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Forced expiration through the nose is a stimulus for NANIPER but not for controls*

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SUMMARY

Objective: Is forced expiration through the nose a mechanical stimulus to which patients with nasal hyperreactivity react? Do parameters, such as peak nasal expiratory flow rate (PNEF), influence nasal airway resistance (NAR) in these patients?
Method: NAR, mucus production and sneezing were measured on 2 occasions two weeks apart. Measurements were conducted before and during a period of 10 minutes after 3 repeated PNEFs in 15 non-allergic non-infectious perennial rhinitis (NANIPER) patients suffering from nasal hyperreactivity, and in 15 controls.
Results: In NANIPER versus controls PNEF measurements attributed to a statistically significant increase in NAR. The main effect was within the first minute after stimulus, suggesting a neuronal mechanism. Mucus secretions and sneezing were hardly present. PNEF (highest of 3) and bronchial peak expiratory flow rate (BpEFR) are lower in NANIPER than controls but are correlated. Impaired bronchial capacity is likely to influence PNEF, resulting in a lower decrease of nasal patency.
Conclusion: PNEF depends on BpEFR and is an adequate mechanical stimulus for NANIPER patients, but not for non-rhinitic controls, resulting in a brief increase in NAR.

Keywords: hypersensitivity, nasal provocation tests, non-allergic perennial rhinitis, Peak Nasal Expiratory Flow Rate, rhinomanometry.

INTRODUCTION

In non-allergic, non-infectious perennial rhinitis (NANIPER) nasal complaints are closely related to exposure of the nasal epithelium to non-specific stimuli (Albegger, 1988). An understanding and appreciation of the importance of nasal hyperreactivity in this nasal disorder would seem to be necessary since, until now, the cause of NANIPER remains unknown and an organic substrate has not been found. Empirical therapies such as topical steroids and antihistamines appear to be insufficient and symptomatology, consisting of nasal reactivity symptoms, fluctuates from week to week (Blom et al., 1997). Avoiding non-specific stimuli seems till now the only rational, if not impossible, ad-vice to follow (Lund, 1994). An example of a non-specific – mechanical – stimulus one can avoid is blowing the nose hard. Blowing the nose is almost similar to testing peak nasal expiratory flow rate (PNEF), although the airway is usually temporarily obstructed by the fingers during nose blowing. Both involve a jet stream of air and mucus particles through both nostrils. When blowing the nose flows up to 5,61 l/s have been recorded (Pertuze et al., 1991). PNEF therefore could cause increased symptomatology (e.g. nasal blockage or production of secretions) in nasal hyperreactive patients due to their extremely sensitive nasal lining. There could be implications for routine nasal histamine challenge associated with the blowing of the nose to collect nasal secretions. Furthermore forced nasal respirations could influence nasal patency by affecting the blood content in sinusoid bloodvessels (Eccles, 1978).

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Therefore a study was designed in NANIPER patients and non-rhinitic controls, in which nasal airway resistance (NAR), the amount of secretion and the number of sneezes were measured before and after 3 repeated PNEFs. As PNEFs and NAR are influenced by lung function (Taylor et al., 1973) standard lung function parameters (bronchial peak expiratory flow rate (BpEFR) , forced 1 second expiratory capacity (FEV1) and forced expiratory vital capacity (FEVC)) were measured once pre-trial. We used PNEFs rather than actual nose blowing as a mechanical stimulus, because nose blowing itself is not a standardised stimulus. The procedure was repeated after 2 weeks in order to assess whether NAR and PNEF fluctuate in NANIPER and whether nasal reactions were reproducible. In addition, NANIPER patients were subdivided in an 'exacerbation' and 'remission' group depending on their own perception of nasal complaints.

Table 1. Study population characteristics

	NANIPER Value (± SD)	Controls Value (± SD)
SEX-Male	7	8
Female	8	7
Length (cm)	172.2 (± 7,3)	176.6 (±12.1)
Weight (kg)	72.4 (± 15,0)	72.8 (± 14.5)
Age (yr)	34.6 (± 9,1)	30.4 (± 11,4)
Tot IgE (E/mml)	55.3 (± 61,6)	116.3 (± 158,3)

Table 2.

