Rhinomanometrically controlled nasal provocation test: a comparison of results using this method in patients with seasonal allergic rhinitis and in healthy volunteers

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SUMMARY

The aim of the study was to assess the clinical application of the rhinomanometrically controlled nasal provocation tests using allergens according to guidelines given by the German Working Group 'Nasal and Bronchial Provocation Tests' in 1990. The study was performed on 24 patients with seasonal allergic rhinitis and 17 patients who were non-allergic volunteers. The results of this method were confronted with a complex allergologic diagnosis based on anamnesis, clinical examination, skin tests and serum IgE. Only a small difference in responses between allergic patients and non-allergic volunteers was observed. The results acquired suggest that the rhinomanometrically controlled nasal provocations with allergens should be used with great care.

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INTRODUCTION

The application of rhinomanometrically controlled nasal provocation tests with allergens has been of great interest to allergologists, as a method of possible improvement in diagnosing allergic rhinitis. In 1990, the German Working Group 'Nasal and Bronchial Provocation Tests' ('Die Nasale und Bronchiale Provokationstests') set guidelines for performing nasal provocation test with allergens in patients with upper airway diseases [1]. After using these guidelines routinely for several years, we have found some inconsistencies between the results of nasal provocation test and other diagnostic methods. Based upon literature, no unequivocal statement could be found regarding the benefits of using rhinomanometrically controlled nasal provocation tests. Therefore, the present study was undertaken, to assess the usefulness of rhinomanometrically controlled nasal provocation tests in diagnosing allergic rhinitis based upon a comparison with other accepted diagnostic methods in seasonal allergic rhinitis (SAR).

MATERIAL AND METHODS

Two groups, a total of forty one patients, were investigated upon. The SAR-group consisted of 24 patients with seasonal allergic rhinitis (15 females and 9 males, aged between 16 and 42, with a mean value of 29.5). Diagnosis of the group was based upon SAR patient's history with typical seasonal appearance of symptoms, physical and laboratory findings including anterior and posterior rhinoscopy, X-ray, and skin tests with common aerial allergens. Comparison of symptoms (recorded in personal calendars including ocular and nasal symptoms) with the intensity of pollination during pollen season preceded the study, as well as an elevated level of serum IgE. Skin tests, which revealed a wheal reaction to a particular allergen, equal or bigger than the control reaction to 0, 1% histamine solution were considered positive. IgE values were compared to the actual cut-off values for adults given by the laboratory, these values varied during selecting subjects to the study between 90 and 105 IU/ml, depending on reagents used in

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particular series. Seven healthy, non-allergic volunteers (6 females and 11 males aged between 22 and 60 with a mean age value of 31.5) formed the control group. Abnormalities in nasal cavity and paranasal sinuses detectable by means of rhinoscopy were excluded in both groups.

In the present study, the results of rhinomanometrically controlled nasal provocation tests (RCNPT) have been compared to the results of a complex allergological diagnosis based upon anamnesis, physical examination, skin test results, and IgE level. In the SAR-group, RCNPTs were performed, following the previously mentioned guidelines [1]. The aerial allergens for intranasal testing were selected, based upon detailed anamnesis and allergological investigation. During the RCNPTs, only specific allergens were used that were present in atmospheric air during the symptomatic period of a particular patient, and which caused a skin reaction equal to or bigger than that of the control solution. All allergens used were purchased from Allergopharma, Germany. The control group did not receive any allergen. In both groups, the nasal airflow and resistance values were measured at intervals of 15 min, and simultaneously, local (sneezing and mucus production) and systemic symptoms (as lacrimation, throat itching, conjunctivitis, urticaria, cough, wheezing) were observed. This procedure was carried out on the right or on the left nasal canal, depending on which side the airflow value was higher at the beginning of the measurements. Airflow and resistance values were measured using the rhinomanometer Rhinotest MP 500 (Joachim Ganzer KG Allergopharma, Germany) on patients who were seated after a 30 min-period of adaptation to the conditions in the testing room. All tests were performed out of pollen season. Further analysis was carried out on airflow

Table 1. Rhinomanometrically controlled nasal provocation test results in the SAR-group (F-female, M-male, R-right, L-left).

