

Original article

Nasal and bronchial response to exercise in patients with asthma and rhinitis: the role of nitric oxide

Background: Physical exercise is associated with a decrease in nasal resistance in rhinitis and an increase in bronchial resistance in asthma. The objective was to evaluate the relationship between the levels of nasal nitric oxide (nNO) and exhaled bronchial nitric oxide (eNO) with bronchial responses to exercise in patients with rhinitis and asthma.

Methods: We submitted 24 subjects with asthma and rhinitis to an exercise test. A decrease in $FEV_1 \geq 15\%$ was considered positive. The volume of the nasal cavity and the minimal cross-sectional area (MCA) was evaluated by means of acoustic rhinometry (AR), and nNO and eNO were evaluated by chemoluminescence. The measurements were recorded at baseline, 15 and 50 min after the end of the exercise test.

Results: The exercise test was positive in 17 cases. Fifteen minutes after exercise test, the nasal volume increased by 57% ($P < 0.0001$) and was still increased by 30% after 50 min ($P < 0.0001$). There was no correlation between decrease in FEV_1 and increase in nasal volume. The baseline value of nNO was 1185 ± 439 ppb, and the value at 15 and 50 min was 1165 ± 413 and 1020 ± 368 ppb, the latter value being significantly lower ($P < 0.01$) than the baseline. The baseline value of eNO was 21 ± 19 ppb, with no significant differences at 15 and 50 min. There was no significant correlation between either the decrease in FEV_1 and the nasal response, or the baseline eNO and nNO values.

Conclusions: The nasal and bronchial response to exercise is completely different in rhinitis and asthma; in the former, an increase in nasal volume occurs, while in the latter there is a drop in FEV_1 . There is no relationship between the values of nasal or exhaled NO and the nasal and bronchial response after exercise.

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Key words: acoustic rhinometry; exercise-induced bronchoconstriction; exhaled nitric oxide; nasal nitric oxide; nasal response to exercise.

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Accepted for publication 27 January 2005

It has been demonstrated that physical exercise is associated with a decrease in nasal resistance in healthy subjects and patients with rhinitis (1–5). It has been thought that these changes could largely be caused by a vasoconstrictive phenomenon that reduces the volume of the venous sinusoids. This vasoconstriction results from an increase in sympathetic activity, although it is possible that other factors, such as the dilatation of the nasal valve due to an increase in muscular activity, can contribute to this phenomenon. Vasoconstriction occurs in both breathing through the nose and through the mouth, and so it does not seem to be motivated by local reflexes or by the increase in ventilation found during exercise, as isocapnic hyperventilation does not in itself alter nasal resistance (2). The change in nasal resistance occurs immediately after exercise, with baseline values being recovered in a period of time ranging between 30 and 40 min. The reduction in nasal resistance is proportional to the intensity of the exercise, as the greater the effort, the greater the reduction (1–3).

Acoustic rhinometry (AR) is a technique that evaluates the geometry of the nasal cavities on the basis of the reflection of a sound wave (6, 7). It is possible to obtain values for the cross-sectional areas and the volumes at various distances from the nostrils. It is a fast, objective, noninvasive, reproducible and reliable technique that requires very little collaboration on the part of the patient and can be performed in cases of intense nasal obstruction (7–10).

Bronchoconstriction induced by exercise is observed in most asthmatic patients and it is thought that is due to alterations in the osmolarity of the liquid covering the epithelial layer, which trigger the release of chemical mediators originating in mast cells.

It is not known why the response in the nose and the bronchi is so different in patients with rhinitis and asthma. Rhinitis and asthma are considered to be two distinct diseases produced by similar mechanisms that affect a common pathway, which explains the frequent association of these two processes (11, 12). The difference

in the response to exercise of the nose of patients with rhinitis and the lower airways of asthmatics is one of the few findings that question the concept of a single disease (13).

Another finding that diverges with respect to the nose and the lower airways is the difference in the concentration of nitric oxide (NO) detected in the air exhaled through the nose and that emerging from the lower airways. The concentration of NO in the nasal air is very high; this is attributed to the high levels of production of this metabolite in the paranasal cavities, from where it flows towards the nasal cavity. In contrast, the concentration of bronchial NO is 100 or more times lower than that detected in the nose.

The synthesis of NO is undertaken by the action of the nitric oxide synthase (NOS) enzyme originating from the aminoacid L-arginine and produced by a wide range of cell types, including epithelial, endothelial, inflammatory and nerve cells. There are three isoforms of NOS, two termed constitutive and calcium dependent (cNOS) – the endothelial and the neuronal, which synthesize NO in normal conditions – and one termed inducible and calcium-independent (iNOS), which is not expressed (or very weakly so) in normal conditions. The fact that iNOS is present in the epithelium of the respiratory airway and in various cell types that take part in the inflammatory process (macrophages, neutrophils, mast cells and endothelial cells) and that it is induced by various pro-inflammatory cytokines (TNF α and β , INF γ , IL-1 β) and bacterial products (endotoxins) has led NO to be considered a marker of inflammation (14).