Inclusion Criteria NANIPER and controls
- Age between 16 and 65 years
- Negative skin prick test and negative RAST score
- Symptoms for more than 1 year (NANIPER only)
- NANIPER exacerbation group: moderate to severe nasal complaints on entry (subjective)
- NANIPER remission group: mild complaints on entry (subjective)

Exclusion criteria NANIPER and controls
- The use of systemic or inhaled corticosteroids within the previous month
- The use of inhaled cromoglycates, astemkol or nedocromil sodium within the previous month
- Inability of the patient to stop taking medication affecting nasal function (e.g. xylometazoline)
- A serious and/or unstable disease and pregnancy or lactation
- Nasal surgery within the previous 3 months
- Significant anatomical abnormalities affecting nasal function
- Nasal polyps or a history of nasal polyps
- Nasal or paranasal sinus infection or abnormal sinus X-ray
- Abnormal laboratory results for blood: Na, K, Ca, total protein, albumin, urea, creatinine, bilirubin, alkaline phosphatase, aspartate aminotransterase, analine aminotransterase, gamma glutamyl transpeptidase, haemoglobin, red blood cell count, plasma cell volume, mean corpuscular volume, platelets, total white blood cell count, lympho & monocytes, neutro-, eosino- & basophils. urine: blood, protein and glucose
- Abnormal findings at physical examinaton
- Smoking
- Daily contact with physical or chemical irritants

METHODS

Patients and Controls

The study consisted of fifteen NANIPER patients and 15 non-rhinitic controls. Patients and controls were matched for sex, length, weight and age. Total IgE was lower in NANIPER than controls (Table 1). The NANIPER patients had experienced nasal complaints such as nasal obstruction, sneezing, and/or rhinorrhea for more than 1 year. These symptoms could not be attributed to an atopic rhinitis, nasal or paranasal sinus infection, anatomic disorders affecting nasal function, pregnancy or lactation, and/or systemic disorders. Inclusion and exclusion criteria were virtually identical to Wihl's (Wihl et al., 1987) and in accordance with previous studies (Blom et al., 1997; Braat et al., 1998), except for inclusion criteria 3-5, regarding pre-trial complaint scores and exclusion criteria 11, regarding non-smoking. Here NANIPER patients were divided into two groups, according to their own subjective feeling of having an exacerbation or a remission of nasal complaints on entry to the study. The controls met the same criteria, except for the nasal complaints (Table 2).

Study design

Medical histories were taken and lung function performed at visit 1. Nasal provocation procedures were performed at visit 1 and 2 with a two-week interval. These procedures were identical for patients and controls. Patients and controls entered the study in random order (Figure 1).

Lung function parameters

BpEFR, FEVI and FEVC were measured with the Vicatest 4 C peak flow meter. The highest of 3 BpEFR measurements was recorded. Analyses were made with percentages of the expected value. These percentages correct for sex and length. Controls were required to have a value ± 2 SD of the expected value. All controls met these requirements.

Nasal provocation procedure = PNEF

PNEFs were measured in sitting position after about 15 minutes of adaptation to the testing room. Nasal challenge consisted of 3 repeated PNEFs within 10 seconds. PNEF was measured under supervision and with a nasal peak flow meter slightly modified compared to Taylor (Taylor et al., 1973): a nasal

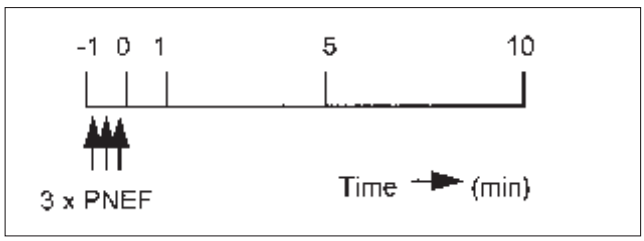

Figure 1. Provocation procedure at both visits: arrows point to 3 PNEFs. At t = -1, 0, 1, 5 and 10 minutes active anterior rhinomanometry measurements were performed.

CPAP-mask, ensuring an airtight fit, was connected to a mini-Wright flow meter. Air leakage through the mouth was therefore impossible. Test subjects were asked, following maximal inspiration, to exhale with maximum effort through the nose into the nasal mask. Highest of 3 PNEFs (by analogy to BpEFRs) were analysed.

Blockage Index

BI was introduced in order to correct errors due to lower respiratory tract impairment, variable effort and body size.
Blockage Index was calculated as follows:
BI = (BpEFR - PNEF)/BpEFR

Rhinomanometry, mucus production and sneeze counts

NAR was measured with active anterior rhinomanometry at low flow rates. This was performed immediately prior to (t = –1), immediately after (t = 0) and 1, 5 and 10 min after the 3 repeated PNEFs, using the rhinoscreen rhinomanometer (Jaeger, Würzburg, Germany). The average inspiratory nasal flow at 150 Pa of 4 breathing cycles in ml/s was registered for both nostrils and the figures obtained were combined to determine total nasal airway resistance in $mmH_2O/l/sec$. NARs at t = 0, 1, 5 and 10 minutes were analysed as percentages of baseline NAR. Mucus production was measured 10 minutes after the stimulus by weighing preweighed paper tissues with a precision balance (Mettler, Germany). Sneezes were counted.

