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To cite this article: S. A. van Nederveen-Bendien, J. Vahl & H. G. M. Heijerman (2018): Specific airway resistance is a better outcome parameter in bronchial provocation testing compared to FEV₁ in patients with bronchial asthma, Journal of Asthma, DOI: [10.1080/02770903.2017.1414238](https://doi.org/10.1080/02770903.2017.1414238)

To link to this article: <https://doi.org/10.1080/02770903.2017.1414238>



Published online: 17 Jan 2018.



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Specific airway resistance is a better outcome parameter in bronchial provocation testing compared to FEV₁ in patients with bronchial asthma

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ABSTRACT

Objectives: Asthma is a chronic inflammatory disease characterized by airway hyperresponsiveness (AHR). A bronchial provocation test (BPT) is used to test for AHR. However forced expiratory volume in one second (FEV₁), used as outcome parameter is effort-related, in contrast to specific airway resistance (sRaw). This research was conducted to provide insight in the usefulness of sRaw as an outcome parameter in BPT. **Methods:** A total of 85 patients performing a BPT were included in the study. Bronchial reactivity was defined as the provocative dosage or provocative concentration causing a 20% decrease in FEV₁ (PC-20) or a 100% increase in sRaw (PC+100). **Results:** No significant response in either FEV₁ or sRaw was found in 20 patients (24%). Twenty-nine patients (34%) only had a positive response for sRaw; 24 out of these 29 patients recognized their symptoms. 36 patients (42%) showed a positive response for both PC-20 and PC + 100. **Conclusions:** Twenty-nine patients (34%) showed a significant increase in sRaw without a fall in FEV₁. As performing sRaw is not a routine investigation, these patients are at risk of being excluded from a diagnosis of asthma. We suggest performing sRaw for patients without a fall in FEV₁ during BPT when they report recognizable symptoms.

ARTICLE HISTORY

Received 25 August 2017
Revised 15 November 2017
Accepted 3 December 2017

KEYWORDS

Bronchial provocation test; airway hyperresponsiveness; asthma diagnosis; airway resistance; body plethysmography; physiology

Introduction

Bronchial provocation testing (BPT) is usually performed either to confirm or exclude airway hyperresponsiveness (AHR), an important characteristic of asthma (1). The test implies administering a substance in increasing dosages (usually methacholine or histamine) to evoke a response that is measured after each new concentration. Commonly the forced expiratory volume in one second (FEV₁) is obtained; however, this procedure is effort-dependent and could possibly lead to variability in the obtained results. Moreover, deep inspiration has the potential of changing airway caliber: a transient bronchodilatation followed by a more protracted bronchoconstriction that can last up to 2 hours (2). Apart from effort-dependence, the FEV₁ is not a direct but an indirect measurement of increased airway resistance. A more direct test is available although not widely used: specific airway resistance (sRaw). This measurement is independent of effort or motivation and is easily obtainable using body plethysmography. However, little is known about the clinical relevance of detecting an abnormal response in airway resistance and its role in assessing AHR. Also, studies comparing FEV₁ and Raw are scarce (3–5). The

American Thoracic Society (ATS) guideline on methacholine challenge testing states that both parameters are useful but FEV₁ seems more suitable to exclude asthma in healthy subjects because of the less complicated equipment required (6,7). On the other hand, sRaw is more sensitive in detecting bronchoconstriction (6). A recent German study also found sRaw, by the use of methacholine, to be the most sensitive parameter to detect AHR (3). Our study was performed to compare FEV₁ and Raw in BPT using histamine. We hypothesized that sRaw would be more sensitive in detecting AHR than FEV₁.

Methods

Eighty-five patients who visited the outpatient clinic with respiratory symptoms suggestive of asthma and who performed a BPT using histamine were included in the study. All patients had a normal spirometry (FEV₁/FVC ratio > LLN (lower limit of normal)) without significant reversibility, which justifies additional pulmonary function testing with a BPT.

