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The nasal response to exercise in patients with cystic fibrosis

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SUMMARY

This study has evaluated the nasal response to exercise in patients with cystic fibrosis (CF), a genetic disease in which factors such as chronic lung disease and/or nasal polyposis might be anticipated to modify nasal function responses. Measurements of nasal resistance (NAR) by posterior rhinomanometry and specific airway resistance (sRAW) were made before and 1, 5, 10, and 30 min after a 4-min period of exhausting legwork exercise (50% predicted maximal) in 19 CF patients (aged 11-29 years) and 10 healthy subjects (aged 11-31 years). One minute after exercise, healthy subjects showed a 54 ± 5% (mean ± SEM; standard error of the mean) relative fall from baseline in NAR and CF patients showed a 31 ± 8% relative fall from baseline ($p < 0.05$). There were no significant differences in the magnitude or pattern of recovery in NAR after exercise (1 to 30 min) between the groups, largely because of the variability in NAR responses in CF patients. Exercise did not result in significant changes in sRAW in either group. We also found that a history or presence of nasal polyposis does not significantly affect functional nasal responses to exercise. Our conclusion is that the CF genotype and its airway sequelae do not substantively affect the control of the nasal response to exercise.

INTRODUCTION

The nasal response to exercise has been characterized in healthy subjects (Dallimore et al., 1977; Forsyth et al., 1983; Hasegawa et al., 1985; Konno et al., 1982; Olson et al., 1987; Syabbalo et al., 1985; Togawa et al., 1981) and in patients with rhinitis and reversible airflow obstruction (Hasegawa et al., 1985; Konno et al., 1985; Strohl et al., 1988; Syabbalo et al., 1985; Togawa et al., 1981). There are few studies in patients with chronic lung disease. It has been suggested that patients with chronic obstructive lung disease may have a lower baseline nasal

resistance than healthy subjects, and that nasal resistance is lower in patients with lung disease to compensate for increased respiratory resistance (Drettner, 1970). We suspected that this circumstance may not be true in patients with cystic fibrosis (CF) for, in addition to progressive lower-airway obstruction, nasal mucosal inflammation and polyps are common manifestations of this genetically determined disease. In the CF patient, nasal resistance and/or the nasal response to exercise might be blunted, or otherwise altered, by the nasal sequelae of CF. In the present study we examined nasal and airway resistance before and after leg-work exercise in CF patients and age-matched healthy subjects.

METHODS

Subjects

Ten healthy, normal subjects (6 males and 4 females, aged 11–31 years) and 20 CF patients (11 males and 9 females, aged 11–29 years) participated in the study. Prior to study we obtained written consent, as approved by the Institutional Review Board for Human Investigation, University Hospitals of Cleveland. CF patients were recruited from the clinic population of the Cystic Fibrosis Center. The diagnosis of CF was on the basis of abnormal sweat test associated with abnormalities of lung function and/or intestinal absorption. All patients had routine pulmonary function testing performed near the time of this study. CF patients were in stable condition and could refrain from taking bronchodilators for 4 hours prior to study. One CF patient had baseline measurements only. Healthy subjects were recruited by word-of-mouth from the university environment. Healthy subjects with a history of recent respiratory illness, chronic respiratory complaints, or exercise intolerance were excluded from study. No healthy subject was on any medication.

Measurements

Transnasal pressure and bulk flow were measured by posterior rhinomanometry. Pressure and flow were displayed in an X-Y format on a storage oscilloscope (Tektronix 5A18N) and stored digitally (1,000 Hz) using an IBM XT microcomputer (Strohl et al., 1988). Twenty seconds of data were recorded during which the subject made inspiratory and expiratory efforts of varying magnitude through the nose at a rate of 0.5 to 1 Hz. Measurements were made while the subject was seated. Subjects were initially coached to achieve equal flow on both inspiration and expiration, even during maximal efforts. However, data were collected using sub-maximal efforts at flows where no flow limitation occurred. Changes in the pressure-flow characteristic associated with exercise were recognized by parallel shifts in the log values (Olson et al., 1987; Strohl et al., 1988). While each set of pressure-flow data could be quantitated at any point along the pressure-flow relationship, we obtained the pressure at an inspiratory

flow rate of 0.4 l/s as a representative value (Hoekje et al., 1987), and define this value as 'nasal resistance'. Values reported for each interval are the average of two sets of consecutive measurements.