The NO is a powerful vasodilator, which, as we have seen above, is found in high concentrations in the nose, with its origin in the paranasal cavities. It is not known whether the changes in the concentration of the NO brought on by exercise could play a role in the nasal response; nor is it clear whether the presence of high levels in the exhaled bronchial air, normally considered a indicator of bronchial inflammation, can enable us to predict the response to exercise in asthmatic patients.

The objective of this study was the evaluation of the relationship between nasal and bronchial responses to exercise with levels of nNO and eNO in patients with asthma and rhinitis.

Materials and methods

Patients

Twenty-four patients with asthma and rhinitis who reported episodes of asthma induced by exercise. The selected patients had not received any treatment with topical, inhaled or systemic corticosteroids in the last 4 weeks, or with antihistamines and long-acting inhaled β_2 in the last week, or with short-acting β_2 in the last 12 h.

Exercise test

An exercise test lasting 6 min was performed – with 2 min of warm-up beforehand – in a room with a temperature of 20–25°C and relative humidity of less than 50%. Dry air of between 12–16°C was breathed in through the mouth; the cardiac frequency, ventilation/minute and respiratory frequency were monitored and the ECG was recorded. The cardiac frequency had to reach 80–90% of the predicted maximum and 40–60% of the maximum ventilation had to be maintained for 4 min. Measurements of the FEV₁ were made at 1, 3, 5, 10, 30, 45 and 60 min after exercise. Patients wore a nose-clip during exercise and forced expiratory manoeuvres. A decrease in FEV₁ equal to or greater than 15% was considered a positive exercise test (15). All parameters described above were recorded using an integrated spirometer and cardiopulmonary monitoring system (MedGraphics cardiopulmonary exercise system CPX, Saint Paul, MN, USA).

Acoustic rhinometry

The AR was carried out at baseline and at 15 and 50 min after the exercise test. An acoustic rhinometer SER 2000 from RhinoMetrics (Lyng, Denmark) was used.

The volume was evaluated in the first 6 cm of the nasal cavity (V_{0-6}) and between the 2 and 6 cm (V_{2-6}), along with the minimum cross-sectional area (MCA) (9, 10).

Determination of the nasal and exhaled NO

The nNO and exhaled nitric oxide (eNO) was measured in 18 subjects at baseline and at 10 and 50 min after exercise. This measurement was performed by means of chemoluminescence with a SIR System N6008 NO tracer (Madrid, Spain), following a standardised method (16). The system uses the light generated by a reaction between environmental ozone and the NO from the sample. The light is then amplified and analyzed by specific software. To evaluate the nNO, the nasal sample was obtained from one nostril using a negative pressure pump with a flow rate of 3 l/min. The patients were instructed to blow up the cheeks to elevate the mouth pressure in order to lift up the palate and isolate the nasal cavity from the rest of respiratory system. To assess eNO, the patients were instructed to exhale at a constant flow rate of 50 ml/seg. Both, nNO and eNO, were measured when the levels reached plateau values.

Statistical analysis

Age and FEV₁ values are presented as means with standard deviation. Rhinometry and NO values are presented as medians and the 25th and 75th percentiles. Differences within groups and between groups were estimated using Wilcoxon and Mann-Whitney analysis, respectively. The relationships between eNO and nNO levels with the nasal and bronchial response to exercise were assessed by Spearman's rank correlation. *P*-values < 0.05 were considered statistically significant. The software used was SPSS Version 10.0.

Results

The 24 subjects (13 men) had a mean age of 27 ± 6.68 years. They were all allergic to domestic dust

mites and, in eight cases, to pollens. All subjects had moderate persistent allergic rhinitis, 13 suffered a mild persistent asthma and 11 had a moderate persistent asthma.

Exercise test

All the patients completed the exercise test. The test was positive in 17 patients (71%) and negative in 7 (29%). In the positive ones, the mean drop in FEV₁ was $42 \pm 12\%$, and in the negative ones it was $6 \pm 3\%$. The maximum decrease in FEV₁ occurred in the first 10 min in 14 patients (82%), and in the first 10–20 min in the remaining three patients.

Acoustic rhinometry

At 15 min after the exercise test, the nasal volumes (V_{0-6} and V_{2-6}) increased by 45 and 57%, respectively, in comparison with the baseline value ($P < 0.0001$), and at 50 min they increased by 25 and 30% ($P < 0.0001$). The minimum cross-sectional area 2–6 (MCA₂₋₆) increased by 37 and 24% at 15 and 50 min, respectively (Fig. 1 and Table 1).