Only patients aged ≥ 16 years were eligible. Patients with a FEV₁ <50% or below 1.2 L were excluded, as was

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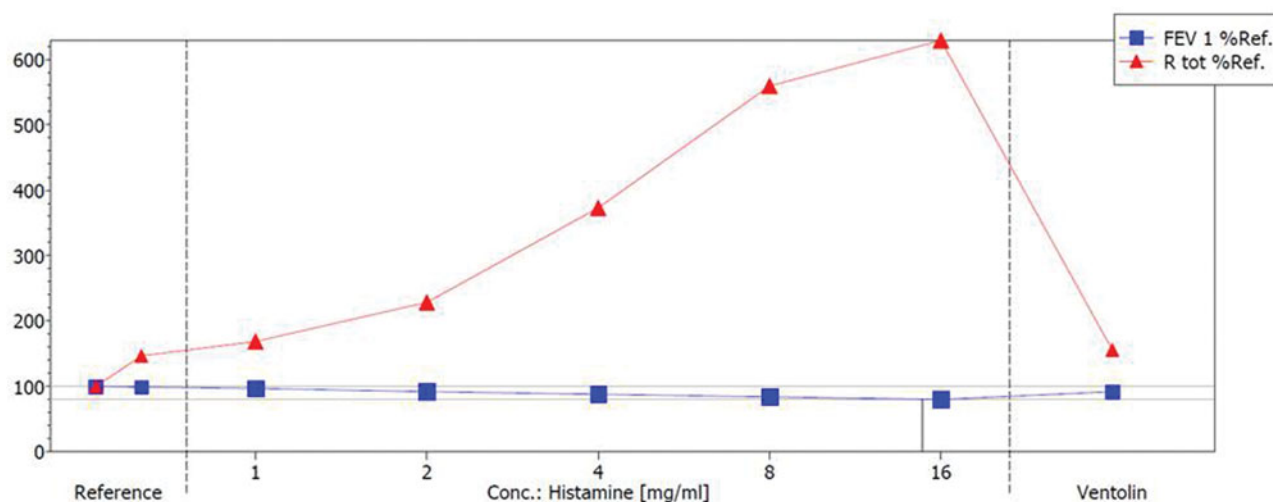


Figure 1. Forced expiratory volume in one second versus specific airway resistance during bronchial provocation testing, showing a response in sRAW but not in FEV₁.

a recent (i.e., within the last 3 months) myocardial infarction. Smoking and use of inhalation medication (e.g., inhaled steroids, adrenergic agents) were no exclusion criteria. The study was approved by the local medical ethics committee and all subjects gave written informed consent.

All patients performed spirometry to obtain baseline values and to exclude spirometer-induced asthma. Also basic information was obtained such as patient demographic details, smoking status, use of inhalers, and presenting symptoms like wheezing, cough, and shortness of breath.

The local protocol for performing BPT was followed (8). Histamine was delivered using a Hudson nebulizer (type micro, output: 130 mg/ml) on tidal breathing during 2 minutes.

Patients received an increasing dosage (interval: 5 minutes) of histamine up to a maximum of 16 mg/ml; the dosage at the start (minimum of 0.03 and maximum of 2.0 mg/ml) depended on a number of variables: FEV₁/VC, FEV₁, reaction on saline, and use of medication. sRaw, specific conductance (sGaw), Raw, conductance (Gaw), and intrathoracic gas volume (ITGV) were recorded by body plethysmography. As airway resistance is dependent on thoracic gas volume, a volume correction is made to obtain specific airway resistance which is the main outcome parameter in this study. ($Raw = sRaw / TGV$ (thoracic gas volume)). Before measuring Raw the bodybox was closed to allow the temperature to stabilize and to minimize disturbances. A reduction of $\geq 20\%$ in FEV₁ (provocative concentration with 20% decline, PC-20) or increase of $\geq 100\%$ in sRaw (provocative concentration of 200% of original sRaw, PC + 100) was considered a positive reaction. The cutoff value of an increase of $\geq 100\%$ in sRaw is based on earlier studies, where a doubling of airway resistance had the best agreement with a 20% decline in FEV₁ [9]. After the PC-20 or PC + 100 was achieved, or

