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Acoustic rhinometry in the evaluation of nasal lysine aspirin challenge

Abstract

Background: Nasal lysine aspirin (Lys-ASA) challenge is an alternative to oral and bronchial challenges in the diagnosis of hypersensitivity to acetylsalicylic acid (ASA) and other non-steroid anti-inflammatory drugs (NSAIDs). The aim of the study was to evaluate the sensitivity and specificity of acoustic rhinometry as an objective method of evaluation of nasal Lys-ASA challenge.

Material and methods: We enrolled 20 patients with ASA-induced asthma confirmed by oral challenge (ASA-S group), 5 patients with allergic rhinitis without hypersensitivity to NSAIDs, and 5 healthy individuals (ASA-NS group). All the subjects underwent challenge with placebo (0.9% NaCl) or 14.4 mg of Lys-ASA applied in a spray into both nostrils (total dose: 16 mg of ASA). Measurements of nasal volume bilaterally were performed with an acoustic rhinometer before and 1, 2, 4, and 24 hours after the challenge. For further calculations we used the sum of both nasal volumes at 2 to 5 cm from the nostrils.

Results: The mean total nasal volume in the AIA group before and 1, 2, 4, and 24 hours after the challenge was 7.75, 6.21, 7.11, 7.12, and 7.24 cm^3 following placebo, respectively, and 7.24, 5.77, 6.31, 6.27, and 6.98 cm^3 following Lys-ASA, respectively ($p=0.048$ and $p=0.02$ at 2 and 4 hours, Lys-ASA vs. placebo, Wilcoxon test). With the cutoff value of nasal volume reduction of 10%, the test sensitivity was 70%, the specificity was 60%, the positive predictive value was 77.78%, and the negative predictive value was 50% at 1 hour after the challenge.

Conclusions: Acoustic rhinometry with the measurement of nasal volume at 2 to 5 cm from the nostrils proved insufficiently sensitive or specific to be used as the sole method for evaluation of nasal Lys-ASA challenge.

Key words: aspirin, acoustic rhinometry, nasal challenge

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Introduction

Hypersensitivity to acetylsalicylic acid (ASA) and other non-steroid anti-inflammatory drugs (NSAIDs) is an important factor associated with increased risk of severe asthma [1]. The mechanisms underlying the pathogenesis of this process are unclear. According to the commonly accepted Szczeklik's hypothesis, inhibition of cyclooxygenase-1 (COX-1) by ASA leads to reduced formation of protective prostaglandins (PGE_2) and increased formation of proinflammatory cysteinyl leukotrienes (Cys-LT) [2]. Other authors believe that ASA changes the structure of COX-2, which results in increased synthesis of lipoxygenase pathway products [3]. The disturbance of proportions between the protective lipoxins and the proinflammatory mediators may also be important [4]. The gold standard in the diagnosis of intolerance of ASA and other NSAIDs is blinded placebo-controlled challenges [5]. Oral ASA challenge is time-consuming and, in addition to lower respiratory tract symp-