Changes in specific airway resistance were monitored by body plethysmography, while the subject was seated, breathing through the mouth and wearing a noseclip. The product of thoracic gas volume and specific airway resistance (specific resistance: sRAW) was computed as described earlier by Cotes (1979). Three measurements of sRAW were obtained at each interval and the result reported is the average of these values.

Baseline measurements of nasal resistance were measured before and after measurements of specific airway resistance. Body plethysmography did not affect nasal pressure-flow measurements in any subject; hence, results of both control values for nasal resistance were averaged. Measurements of nasal and specific airway resistance were repeated at 1-, 5-, 10-, and 30-min intervals following exercise.

The exercise task was 4 min of cycle ergometry (Pedalmate, W.E. Collins). The work rate initially chosen for any given subject was approximately 50% of predicted maximal oxygen consumption (Jones et al., 1982). Exercise was performed without constraining the route of airflow and while breathing ambient air (20–23 °C, 30–40% relative humidity). Thus, a subject could breathe through the mouth or through the nose, although at these work loads and with brief exercise, a subject would generally breathe oronasally (Niinimaa et al., 1980).

Grouped results are expressed as the mean ± SEM, with SEM being the standard error of the mean. Comparisons between groups were analyzed with the Student's *t* test and the non-parametric Wilcoxon rank-sum test for two groups. The threshold for statistical significance was at $p < 0.05$. Examination of the recovery of nasal resistance was analyzed for each individual as the slope of changes in nasal resistance over time (1 to 30 min after exercise) and an intercept of resistance with the time axis was extrapolated from this data set.

RESULTS

All CF patients had abnormalities in one or more indices of lung function consistent with airway obstruction. The degree of airflow obstruction varied from mild ($FEV_1/FVC > 70\%$) to severe ($FEV_1/FVC < 50\%$). All but one CF patient showed air-trapping as indicated by a residual volume > 120% as predicted by Cotes (1979). In the CF patients, sRAW at baseline was 1.02 ± 0.14 kPa.s, and nasal resistance at baseline was 0.29 ± 0.05 kPa/l/s. Healthy subjects were not routinely screened with pulmonary function testing. In healthy subjects, sRAW at baseline was 0.55 ± 0.07 kPa.s, and nasal resistance at baseline was 0.45 ± 0.10 kPa/l/s. Baseline sRAW and nasal resistance data for each subject are presented in Table 1.

Table 1. Presentation of baseline sRAW and NAR in healthy subjects of CF patients.

cystic fibrosis patients					healthy subjects			
age (years)		sex	B-NAR*	B-sRAW**	age	sex	B-NAR*	B-sRAW**
	11	F	5.55	7.83	11	F	11.3	7.91
	11	F	9.22	10.22	15	M	3.17	7.61
	15	M	-	8.18	18	M	1.72	4.10
	16	F	2.59	3.44	19	F	4.68	5.67
	16	M	1.40	8.84	20	M	4.78	6.08
	17	M	2.16	10.30	22	M	5.22	2.58
	17	F	5.14	2.88	23	M	1.34	4.68
	18	M	2.88	4.30	26	F	2.50	5.03
	18	M	1.52	23.45	28	F	8.82	9.01
	20	F	2.96	5.72	31	M	2.72	2.84
	21	M	1.98	16.03				
	21	M	2.10	4.10				
	22	F	6.05	15.13				
	22	F	0.83	7.58				
	22	F	1.52	20.09				
	22	F	1.22	7.95				
	23	M	0.66	3.16				
	26	M	2.32	17.45				
	28	M	5.05	13.80				
	29	M	1.80	17.48				
all subjects								
N	20	20	19	20	10	10	10	10
mean	19.75		3.00	10.40	21.30		4.62	5.55
SEM	1.12		0.52	1.41	2.01		1.07	0.71
males only								
N	11	11	10	11	6	6	6	6
mean	21.09		2.19	11.55	21.50		3.16	4.65
SEM	1.47		0.37	2.09	2.23		0.65	0.79
females only								
N	9	9	9	9	4	4	4	4
mean	18.11		3.90	8.98	21.00		6.82	6.90
SEM	1.63		0.99	1.96	3.85		1.98	0.94

* Baseline Nasal Resistance (cm H_2O/l/s); 1 cm H_2O/l/s equals 0.098 kPa/l/s.
** Baseline sRAW (cm H_2O.s); 1 cm H_2O.s equals 0.098 kPa.s.