There was no correlation between the maximum drop in FEV₁ and the increase in the nasal volume at 15 and 50 min ($r = 0.11$, $r = 0.09$; $P = \text{NS}$).

In the group of patients with a positive exercise test, the maximum increases in V_{0-6} and V_{2-6} were 46 and 61%, respectively, in comparison with the baseline value ($P < 0.0001$). In the group of patients with a negative exercise test, the maximum increases in V_{0-6} and V_{2-6} were 31 and 48%, respectively. There were no significant differences between the two groups (Table 2). The variations in the V_{0-2} (obtained from the difference between the V_{0-6} and V_{2-6}) were 5.5 and 6.5%, at 15 and 50 min ($P = \text{NS}$).

The decrease in FEV₁ was inversely correlated with the baseline nasal volumes: $r = -0.5$ and $P < 0.01$ for V_{0-6} and $r = -0.52$ and $P < 0.009$ for V_{2-6} . No significant correlations were found after analysing the subgroups with positive or negative exercise tests.

Nasal and exhaled nitric oxide

The nNO could be determined in 18 patients. The median and 25th–75th percentiles of the baseline value of nNO were 1222, 894–1575 ppb. At 15 min after exercise its

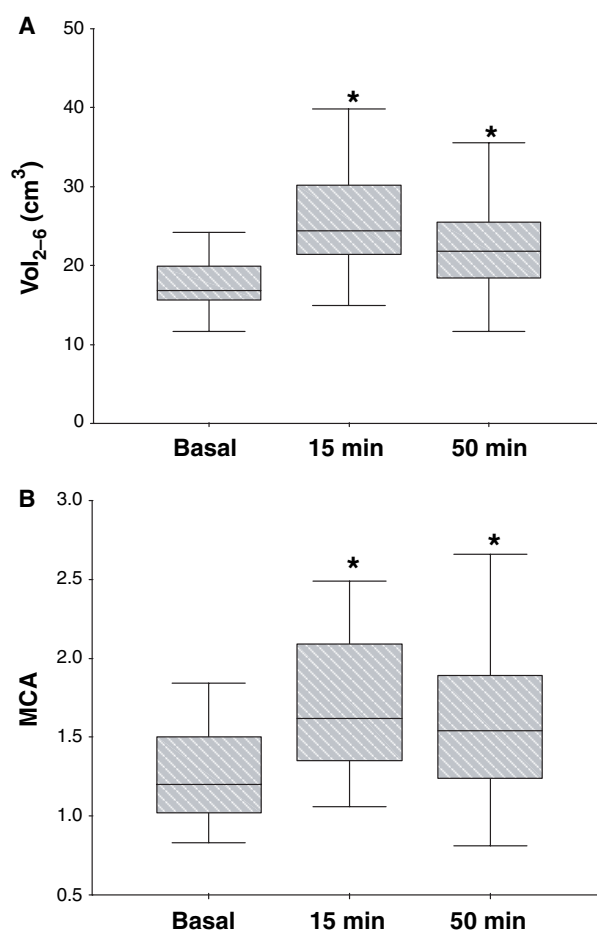


Figure 1. Results of AR at baseline, 15 and 50 min ($n = 24$). (A) Nasal volume between 2 and 6 cm (V_{2-6}). (B) Minimal cross-sectional area (MCA).

value was 1252, 900–1510 ppb, and at 50 min it was 960, 755–1280 ppb, the latter value being significantly lower ($P < 0.01$) than the baseline (Table 1). In the subgroups of patients with positive or negative exercise tests, no significant differences were obtained.

The nNO values at baseline, 15 and 60 min correlated significantly with the nasal volume at the same time points ($r = 0.50$, $P < 0.04$; $r = 0.71$, $P < 0.001$; and $r = 0.61$, $P < 0.01$, respectively). There was no significant correlation between the percentage of the increase in nasal volume and the degree of variation in nNO at 15 and 50 min.

Table 1. Nasal patency (volume and MCA) and eNO and nNO values at baseline, 15 and 50 min expressed as medians and percent deviation 25th–75th

Time	V_{0-6} ($n = 24$)	V_{2-6} ($n = 24$)	MCA ($n = 24$)	nNO ($n = 18$)	ENO ($n = 18$)
Baseline	16.8, 15.6–20.1	13.0, 12.3–16.3	1.12, 0.95–1.5	1222, 894–1575	17, 9–22
15 min	24.4, 21.4–30.4*	21.8, 18.4–25.5*	1.60, 1.33–2.08*	1252, 900–1510	16, 10–17
50 min	21.6, 18.1–25.0*	17.4, 14.5–20.8*	1.54, 1.22–1.89	960, 755–1280*	17, 13–19

* $P < 0.0001$.