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toms, it triggers nasal symptoms (blocked nose, watery discharge, pruritus, sneezing) and cutaneous symptoms (urticaria, oedema). Inhalation and nasal challenges are an alternative to oral challenge. The first studies evaluating the upper respiratory tract response concerned the assessment of oral ASA challenges [6]. Świerczyńska et al. [7] investigated a group of 23 patients with ASA hypersensitivity and observed in 8 of them symptoms confined to the upper respiratory tract only. The availability of lysin aspirin (Lys-ASA), which is more readily soluble than ASA itself and is characterised by a near-neutral pH, has made it possible to conduct the first studies investigating nasal challenge [8–11]. Pawłowicz administered Lys-ASA nasally to patients with ASA hypersensitivity confirmed by oral challenge. An FEV_1 reduction of at least 15% was observed in all subjects, a significant increase in nasal airways resistance (NAR) of more than 400% in two of them, and urticaria in one of them [8]. Kowalski et al. [9] performed nasal Lys-ASA challenge (at the dose of 12 mg) in a group of 6 subjects with ASA intolerance and observed the characteristic symptoms: blocked nose, watery discharge, and sneezing. They also observed cell migration, including eosinophil migration (51% v. 24%, $p<0.03$), increased eosinophil cationic protein (ECP) levels (140.9 μg/l v. 9.3 μg/l) and increased tryptase activity (16 U/l v. 2 U/l, $p<0.01$) in nasal washings obtained at subsequent time points (every 15 minutes) following the challenge. No similar changes were observed in the control group composed of aspirin-tolerant subjects. Milewski et al. [10] performed nasal challenge with Lys-ASA at the dose of 16 mg in a group of 41 patients with confirmed ASA intolerance. An upper respiratory tract symptom score and rhinomanometry were used to evaluate the test results. The test was positive if at least a 40-per cent reduction in flow in at least one of the nasal passages was observed (compared to the value obtained following administration of saline) in combination with clinical symptoms. The sensitivity and specificity of the method was 78% and 95.6%, respectively, with a high positive predictive value (78.6%). Rhinomanometry could not be performed in 10 of the subjects potentially qualified for the challenge (as much as 19.6% of the subjects) because of the considerable obstruction of at least one of the nasal passages or because of the considerable discrepancies between individual nasal flow values (exceeding 40%). Of note is the fact that blocked nose in patients with ASA intolerance is quite common due to coexistence of nasal polyps and chronic sinusitis. Alonso-Llamazares et al. [11] performed nasal challenge with increasing doses of Lys-ASA (0.1 ml at the following concentrations: 5, 25, 50, and 100 mg/ml of Lys-ASA) in a group of 20 patients with ASA hypersensitivity. The test results were based, as in the previous paper, on clinical symptoms and rhinomanometry. The sensitivity and specificity of the method was 80% and 92.5%, respectively, with positive and negative predictive values of 84.2% and 90.2%, respectively. Casadevall et al. [12] evaluated challenge results using acoustic manometry, successfully used previously for the evaluation of nasal challenge with inhalation allergens [14, 15]. In a group of 15 subjects with ASA intolerance, they performed nasal challenge with 25 mg of Lys-ASA and evaluated clinical symptoms and nasal volumes. With the assumption of a reduction in nasal volume of at least 25% (according to the definition of a positive challenge result) the sensitivity and specificity of the method was 73% and 94%, respectively. The follow-up period in the study was only two hours following the challenge.

Nasal lysine aspirin challenge seems particularly indicated in patients with a potentially low ASA sensitivity threshold, with low spirometric values coupled with a high risk of post-challenge systemic reactions. Further studies are, however, necessary to look for better methods of nasal Lys-ASA challenge assessment than those described so far, which would allow for easy and safe performance of the test and provide, at the same time, a relatively high sensitivity and specificity. The aim of our study was to investigate acoustic rhinometry as an objective method for evaluation of nasal lysine aspirin challenge results in patients with aspirin hypersensitivity.

Material and methods

We enrolled 30 subjects in the study: 20 patients with aspirin-induced asthma confirmed by oral challenge (ASA-S group), 5 patients with allergic rhinitis (positive skin tests using seasonal allergens) without hypersensitivity to NSAIDs, and 5 healthy individuals (ASA-NS group). No history of hypersensitivity to aspirin or other NSAIDs was defined as the absence of intolerance symptoms following the ingestion of ASA or other NSAIDs. Table 1 summarises the characteristics of the study group. Preparation of the subjects for the challenge involved discontinuation of drugs that might affect the test results. The subjects had been on stable doses of anti-asthmatic medication (inhalation glucocorticosteroids and reliever medication). Antileukotrienes, antihistamines, and a-ago-

Table 1. Basic characteristic of the study group

	ASA-S	ASA-NS	p
n	20	10	–
Age (years ± SD)	44.39 ± 10.26	38.35 ± 13.06	p = 0.877^{+}
Sex (women:men)	11:9	6:4	p = 0.568$^{\#}$
Asthma	**20**	**0**	**p = 0.0001**$^{\#\#}$
Allergy*	8	5	p = 0.09$^{\#\#}$
FEV_1 before challenge (L/min)	**3.61**	**3.97**	**p = 0.049**$^{+}$
FEV_1 before challenge (% of normal value)	75%	98%	–
FEV_1 1 hour after challenge (L/min)	**3.52**	**3.92**	**p = 0.036**$^{+}$
FEV_1 hour after challenge (% of normal value)	74%	97%	–
Number of polypectomies (mean, median, min.-max)	**2.61 (0; 0–8)**	**0.76 (0; 0–2)**	**p = 0.035**$^{+}$