For the healthy subjects and for CF patients the association between baseline measurements of sRAW and nasal resistance did not reach statistical significance. Hence, there was no apparent relationship between sRAW and nasal resistance for either group.

Exercise resulted in a fall in nasal resistance in both groups of subjects. Nasal resistance was lowest when measured 1 to 5 min following exercise and returned to baseline values by 30 min. Exercise did not result in significant changes in sRAW in either group.

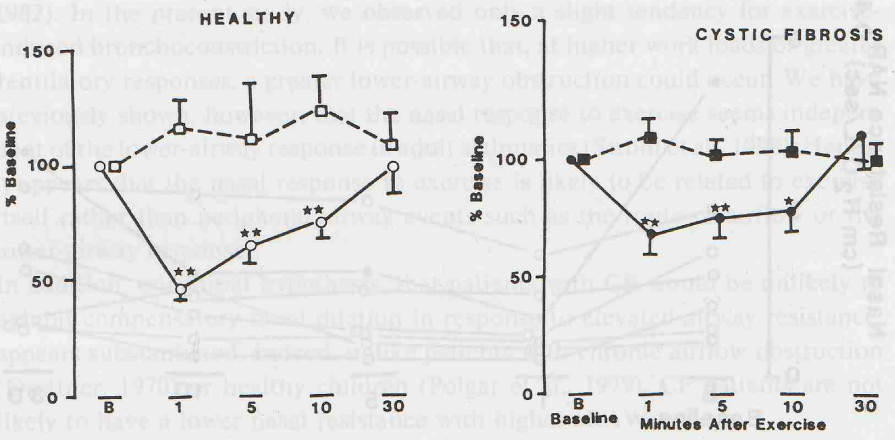

Figure 1. Relative changes (expressed as percent of baseline values, mean ± SEM) in nasal resistance (NAR, circles) and specific airway resistance (sRAW, squares) for healthy subjects (left graph, open symbols) and CF patients (right graph, closed symbols). (*) $p < 0.05$; (**) $p < 0.01$.

The relative changes in sRAW and nasal resistance, expressed as the percentage of baseline values, is shown in Figures 1A and 1B. There are no significant differences in the relative change in sRAW and nasal resistance between healthy subjects. We also examined this data for differences in the rate of change (absolute and relative) and intercept for nasal resistance from 1 to 30 min post-exercise and could find no differences between groups. This variability in the nasal response to exercise in healthy or CF patients was not a function of sRAW, age or nasal problems, including nasal polyposis. There is no significant difference in baseline nasal resistance for the healthy subjects compared to the CF patients, whereas baseline sRAW is significantly higher in the CF patients as compared to the healthy subjects ($p < 0.05$).

Within the group of patients with CF, six had a history of nasal polyposis and polypectomy with symptomatic relief of nasal obstruction; one additional patient had current symptoms and evidence of nasal polyps. Each responded to exercise with a fall in nasal resistance (Figure 2). The one patient with current symptoms and signs of nasal polyps showed the highest baseline nasal resistance and the greatest absolute fall in resistance with exercise. However, this patient exhibited a relative fall, 81% from baseline 1 min after exercise in nasal resistance, which was equivalent to one other CF patient with a history of polyposis, but without current symptoms.