Statistical analysis

Statistical analysis comparing data of the NANIPER patients versus controls and remission versus exacerbation in the NANIPER group was carried out using the Mann Whitney U-test. Correlations were calculated using Pearsons bivariate correlation coefficient. Percentile NAR results were pooled over both visits and changes in time after repeated PNEFs between NANIPER patients and controls were analysed with Biomedical Package software (BMDP), using a random coefficients model with a between grouping factor. $P < 0,05$ was accepted as significant.

RESULTS

Changes in baseline NAR and PNEF between the visits

No significant differences were found between baseline NAR and PNEFs in NANIPER patients and controls, on the 2 occasions.

Changes in NAR after 3 repeated PNEFs

After 3 repeated PNEFs, the NARs of NANIPER patients were significantly different compared to controls at all points in time (p = 0,045). Figure 2 shows pooled percentile NAR results of visit 1 and 2. NAR curves at visit 1 and 2 separately showed similar curves (results not shown). At visit 1, immediately after forceful blowing of the nose (t = 0) NAR increased significantly in the NANIPER group (p = 0.03), but not in controls. At the second visit the change did not fully reach significance (p = 0,12). In NANIPER patients, NAR returned to its baseline value soon after t = 1 min, demonstrating an instant increase of NAR after a mechanical stimulus. NAR in controls showed no significant changes over time.
Sneezing and rhinorhea did not occur to any significant extent 10 minutes after nasal challenge (results not shown).

Table 3. Results of nasal and lung function parameters (± SD)

	NANIPER		Controls	
Baseline NAR 1e and 2e visit (mmH20/l/sec)	21.6 (± 7.4)	26.5 (± 15.9)	25.5 (± 11.6)	23.8 (± 9.1)
PNEF 1e and 2e visit(l/min)	326.0* (± 93.6)	338.0* (± 75.3)	392.0* (± 76.7)	386.4* (± 83.7)
BI	0.35 (± 0.18)		0.36 (± 0.11)	
BpEFR	105.3* (± 18.5)		120.3* (± 19.3)	
FEV1	99.1 (± 9.6)		101.4 (± 6.15)	
FEVC	99.6 (± 12.2)		102.1 (± 8.6)	

* = $p < 0,05$

Bronchial and nasal peak flow rates (BpEFR and PNEF) and baseline NAR

Age and length corrected bronchial peak flow rates were significantly lower in the NANIPER group compared to controls (105,3 v. 120,3; p = 0,046). Absolute PNEFs were significantly lower in NANIPER patients compared to controls too on both visits (visit 1: 326,0 v 392,0; p = 0,029 and visit 2: 338,0 v. 386,4; p = 0,041). Baseline NAR was not different between patients and controls on either visit (visit 1: 21,6 v. 25,5; p = 0,25 and visit 2: 26,5 v. 23,8; p = 0,33) (See Table 3).
PNEF had a high positive correlation coefficient with BpEFR (r = 0,57) and less with FEV1 and FEVC, while baseline NAR and BpEFR showed a negative, but less correlation (r = -0,45) and even less with FEV1 and FEVC (Table 4). Correlations of baseline NAR and PNEF were non-significant and are not shown.

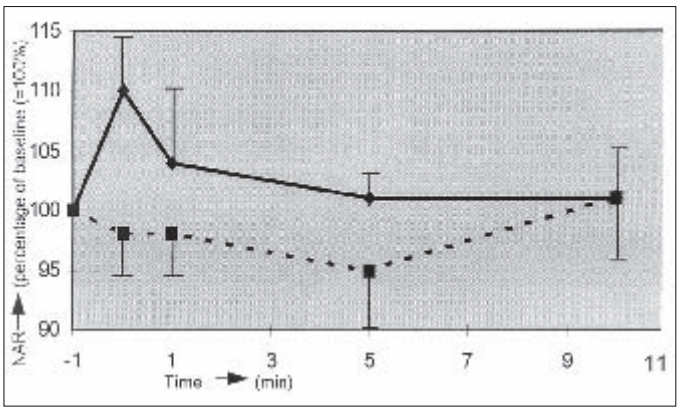

Figure 2. NAR (mean ± SE) in NANIPER patients (dots and bold line) and controls (dots and dashed line) before and after (t = 0, 1, 5 and 10 minutes) 3 repeated PNEFs. NAR in NANIPER increases immediately after the stimulus and returns to baseline at t = 1 min, while in controls this stimulus results in a small decrease of NAR.