P value was calculated with: χ^2 test, fisher test, U Mann-Whitney test; atopy was defined as at least one positive (≥ 3 mm) skin prick test with standard battery of allergens; ASA-S — patients with ASA-induced asthma; ASA-N — healthy subjects; SD — standard deviation

nists were discontinued 1 week, 2 weeks, and at least 48 hours before the challenge, respectively. The subjects had not been using nasal and systemic glucocorticosteroids for at least 2 weeks before the challenge, which was performed in the stable period of the disease avoiding potential exacerbations that might be brought about by infectious or allergic factors. All the subjects underwent nasal challenge with 14.4 mg of lysine aspirin (Aspisol®, Bayer, Germany) administered as a spray into both nostrils (equivalent to a total dose of 16 mg of ASA). The challenge proper was preceded by a challenge with the aspirin solvent only (0.9% NaCl) performed the day before. The dose of aspirin we selected was based on our own experience and the studies by Picado et al. [13] and Milewski et al. [10].

The objective evaluation of the challenge results was performed by acoustic rhinometry. The measurements of the total nasal volume before and 1, 2, 4, and 24 hours after the challenge with placebo or Lys-ASA were performed with an SRE2000 acoustic rhinomanometer (RhinoMetrics, Denmark). For the purposes of further analysis, in order to minimise the potential effect of the circadian cycle of nasal volume changes on the results, we used the sum of volumes of both nasal cavities measured at the depth of 2–5 cm from the nostrils.

The statistical analysis was performed using Statistica 6.0 software (StatSoft Inc., Tusla, OK, USA) using methods of descriptive statistics, the Wilcoxon test for two groups of related variables, and the U Mann-Whitney test for two groups of unrelated variables. In order to evaluate nasal Lys-ASA challenge for the diagnosis of hypersensitivity to aspirin we calculated the sensitivity, specificity, and accuracy of the test as well as the positive and negative predictive values for numerous selected criteria. Using SPSS 13.0 (SPSS Inc., Chicago, IL, USA) we constructed receiver operating characteristic (ROC) curves.

The study protocol had been approved by the Ethics Committee of the Medical University of Łódź (resolution number RNN/128/03/KE dated 10 June 2003). Each of the subjects provided consent to participate in the study having read the relevant information about it.

Results

We analysed total nasal volume (the sum of volumes of the right and left nasal cavity) measured at 2–5 cm from the nostrils. Rhinometry was not performed in 2 subjects (in 1 subject from the ASA-S group and 1 from the ASA-NS group) due to a failure of the rhinometer on the day of the challenge. The mean total nasal volume in the ASA-S group following placebo was: 7.74, 6.21, 7.11, 7.12, and 7.24 cm^3 and 7.24, 5.77, 6.31, 6.27, and 6.98 cm^3 following Lys-ASA (before and 1, 2, 4, and 24 hours after the challenge, respectively; Table 2, Figure 1). These values were significantly lower on the day of placebo administration 1 hour after the challenge versus baseline and on the day of Lys-ASA administration 1, 2, and 4 hours after the challenge ($p < 0.05$; Wilcoxon test). When we compared individual time points between the day of Lys-ASA challenge and the day of placebo administration in the ASA-S group, we observed significant differences at 2 and 4 hours after the challenge only ($p=0.048$ and $p=0.02$; Wilcoxon test). The mean total nasal volume in the ASA-NS group following the administration of placebo was: 7.46, 7.04, 6.57, 7.10, 7.55 cm^3 and 7.55, 6.61, 6.53,

Table 2. Mean volumes of nasal cavities (2–5 cm from nostrils) in patients from ASA-S and ASA-NS groups after placebo and Lys-ASA challenge (baseline *v.* consecutive time points, Wilcoxon's test)

	ASA-S Placebo day	p	ASA-S Lys-ASA day	p	ASA-NS Placebo day	p	ASA-NS Lys-ASA day	p
Before	7.74	–	7.24	–	7.46	–	7.55	–
1 hour	6.21	**0.002**	5.77	**0.0003**	7.04	0.17	6.61	**0.04**
2 hours	7.11	0.18	6.31	**0.002**	6.57	0.21	6.53	0.37
4 hours	7.12	0.13	6.27	**0.002**	7.1	0.44	7.09	0.515
24 hours	7.24	0.38	6.98	0.18	7.55	0.26	6.38	**0.011**