No	Sex	Age	Side	Allergen	Rhinomanometrical measurements (timepoint of the observation)								Symptom score	Result
					Nasal airflow (cm^3s^{-1})				Nasal resistance ($Pa\ cm^{-3}s$)					
					0 min	15th min	30th min	45th min	0 min	15th min	30th min	45th min		
1	M	23	R	–	307	172	-	–	0.25	0.44	–	–	–	*
2	F	39	R	Trees II	174	178	272	232	0.44	0.44	0.27	0.32	0	negative
3	F	22	R	Trees I	154	128	117	85	0.50	0.62	0.68	0.93	1	negative
4	M	31	L	Trees II	196	263	94	58	0.39	0.28	0.83	1.50	0	positive
5	M	22	L	–	241	144	–	–	0.31	0.53	–	–	–	*
6	M	23	R	Linden	436	596	525	259	0.17	0.12	0.14	0.30	2	positive
7	M	21	L	Grasses	330	285	142	214	0.22	0.26	0.53	0.35	0	positive
8	M	24	L	–	314	217	–	–	0.24	0.35	–	–	–	*
9	M	22	L	Linden	92	113	196	64	0.83	0.68	0.39	1.25	1	positive
10	M	35	R	–	452	271	–	–	0.17	0.27	–	–	–	*
11	F	19	R	Grasses	188	194	124	130	0.41	0.39	0.62	0.57	1	negative
12	F	37	R	Trees II	119	98	82	44	0.68	0.83	0.93	1.87	2	positive
13	F	34	L	Grasses	362	317	176	193	0.20	0.24	0.44	0.39	1	positive
14	F	36	L	Trees II	312	321	139	80	0.24	0.23	0.57	0.93	4	positive
15	F	38	R	–	149	56	–	–	0.53	1.50	–	–	–	*
16	F	29	R	Linden	195	226	145	72	0.39	0.34	0.53	1.07	1	positive
17	F	31	L	–	378	225	–	–	0.20	0.34	–	–	–	*
18	F	41	R	–	184	126	–	–	0.41	0.62	–	–	–	*
19	F	37	R	Linden	89	88	92	102	0.93	0.93	0.83	0.75	1	negative
20	F	42	R	Maple	56	88	72	38	1.50	0.93	1.07	2.50	1	positive
21	F	22	L	Acacia	240	225	218	138	0.31	0.34	0.35	0.67	1	positive
22	F	36	R	Grasses	286	233	274	126	0.26	0.32	0.27	0.62	1	positive
23	M	16	R	Poplar	250	200	252	141	0.30	0.39	0.30	0.53	1	negative
24	F	27	L	Grasses	294	290	208	54	0.25	0.25	0.37	1.50	0	positive

and resistance data obtained at a different pressure value of 75 Pa. The interpretation at the test results followed the guidelines of the Working Group 'Nasal and Bronchial Provocation Tests' [1]. In short, a test result was regarded as positive, when at least one of the following three conditions were fulfilled:

1. The application of the allergen caused a fall of nasal airflow by more than 40% as compared to the value after administration of a pure solvent;
2. Nasal resistance rose by more than 60% under the above conditions;
3. The sum of scores describing clinical symptoms was bigger than 3.

The RCNPTs were not continued in cases where, after administration of a pure solvent, the nasal airflow decreased by more than 20% or nasal resistance rose by more than 30%.

The sensitivity of the RCNPTs was assessed, as a proportion of the number of subjects with positive test result in comparison to the number of all 'really sick' subjects tested [2]. 'Really sick' meaning - 'diagnosed as having SAR according to signs of symptoms of complex diagnosis'. To compare distribution of test results in both groups, the Chi-square test was used with the significant level value less or equal to 0.05 regarded as statistically significant [3].