Table 4. Pearson Correlation coefficients of bronchial and nasal parameters

↓ Nasal parameters/bronchial parameters →			
NANIPER+CONTROLS	BpEFR	FEV1	FEVC
PNEF	0.57*	0.45*	0.45*
Baseline NAR	-0.45*	-0.24	-0.25
BI	0.50*	0.19	0.20
NANIPER			
PNEF	0.39*	0.50*	0.35
Baseline NAR	-0.34	-0.33	-0.32
BI	0.55*	0.048	0.39*
CONTROLS			
PNEF	0.45*	0.50*	0.35
Baseline NAR	-0.34	-0.33	-0.32
BI	0.49*	0.36	0.42*

* = $p < 0,05$

Variables in NANIPER-subgroups

As stated previously NANIPER patients were divided in subgroups 'exacerbation' or 'remission' on the basis of their own assessment at visit 1. Interestingly, perception of nasal reactivity correlated poorly with clinical tests: no significant differences between the exacerbation and remission group were found for nasal parameters (PNEF and baseline NAR) or bronchial parameters (BpEFR, FEVI, FEVC, BI).

DISCUSSION

This study was performed to evaluate the effect of nose blowing/PNEF on nasal symptoms in NANIPER patients and controls. Mechanical stimuli and their effect on hyperreactive nasal mucosa have, to our knowledge, not been studied before in an experimental setting. In NANIPER patients we found a small, though statistically significant, increase in NAR after the mechanical stimulus of 3 PNEFs, but not in controls. NAR peaked immediately after the stimulus and then returned to normal within 1 minute. Significant mucus production or sneezing was not measured in the 10-minute test period. The routinely used method of collecting nasal secretions by gently blowing the nose could not be performed during the test period, because of possible interference with NAR measurements. On the other hand participants did not sense a wet nose nor an anterior drip was seen. Paper disks (Philip et al., 1993) could have been helpful in this respect, but not practical because of the short time span of 10 minutes in which 5 NAR measurements had to be performed.

PNEFs (Youlten, 1983; Frolund et al., 1987) and probably PNIFs too, are frequently used as means to measure nasal patency. PNIFs and PNEFs are quick, cheap and easy to perform (Wihl and Malm, 1988; Viani et al., 1990; Benson, 1971). PNIF measurements are mostly preferred over PNEF because nasal secretions frequently dirty peak flow meters and disturb measurements in PNEF. Moreover, PNIF correlates better with NAR than PNEF (Viani et al., 1990). However, some authors prefer PNEF, because PNIF is often complicated by alar collapse and extreme turbulence (Larsen et al., 1990). For assessment of nasal patency PNIF and PNEF are equally sensitive (Phagoo et al., 1997).

We found lower baseline values for PNEF and BpEFR in NANIPER patients compared to controls. Ahman (Ahman, 1992) found lower PNEFs in rhinitis suffers, compared to healthy controls. The relationship was less when average of 3 PNEFs was taken. BpEFRs showed a close correlation with PNEFs. This stresses that nasal peak flow rates depend on variations in lung capacity (Wihl and Malm, 1988). Consequently, impaired lung capacity in NANIPER patients could have reduced the size of the mechanical stimulus we studied. This means that the immediate increase in NAR could have been larger if PNEFs had been corrected for the decreased BpEFRs! Because of this and the relatively small study population studied, we think this immediate increase in NAR, though just not reaching significance in the second provocation series, is definitively present. Moreover the finding that NARs of NANIPER patients were significantly different compared to controls at all points in time ($p = 0,045$) confirms this.

Neither in NANIPER patients or controls, did we observe high correlations between baseline NAR and Blockage Index, as described by Forstad and Taylor in controls (Taylor et al., 1973; Wihl et al., 1987; Frostad, 1980). Contrary to our expectations, no differences were found in the peak flow or NAR measurements between the exacerbation and remission NANIPER subgroup. The small changes we found were not significant, probably as a result of the small numbers studied.

The rapid congestion-decongestion effect within 1 minute after a mechanical stimulus is independent of the normal physiological nasal cycle. Nasal cold dry air provocations evoke sudden nasal responses of the same kind in 'cold dry air susceptible' patients (Philip et al., 1993; Braat et al., 1998). This could suggest the same neuronal response of physical stimuli on the nose. Further studies need to be performed to assess whether other factors, e.g. environmental, determine nasal reactivity and whether neurogenic structures and mediators play a role in NANIPER.

In conclusion: PNEF depends on BpEFR and is an adequate mechanical stimulus for NANIPER patients, but not for non-rhinitic controls, resulting in a brief increase in NAR. Advising patients to blow their nose less hard seems clear, especially in NANIPER patients hampered by ongoing nasal complaints with little possibilities for therapeutic intervention. In patients with hyperreactive nasal mucosa this is an important factor to keep in mind during nasal challenges, which depend on blowing the nose to collect nasal secretions, and nasal patency measurements, such as PNEFs and PNIFs.

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