when 16 mg/ml was applied, either salbutamol 400 µg, or ipratropiumbromide 80 µg was administered via metered dose inhaler and spacer. An example of the results of a BPT of one of the study subjects is shown in Figure 1.

Furthermore, patients were asked if they experienced symptoms like shortness of breath and cough during the test, and if so, if these specific symptoms were recognized as the reason for seeking medical advice.

After each dosage, firstly Raw and secondly FEV₁ were obtained. Both were performed twice. To minimize the effect of measuring FEV₁ on airway resistance, this specific order was followed throughout the entire test.

Data analysis

Prior to commencing the study, it was estimated that a sample size of 80 participants would be adequate. This sample size was based on previous studies (3,9). SPSS was used for all statistical analyses. Differences between groups were analyzed via chi-square test. Differences were considered significant for $P < 0.05$.

Results

Eight-five patients were included in the study. Patient characteristics are visualized in Table 1. Sixty-three percent of the subjects were female. Seventeen percent were actively smoking, leaving the remainder former smoker or never smoker. Twenty-nine percent was currently using inhaled corticosteroids (ICS). No other medication known to affect the magnitude of airway responsiveness was used.

Specific asthma symptoms were recorded, including shortness of breath, wheezing, coughing, known allergies, asthma during childhood, and familial predisposition. Shortness of breath and cough were the most frequent symptoms (81% resp. 82%) (Table 1).

Table 1. Patient characteristics.

Patient characteristics (n = 85)	Mean (range)	n (%)
Age	43.3 (16–81)	
Sex (F)		55 (63)
BMI	26.9 (17–43)	
Currently smoking		15 (17)
Use of ICS		25 (29)
Known allergy		27 (31)
Symptoms		
Cough		70 (82)
Wheezing		50 (58)
Asthma in childhood		16 (19)
Familial predisposition		21 (25)
Shortness of breath		69 (81)
Parameters of lung function		
FEV ₁ at baseline (L, % pred)	3.29 (1.50–6.87) 95% (69–132)	
FEV ₁ /FVC (%)	74.72 (63.82–88.75)	
sRaw at baseline (kPa/L*s, % pred)	0.64 (0.12–3.33)	
	119% (40–212)	

Table 2. Response versus symptoms.

Total: 85	FEV ₁ –/sRAW –	FEV ₁ –/sRAW +	FEV ₁ +/sRAW +
n (%)	20 (24)	29 (34)	36 (42)
Recognizable symptoms +	9 (45)	24 (83)	35 (97)
Recognizable symptoms –	11 (55)	5 (17)	1 (3)

Table 2 shows that 20 patients (24%) had no significant response in FEV₁ and sRaw, of which 9 reported recognizable symptoms. Twenty-nine (34%) only had a positive response for sRaw, without a significant fall in FEV₁. Twenty-four (83%) of these reported recognizable symptoms. The remaining 36 patients (42%) had both positive PC-20 and PC + 100, all except one reporting recognizable symptoms.

The mean PC-20 of patients who showed a significant response in both FEV₁ and Raw was 2.97 mg/ml, with a PC + 100 of 1.83 mg/ml. In those only positive for Raw the PC + 100 was 4.18 mg/ml (Table 3).

We compared the group positive for FEV₁ and Raw with those only responsive for Raw. We found no significant difference in use of ICS ($p = 0.30$) or in smoking status ($p = 0.52$); see Table 4.

On average, the procedure lasted 90 minutes, compared with 45–60 minutes normally.

Table 3. Mean responses.