ASA-S — patients with ASA-induced asthma; ASA-s — healthy subjects; Lys-ASA — lysine aspirin

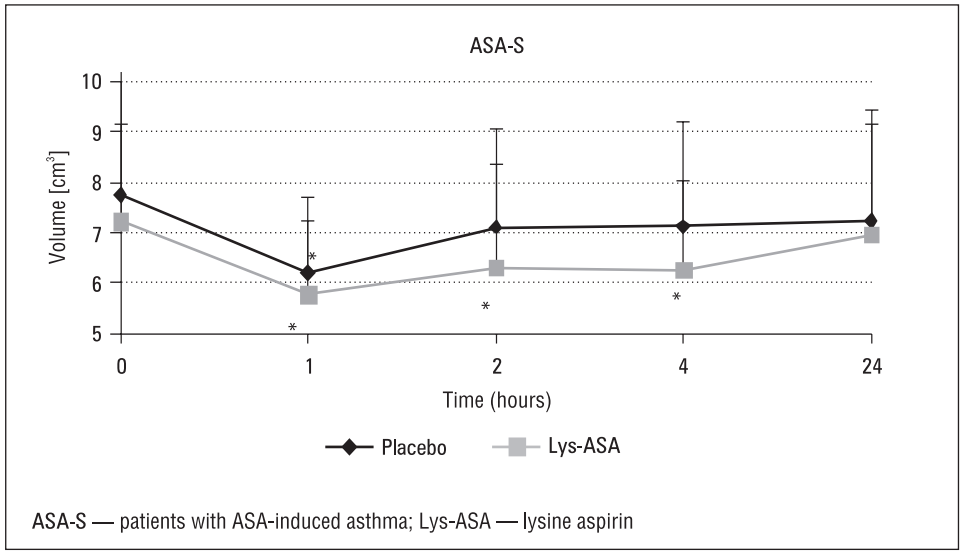


Figure 1. Mean (+ SD) volumes of nasal cavities (cm^3) in ASA-S group after placebo and Lys-ASA challenge (*$p < 0.05$, baseline *v.* consecutive time points, Wilcoxon's test)

7.09, 6.38 cm^3 following the administration of Lys-ASA (before and 1, 2, 4 and 24 hours, respectively; Table 2, Figure 2). These values were significantly lower on the day of Lys-ASA administration 1 hour and 24 hours after the challenge versus baseline ($p < 0.05$; Wilcoxon test). When we compared individual time points between the day of Lys-ASA challenge and the day of placebo administration in the ASA-NS group, we observed significant differences at 24 hours after the challenge only ($p = 0.01$; Wilcoxon test). We found no significant differences in nasal volumes when we compared the study groups (ASA-S v. ASA-NS) at individual time points ($p > 0.05$; U Mann-Whitney test).

When we analysed the individual stages of the diagnostic process, we calculated the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value depending on the adopted criteria for positive nasal challenge using acoustic rhinometry. We analysed the total nasal volume measured at 2–5 cm from the nostrils. As subsequent cutoff values for the assessment of the sensitivity and specificity of the rhinometric analysis we proposed nasal volume reductions by 10%, 20%, and 30% versus baseline before the challenge (Tables 3–5). Figure 3 shows the ROC curve. A reduction of more than 40% was observed in 2 subjects from the study group 1 hour after Lys-ASA challenge only, which is why this criterion was no longer analysed. Assuming a 10-per cent reduction in total nasal volume as the cutoff criterion, we obtained the following values 1 hour after the challenge: sensitivity 70%, specificity 60%, accuracy 66.67%, positive predictive value 77.78%, and negative predictive value 50%.