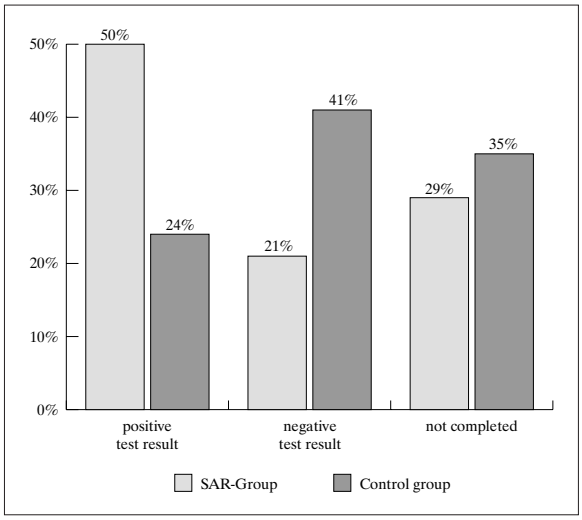
RESULTS

The results of the SAR-group (patients exposed to specific allergens) are shown in table 1. In 7 out of 24 people (29%) the testing procedure was stopped due to a decrease in nasal airflow by more than 20% or a rise in nasal resistance by more than 30% after the administration of a pure solvent. In table 1, the results of these patients are marked with asterisks. The test results in five further patients (21%) from SAR-group were regarded as negative. The positive nasal provocation test was noted in 12 patients (50%). The sensitivity of the RCNPTs equaled 50%. The results of the control group (unprovoked healthy subjects) are shown in table 2. In 6 out of 17 patients (35%) who were observed for 15 min, nasal resistance rose by more than 30%, and/or nasal airflow decreased by more than 20%, although no substance had been administered. According to the guidelines during 'real' RCNPTs, such reactions should be considered as hyperreactivity of nasal mucosa to a solvent allow us to break the procedure. In such patients, obser-

Table 2. Results in the control group (F-female, M-male, R-right, L-left).

No	Sex	Age	Side	Allergen	Rhinomanometrical measurements (timepoint of the observation)								Symptom score	Result
					Nasal airflow (cm^3s^{-1})				Nasal resistance (Pa $cm^{-3}s$)					
					0 min	15th min	30th min	45th min	0 min	15th min	30th min	45th min		
1	F	27	R	–	442	265	–	–	0.17	0.28	–	–	–	*
2	M	26	R	–	338	389	322	264	0.22	0.19	0.23	0.28	0	negative
3	M	25	R	–	238	221	244	192	0.32	0.34	0.31	0.39	0	negative
4	M	28	L	–	432	372	380	340	0.17	0.20	0.19	0.22	0	negative
5	F	27	R	–	354	324	346	341	0.21	0.23	0.22	0.14	0	negative
6	F	30	L	–	196	196	206	96	0.39	0.39	0.37	0.83	0	positive
7	F	23	L	–	56	38	–	–	1.5	2.50	–	–	–	*
8	M	22	R	–	176	246	208	144	0.44	0.31	0.37	0.53	1	positive
9	M	60	R	–	297	604	4121	285	0.25	0.12	0.18	0.26	0	positive
10	F	32	R	–	225	224	164	198	0.34	0.31	0.46	0.39	0	negative
11	M	42	R	–	178	225	205	194	0.44	0.34	0.37	0.39	0	negative
12	M	43	L	–	256	109	–	–	0.29	0.74	–	–	–	*
13	F	29	R	–	304	238	–	–	0.25	0.32	–	–	–	*
14	M	30	R	–	164	232	94	70	0.46	0.32	0.83	1.07	0	positive
15	M	31	R	–	316	236	–	–	0.24	0.32	–	–	–	*
16	M	26	R	–	308	264	336	296	0.25	0.28	0.22	0.25	0	negative
17	M	37	L	–	420	254	–	–	0.17	0.30	–	–	–	*

Figure 1. The rhinomanometrically controlled nasal provocation test results in the SAR group as in comparison to the control group (unprovoked, healthy subjects).



vations were stopped at this stage. In further four unprovoked control subjects (24%), nasal airflow values decreased by more than 40%, and/or nasal resistance rose by more than 60%, compared to previous values. According to the guidelines, such a 'result' should be considered as 'positive'. In the remaining seven control subjects (41%), the results of observations were interpreted as negative, based upon both rhinomanometric measurements and absence of clinical symptoms. An overview of the results in both groups is presented in figure 1. There were no statistically significant differences in distribution of test results in both groups (chi-square = 5.99; $p > 0.05$)