	Mean (Range)
PC-20 (in group both FEV ₁ and Raw positive, mg/ml)	2.97 (0.13–13.7)
PC + 100 (in group both FEV ₁ and Raw positive, mg/ml)	1.83 (0.25–8.0)
PC + 100 (in group only Raw response, mg/ml)	4.18 (1.1–15.0)

Table 4. Differences in ICS use and smoking status.

	FEV ₁ +/sRAW +	FEV ₁ –/sRAW +	FEV ₁ –/sRAW –
Total	36	29	20
Use of inhaled corticosteroids (n, %)	16 (44)	9 (31)	0 (0)
Active smokers (n, %)	8 (22)	4 (14)	3 (15)

Discussion

In this study, we performed BPT measuring both FEV₁ and Raw. In our clinic, common practice is using FEV₁, and hence PC-20, to confirm AHR as an indirect measure of airway inflammation. Although the differential diagnosis of AHR is wide (e.g., COPD, heart failure, postinfectious causes) the combination of AHR and symptoms typical for asthma is usually enough to commence therapy. Often, significant reversibility in FEV₁ is absent during spirometry, and symptoms reported are nonspecific (10). A negative BPT safely excludes asthma (11,12) and warrants further investigation or empirical therapy for alternative causes (e.g., antibiotics when infection is suspected or proton pump inhibitors for esophageal reflux as cause of chronic cough). However, in our research 29 patients (34%) showed no response in FEV₁ but did report recognizable symptoms during the procedure and had a significant increase in Raw. Had Raw not been assessed, these patients would have been excluded of having AHR and asthma and possibly exposed to further diagnostic tests and/or therapies.

It is notable that still 45% of the patients with no significant response in neither FEV₁ or Raw, reported recognizable symptoms during BPT (Table 2). However this group consists of only 20 patients, which is too small to lead to conclusions. Moreover, in relation to the other groups FEV₁–/Raw+ and FEV₁ +/Raw+, the proportion of patients with recognizable symptoms is much smaller (45% compared to 83% resp 97%).

When, on clinical basis, after a negative BPT the suspicion of asthma remains high, one should always consider additional diagnostic tests as impulse oscillometry, exercise testing, indirect mannitol provocation testing, or RV/TLC ratio. Interestingly the findings of Perez et al. (13) already showed that elevated RV (Residual volume) or an abnormal RV/TLC ratio might be a better parameter than FEV₁/VC to diagnose distal airway obstruction and small airway disease in patients with asthma. This might also explain the discordance, one can experience, between asthma symptoms and abnormal FEV₁/FVC ratio.

It is known that use of ICS could mask underlying AHR (19); however, we found similar rates in the group positive for both Raw and FEV₁ and the group only responsive for

Raw. The use of ICS was much lower in those negative for both parameters. We also compared the two groups for smoking status, which is known to be a cause of AHR (14). However, the proportion of smoking patients was relatively low, especially in the non-responsive group, possibly indicating an alternative cause for their symptoms than AHR such as the smoking itself. Moreover we tried to mimic a real-life situation in our study, so it could be extrapolated to daily practice of the pulmonary physician. Patients referred to our hospital for diagnosing asthma often use inhalation medication and may be smoking.

We found that PC-20 and PC + 100 in the groups only responsive for 1 parameter were higher than the dosages found in the group responsive for both FEV₁ and Raw (Table 3). This finding is coherent with data obtained by Goldstein et al. (5) and indicates a more sensitive airway when both parameters are positive, possibly related to more severe asthma.

