-up clinical examination because of organizational and financial reasons. Also, follow-up bronchial challenge testing might be regarded as ethically problematic in the absence of a clinical indication, because of possible adverse effects. Additionally, it became clear that bronchial challenge testing alone is not a perfect reference standard but will always have to be interpreted in the overall context of the clinical symptoms, since 30 patients had bronchial hyperreactivity at t_0 in whom no bronchial asthma was diagnosed. The problem of false-positive results could not have been resolved by using repeated bronchial challenge testing after a year. The only option for setting the diagnostic precision of a reference standard (14, 24) is therefore a detailed medical history, documenting the clinical course, in the sense of a delayed-type of diagnostic study as assessed by an expert panel. It should also be borne in mind that the results come from a secondary analysis. However, it still is obvious that WBP confers a high added diagnostic value not only per se (9) but especially when paired with a bronchial challenge test.

Conflict of interest statement

The authors declare that no conflict of interest exists.

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