Discussion

In the study presented above we used acoustic rhinometry as one of the objective methods for evaluating challenge results. Rhinometry has been

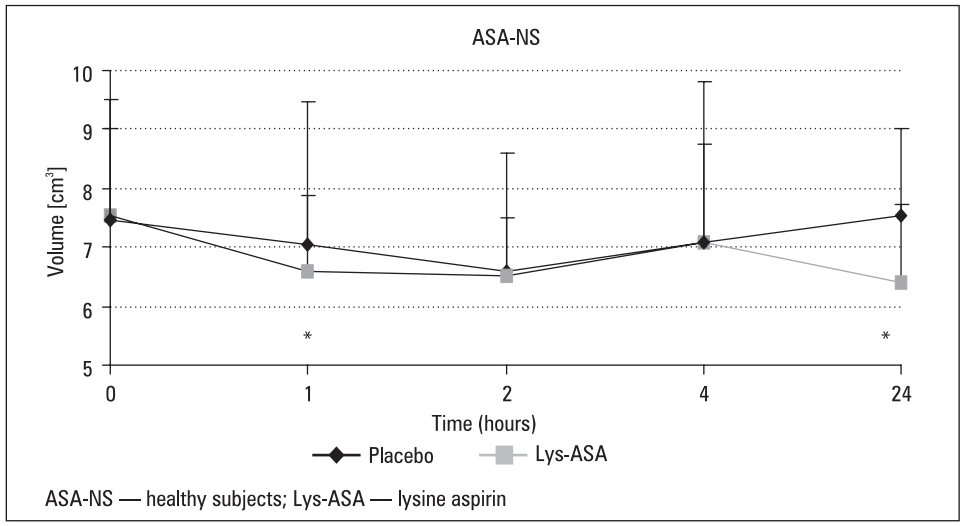


Figure 2. Mean (+ SD) volumes of nasal cavities (cm^3) in ASA-NS group after placebo and Lys-ASA challenge (*$p < 0.05$, baseline *v.* consecutive time points, Wilcoxon's test)

successfully used in the evaluation of allergen challenges [14, 15]. There have also been reports of using this method during Lys-ASA challenge [12]. Acoustic rhinometry is an alternative to rhinomanometry, which in many cases (particularly in patients with ASA hypersensitivity and nasal polyps) cannot be used due to a considerable obstruction of at least one nasal passage and significant variations in nasal air flow. This has been reported by Milewski et al. [10]. Rhinometric assessment could not be performed in as many as 10 patients preliminarily qualified for the nasal challenge procedure, which accounted for 19.6% of the study group. Acoustic rhinometry is based on the phenomenon of sound wave reflection. In contrast to rhinomanometry, it may be performed in patients with a very considerable or complete blockade of one of the nasal cavities. It also has its limitations: the presence of pathological spaces (e.g. perforation of the nasal septum) significantly interferes with the diagnostic possibilities. Factors affecting the sensitivity of the method include the nasal cycle or the numerous alternate natural changes in the volume of nasal cavities that depend on the filling of submucosal venous plexuses. The cycle is characterised in humans by an individually variable frequency and intensity. The result of acoustic rhinometry is depicted as a curve reflecting the cross-sectional surface area of the nasal cavity relative to the distance from the nostrils. Two deflections are distinguished: one corresponding to the nasal valve (deflection I) and the other corresponding to the inferior turbinate region (deflection C). These deflections are reflected by cross-sectional surface areas I and C (CA-I and CA-C). In practice, following allergen challenge, the greatest changes reflected by the mucosal oedema occur at the region of the inferior turbinate head and at a distance of about 3 cm from it [16]. International expert groups recommend that the allergen should be administered into both nostrils during the challenge and that the challenge results should be evaluated for both sides of the nose [17]. We followed these recommendations while conducting the challenge and rhinometry in our study. Due to the large variability of the results and the absence of unequivocal international standards for the evaluation of rhinometry results during Lys-ASA challenge, further studies investigating the possibilities and limitations of the method are warranted. There are ongoing discussions about the optimal method for the measurement of the mucosal oedema observed after the challenge. The most common methods involve measurement of the cross-sectional surface area at the head of the inferior turbinate [18, 19] or of the volume of the nasal cavities [12, 20]. In our study we evaluated the sum of the volumes of both nasal cavities 2–5 cm from the nostrils. Following this procedure seems to minimise the effect of the nasal cycle on the test results. Over the course of the nasal cycle a reduction in the volume of one nasal cavity is coupled with an increase in the volume of the contralateral one, and the sum of both measurements is near-constant. Evaluation of the transverse area at the level of the inferior turbinate requires a foolproof identification of the C deflection on the curve. This process should be confirmed by rhinoscopy, and the next step should involve determination of the course of the nasal cycle in the

Table 3. Sensitivity and specificity of nasal Lys-ASA challenge. Positive result of challenge is predefined as 10% decrease in mean volume of nasal cavities