According to the ATS guideline, the PC-20 of 5.8 mg/ml indicates borderline AHR (7). For Raw, no qualification is mentioned. A positive PC + 100 without PC-20 combined with symptoms concordant with asthma might incorporate a risk of over-diagnosis, as was found previously (15). Also, it has been suggested that FEV₁ is a more specific parameter for predicting the future development of asthma than Raw. Khalid et al. found in patients with a negative BPT but with a 10–20% decline in FEV₁ an association with a future diagnosis of asthma (16). In this study, the decline in sGaw in negative BPT had no clinical significance. (sGaw = specific airway conductance: the reciprocal of Raw, Gaw, is divided by thoracic gas volume (TGV) to obtain sGaw).

On the other hand, it has also been appreciated that obtaining more data during BPT increases the sensitivity of this test (positive predictive value). To our knowledge there are only three other studies directly comparing the diagnostic value of FEV₁ and Raw in BPT (3–5). Goldstein et al. performed a retrospective analysis of metacholine inhalation challenges and added FEF_{25–75%}, FVC, sGaw, and TGV to FEV₁, thereby increasing sensitivity from 60.6% using only FEV₁ to 97.2% using all 5 parameters (5). Nensa and Parker showed comparable results to our study. The first study was performed in a population of patients with suspected asthma or chronic cough, with a significant group (43%) only responding to metacholine by sRaw and not by FEV₁ (3). The study of Parker, analyzed 248 patients referred for BPT (with metacholine). They found that 22% of patients ($n = 40$) only had a reduction in sGAW without a significant change in FEV₁ (4). Our study is the first study confirming these results with histamine instead of metacholine and taking into account recognizable symptoms during the test. In general, the strength of BPT lies more in excluding asthma

than in confirming it, through a higher negative predictive value than positive predictive value caused by the alternative causes of AHR.

Differences in Raw and FEV₁ might reflect changes at different levels of the tracheobronchial tree during BCT. FEV₁ is dependent on what happens upstream from the choke point (the point of airway collapse during forced expiration), whereas the Raw reflects the resistance of the entire length of the airway. It is unclear if this could explain the differences in behaviour between Raw and FEV₁. An alternative explanation might be the bronchoprotective effect of a forced inspiration in people with mild asthma leading to a bronchodilatation leaving the FEV₁ uninfluenced and thus leaving only Raw to show responsiveness (17).

A mean PC + 100 of 4.18 mg/ml in patients only responsive in Raw seems a considerable low concentration indicating a reactive airway. This finding, in combination with recognizable symptoms and a history suggestive of asthma might cause the clinician to start therapy with ICS. On the other hand one should be aware of the risk of over-diagnosing asthma using Raw in BPT. Further research is needed to assess the value of Raw in BPT, for instance to investigate what happens with the Raw in this specific group after treatment with ICS and the behavior of Raw in healthy non-asthmatic controls. Whenever interpreting pulmonary function tests, pretest probability of asthma including asthma symptoms should be taken into consideration.

Our study has some limitations. First, in the absence of a spirometry showing significant reversibility, a gold standard for diagnosing asthma is lacking. Asthma remains a syndrome with more and less specific symptoms and findings from laboratory results and pulmonary function tests challenging the clinician in deciding when to start therapy with ICS. Recent studies even argue that the diagnostic accuracy of BPT can be improved by combining direct and indirect provocation tests (18). Secondly, Raw is a calculated value derived from the slope (and hence Raw) of the flow-versus-box pressure diagram. This line is drawn between two points chosen by convention, which in our institution is defined as the line connecting the most right and left points on the flow-versus-box pressure diagram. Third, the selection of patients in our clinic was during a random period and included every BPT performed, but only those with complete data were included leading to possible selection bias.

Conclusion

In conclusion, a significant response in sRaw without a response in FEV₁ was demonstrated in 34% of patients tested for AHR. These patients are at risk

of being excluded from a diagnosis of asthma, but much is unknown about the utility of Raw in assessing AHR. Treatment with ICS might be considered in these patients.

Declaration of interest

We hereby declare that none of the authors have received any financial support or other benefits from commercial sources for the work reported on in this manuscript; neither do they have any financial interest, which could create a potential conflict of interest.

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