DISCUSSION

Contradictory opinions regarding the clinical application of rhinomanometry can be found in literature. Small and Biskin observed two reaction patterns in patients with allergic rhinitis after a nasal provocation, and divided patients into 2 different groups - low and high responders [4]. They found out that a statistically significant correlation between the results of skin tests and nasal provocation tests is present only in high responders (75%). Pastorello et al. [5] proposed a score-system describing nasal secretion, nasal- ear- and throat itching, sneezing and conjunctivitis. They found no relationship between clinical symptoms and rhinomanometric measurements. However, after taking into consideration particular clinical symptoms, they found a moderate correlation (r = 0, 448) between the nasal blockage score and nasal resistance value. Samoliński et al. [6] claim that the only advantage of using rhinomanometrically controlled nasal provocation tests was the simplicity of statistical processing of obtained numerical data. In contrast, Olive-Perez [7] after comparing skin test results and specific IgE levels to RCNPTs, concluded that the latter were not only the best, but they could even replace other diagnostic methods. The Working Group 'Nasal and Bronchial Provocation Tests' of the German Society for Allergy and Immunity Investigations recommends that besides measurements of nasal airflow and resistance values, sneezing and mucus production should be additionally observed [1]. However, the latter seem to be regarded of secondary importance compared to rhinomanometry. Members of the Committee for Upper Airway Allergy (USA) are far more sceptic about the rhinomanometric measurements during intranasal provocation [8]. They stress that on intranasal provocations, rhinomanometric results can be contradictory to clinical status and in such cases the clinical manifestations are decisive. The results of the present study support the view that rhinomanometric measurements should be taken with appropriate scepticism. The differences between results in patients with SAR and non-allergic, healthy control subjects were surprisingly small. Only in one case (patient N(14), could the test result be interpreted as positive, based not only on rhinomanometrical measurements but also the presence of clinical symptoms. This suggests that one of the possible causes of the low sensitivity of the test might be due to too low a concentration of allergen in commercially available test solutions. On the other hand, however, the high percentage of results to be assessed as positive according to the guidelines, in subjects not exposed to any substance - that is, false positive results - suggests caution with using the present procedure. The numerous false-positive reactions in the control group suggest both considerable spontaneous variability of the nasal patency during the rhinomanometrically controlled nasal provocation. Moreover, the sensitivity of the method also seems to be low, as it was calculated to 50% based upon the low number of positive reactions to specific allergens in patients with allergy confirmed based on the complex diagnostic procedure [2]. This is clearly visible in figure 1. In six control subjects (35%) the nasal patency decreased within 15 min by a value unacceptable even after giving a solvent, although no substance was administered to these subjects. Furthermore, four patients with false-posi-

tive results constituted 24% of the control group. Therefore, the contemporary guidelines for performing the RCNPTs with allergens are connected with a high risk of false-positive results. As a consequence, irrelevant substances can be mistakenly considered as allergens of clinical importance. On the other hand, the absence of positive nasal provocation results in 5 out of 17 SAR patients who were exposed to specific allergens, also suggests a presence of false-negative results. This fact supports the low sensitivity of the method although it should be borne in mind that skin tests, serving here partly as a reference method, show also a considerable variability [9]. A possible explanation of the variability of nasal patency could be the circadian nasal cycle. According to different authors, one nasal cycle lasts from 1 to 5.5 hours [10,11,12], and the amplitude can change by up to 60% of the baseline airflow or resistance value [13]. This means that within half an hour the nasal patency can decrease or increase spontaneously by up to 60%. According to the guidelines, the rhinomanometrically controlled nasal provocation result is regarded as positive when the nasal airflow decreases by 40% within 15 min after intranasal allergen application. Therefore, if an irrelevant allergen is given during a declining phase of nasal cycle, a spontaneous decrease of nasal airflow could be falsely considered as a proof of a specific hypersensitivity to this particular allergen. Moreover, an obstructive reaction to a relevant allergen could be neutralized by increasing phase of the spontanous variability. Sipilä et al. [14] claimed that the physiological variability of nasal patency cannot bias results of nasal provocation. The interpretation of present results remains, however, in contradiction to this statement. A possibly better solution for performing reliable RCNPTs is the bilateral allergen application, with subsequent measurements of the total nasal patency as bilateral nasal airflow and resistance values seem more stable than unilateral [15,16]. Theoretically, the problem could be solved by the use of Fourier's analysis with approximation of the baseline nasal cycle and analysis of its changes after a nasal provocation. In this case, a very sophisticated method of harmonic analysis would be necessary, according to which an individual provocation schema for each patient would have to be worked out.

CONCLUSION

The rhinomanometrically controlled nasal provocation tests carried out according to the guidelines of the Working Group 'Nasal and Bronchial Provocation Test' are characterized by both low sensitivity and high ratio of false-positive results in seasonal allergic rhinitis. Therefore, a set of new, more reliable guidelines seems to be needed to be put into life.

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