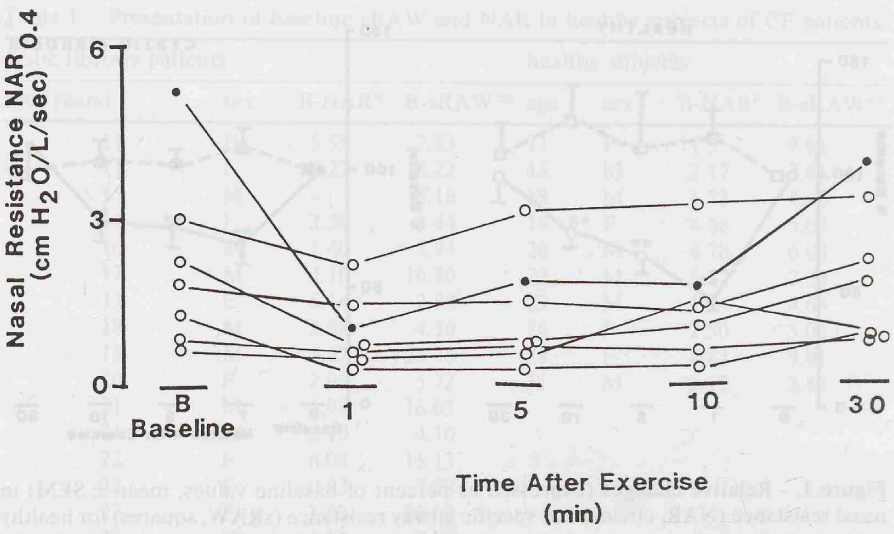

Figure 2. Individual values for nasal resistance before and after exercise for six CF patients, each with a history of polyps (open symbols) and one CF patient with symptomatic, evident polyposis (closed symbol). Conversion to SI units: 1 cm H_2O/l/s equals 0.098 kPa/l/s.

DISCUSSION

The fall in nasal resistance with exercise is nearly eliminated by blockade of the cervical sympathetics in humans (Richerson et al., 1968) and, as a result, the response is ascribed to neural action on the nasal mucosa rather than to circulating substances. The finding that exercise results in a fall in nasal resistance in CF suggests that the CF genotype, its sequelae, and treatment do not alter the neural responses affecting nasal resistance. Furthermore, the finding of qualitatively similar responses in CF patients and in healthy subjects suggests that in the CF genotype, airflow obstruction, and hyperinflation do not substantively modify the nasal response. This lack of an influence of lung disease and hyperinflation is surprising since vagal reflexes in animals can have a potent effect on nasal resistance (Eccles et al., 1982). Hence, the initial hypothesis, that chronic lung disease should modify the nasal response to exercise, is not supported by our data.

We did not observe or constrain the route of airflow (nose vs. mouth) during exercise. While intuitively this might be an important variable, experimental evidence suggests that the fall in nasal resistance with exercise is similar whether a subject breathes exclusively through the nose or the mouth. The route of airflow, however, can influence the lower-airway response to exercise, since exclusive mouth-breathing will result in greater respiratory heat loss and exercise-induced bronchoconstriction in susceptible subjects (Griffin et al.,

1982). In the present study, we observed only a slight tendency for exercise-induced bronchoconstriction. It is possible that, at higher work loads or greater ventilatory responses, a greater lower-airway obstruction could occur. We have previously shown, however, that the nasal response to exercise seems independent of the lower-airway response in adult asthmatics (Strohl et al., 1988). Hence, it appears that the nasal response to exercise is likely to be related to exercise itself rather than peripheral airway events such as the route of airflow or the lower-airway response.

In addition, our initial hypothesis, that patients with CF would be unlikely to exhibit compensatory nasal dilation in response to elevated airway resistance, appears substantiated. Indeed, unlike patients with chronic airflow obstruction (Drettner, 1970) or healthy children (Polgar et al., 1979), CF patients are not likely to have a lower nasal resistance with higher sRAW.

Finally, we were surprised to find that the one CF patient with current nasal polyps showed a significant nasal response to exercise. If one assumes that the polyps were flow-limiting, we would ascribe the response either to movement of polyps, with exercise permitting increased nasal airflow, or to constriction of the nasal vasculature to the polyps. More likely, however, is that the site of flow limitation in this patient is in the anterior nares and that change in nasal resistance with exercise is mainly due to shrinkage of the mucosa at the nasal valve. In any event, the clinical observation of nasal polyposis does not necessarily indicate fixed nasal obstruction.

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