	Criterion: 10% decrease							
Time point	**After 1 hour**		**After 2 hours**		**After 4 hours**		**After 24 hours**	
Test result	**NPT+**	**NPT–**	**NPT+**	**NPT–**	**NPT+**	**NPT–**	**NPT+**	**NPT–**
ASA-S	14	5	10	9	11	8	9	10
ASA-NS	4	5	4	5	4	5	5	4
Sensitivity	73.68%		52.63%		57.89%		47.37%	
Specificity	55.56%		55.56%		55.56%		44.44%	
Accuracy	67.86%		53.57%		57.14%		46.43%	
PPV	77.78%		71.43%		73.33%		64.28%	
NPV	50%		64.28%		66.67%		71.43%	

PPV — positive predictive value; NPV — negative predictive value. ASA-S — patients with ASA-induced asthma; ASA-NS — healthy subjects

Table 4. Sensitivity and specificity of nasal Lys-ASA challenge. Positive result of challenge is predefined as 20% decrease in mean volume of nasal cavities

	Criterion: 20% decrease							
Time point	**After 1 hour**		**After 2 hours**		**After 4 hours**		**After 24 hours**	
Test result	**NPT+**	**NPT–**	**NPT+**	**NPT–**	**NPT+**	**NPT–**	**NPT+**	**NPT–**
ASA-S	8	11	6	13	5	14	5	14
ASA-NS	2	7	4	5	3	6	3	6
Sensitivity	42%		31.58%		26.32%		26.32%	
Specificity	77.78%		55.55%		66.67%		66.67%	
Accuracy	53.57%		39.28%		39.28%		39.28%	
PPV	80%		60%		62.5%		62.5%	
NPV	61.11%		72.22%		70%		70%	

PPV — positive predictive value; NPV — negative predictive value. ASA-S — patients with ASA-induced asthma; ASA-NS — healthy subjects

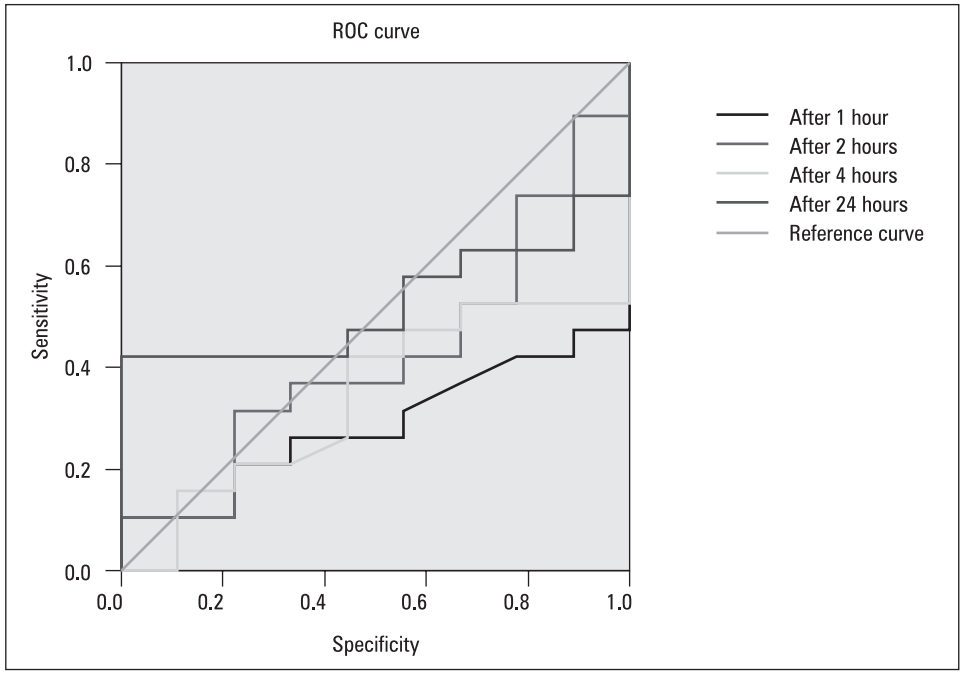
individual patient. This is possible in research studies. In the case of a routine diagnostic evaluation, however, the procedure is definitely too time-consuming. The proposed simplification of the evaluation by using the sum of the volumes of both nasal cavities at a depth of 2–5 cm (which in the overwhelming majority of cases includes the deflection C region and its neighbourhood) would make the test more efficient.

The analysis of acoustic rhinometry showed a significant reduction in total nasal volume between 1 and 4 hours after the challenge in patients with ASA hypersensitivity. We observed a reduction from 7.24 cm^3 before the challenge to 5.77, 6.31, and 6.27 cm^3 after administration of Lys-ASA (1, 2, and 4 hours after the challenge, respectively). When we compared individual time points between the day of Lys-ASA challenge and the day of placebo administration in the ASA-S group, we observed significant differences only 2 and 4 hours after the challenge. Changes in nasal volumes were also observed in the ASA-NS group on the day of Lys-ASA challenge 1 and 24 hours after the challenge. The placebo day was characterised by a marked variability of results, which considerably interfered with the assessment of response following administration of ASA. When we analysed the significance of acoustic rhinometry for the evaluation of ASA hypersensitivity and adopted a cutoff value of 10% reduction in total nasal volume, we achieved a sensitivity of 70% and specificity of 60%, the positive predictive value was 77.78% and the negative predictive value was 50% at 1 hour following the challenge. Increasing the cutoff threshold for the positive result of the test to 20% resulted in a decrease in sensitivity of the method to about 40%. These results are inconsistent with the previous observations by Casadevall et al. [12], who used a 25-per cent cutoff value and showed a 94-per cent specificity and 73-per cent

Table 5. Sensitivity and specificity of nasal Lys-ASA challenge. Positive result of challenge is predefined as 30% decrease in mean volume of nasal cavities

	Criterion: 30% decrease							
Time point	**After 1 hour**		**After 2 hours**		**After 4 hours**		**After 24 hours**	
Test result	**NPT+**	**NPT–**	**NPT+**	**NPT–**	**NPT+**	**NPT–**	**NPT+**	**NPT–**
ASA-S	5	14	2	17	1	18	0	19
ASA-NS	1	8	2	7	1	8	1	8
Sensitivity	26.32%		10.53%		5.26%		–	
Specificity	88.89%		77.78%		88.89%		–	
Accuracy	42.86%		32.14%		32.14%		–	
PPV	83.33%		50%		50%		–	
NPV	63.63%		70.83%		69.23%		–	

PPV — positive predictive value; NPV — negative predictive value. ASA-S — patients with ASA-induced asthma; ASA-NS — healthy subjects



Variable	AUC	SE	p	95% CI
After 1 hour	0.287	0.095	0.073	0.100–0.473
After 2 hours	0.427	0.114	0.539	0.204–0.650
After 4 hours	0.342	0.103	0.184	0.139–0.545
After 24 hours	0.526	0.108	0.825	0.315–0.738

Figure 3. ROC curve has been analysed to evaluate the usefulness of Lys-ASA challenge as a diagnostic tool in consecutive time points (1, 2, 4 and 24 hours after the challenge). Table presents area under the curve (AUC), statistical error (SE), p value (p) and 95% confidence interval (CI)

sensitivity of acoustic rhinometry. It is unclear, however, what criteria related to acoustic rhinometry were adopted by Casedavall et al. in their paper [12]. In the methods section they described measuring the nasal cavity volume from the tip of the device to a depth of 12 cm without explaining whether this applies to the measuring capabilities of the device or to the test result assessment criterion. On one hand, it seems that the method should be associated with a high risk of considerable variability of results, as the sensitivity of the rhinometer decreases with depth because at a level

of 10–12 cm from the nostrils the sound wave dissipates in relatively larger spaces of the nasopharynx. On the other hand, the results presented by the authors show that the method, in practice, led to the achievement of a satisfactory sensitivity and specificity of the diagnostic test.

Our results suggest that acoustic rhinometry should not be the only method for the evaluation of aspirin challenge results. The relatively low sensitivity and specificity of the test may falsify the results of the challenge. It seems justified to use rhinometry as an objective supplementary method and to include it in the model of a multivariable parameter for the evaluation of the test results (including, for instance, clinical parameters and inflammatory cell migration). Analysing the available bibliography we could hypothesise that increasing the dose of aspirin might have allowed us to better differentiate between the two study groups. However, this would have been associated with a significant increase in the severity of clinical symptoms and an increased risk of severe side effects.

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