Table 2. Comparison in nasal dilatation between those with positive and negative exercise challenge test

Exercise challenge test	Parameter (cm ³)	Basal	15 min	50 min
Positive (<i>n</i> = 17)	<i>V</i> ₀₋₆	16.0, 15.1–18.2	23.6, 20.4–29.2	20.7, 18.0–23.4
	<i>V</i> ₂₋₆	12.5, 11.7–14.3	21.7, 17.2–24.7	16.5, 14.5–19.2
	MCA	1.10, 0.90–1.47	1.53, 1.28–2.06	1.44, 1.19–1.82
Negative (<i>n</i> = 7)	<i>V</i> ₀₋₆	20.2, 18.6–22.6	28.2, 23.0–31.7	24.8, 18.3–34.3
	<i>V</i> ₂₋₆	16.4, 15.0–19.1	23.8, 19.3–28.1	20.7, 15.1–30.2
	MCA	1.30, 1.10–1.60	1.67, 1.62–2.24	1.75, 1.47–2.07

Values are expressed as medians and percentile deviation 25th–75th.

No significant difference between the two groups was found.

The eNO could be measured in 18 patients. The median and 25th–75th percentiles of the baseline value were 17, 8.5–22 ppb, with no significant differences in comparison with the values at 15 (16, 10.5–17 ppb) and 50 min (17, 12.7–19 ppb) (Table 1); nor did we find any differences after analysing the cases with positive or negative exercise tests.

There was no significant correlation between the decrease in FEV₁ and the baseline values of eNO and nNO, or between the baseline nasal volume and the baseline eNO, or between the values of eNO and nNO at baseline and at 15 or 50 min.

Discussion

Our study indicates that the response to exercise is clearly different in the nose compared to lower airways in patients with rhinitis and asthma. There is no convincing explanation for this phenomenon to date. We have not found any relationship between the nasal and bronchial responses in our patients with rhinitis and asthma after exercise with the baseline levels of nNO and eNO, or with any changes that occurred during exercise.

As the concentration of NO in the nasal and bronchial air also presents great differences and as NO is a powerful vasodilator, in our study we evaluated the possibility that exercise could cause changes in the concentration of nasal NO that could contribute to the development of vasoconstriction during exercise. We could not find any significant change in the concentration of nNO early after exercise, which leads us to believe that this metabolite does not help to explain the differences in the baseline nasal and bronchial responses to exercise in patients with rhinitis and asthma.

In our patients with asthma and rhinitis, the mean of the baseline values of eNO and nNO was high with respect to our values in a healthy population (eNO ≤ 12 ppb; nNO ≤ 900) (17, 18). At 15 min we found a nonsignificant decrease in eNO that coincided with the time of the greatest decrease in FEV₁; this finding could be related to an increase in bronchial obstruction. Other authors have demonstrated a drop in eNO values after exercise, but the duration of this drop is

not known, so it is advisable not to take exercise in the hour before the measurement of eNO (16, 19–21).

In our study, we have not found any significant relationship between the bronchial response after exercise and the baseline values of eNO and nNO.

In contrast with our study, Scollo et al. (22) did find a significant correlation between the concentrations of nNO and the intensity of the bronchoconstriction induced by exercise in a group of asthmatic children treated with inhaled glucocorticoids. It has also been reported that children who develop exercise-induced bronchoconstriction have higher eNO values than those who do not develop it (23). Differences in the characteristics of the population – some of whom were being treated with inhaled glucocorticoids and others not – could explain the divergence between the results of this study and our own, as it is well known that glucocorticoids quickly and dramatically reduce the levels of nNO.

The influence of the characteristics of the exercise on the nasal response has been studied, and it has been shown, through posterior rhinometry on healthy subjects, that a greater intensity of exercise produces a greater decrease in nasal resistance, although this is not the case when the duration of the exercise is increased. However, both the intensity and the duration of the exercise exert an influence on the length of the decrease in nasal resistance after exercise (24).

Serra et al. (3) studied the nasal response by means of posterior rhinometry in a group of healthy subjects and other groups with rhinitis, with asthma, and with concomitant asthma and rhinitis, after taking exercise on a bicycle. They found that the decrease in nasal resistance was similar in all four groups, which returned to their baseline values after 30 min. When a separate analysis was carried out on those who had and those who had not developed a bronchospasm, they verified that the nasal resistance had stayed decreased for longer in the patients with bronchospasm after exercise, which would suggest the existence of a bronchio-nasal reflex mechanism responsible for increasing the nasal response in patients with bronchoconstriction induced by exercise.

Strohl et al. (5) used posterior rhinomanometry to study the nasal response to exercise in healthy subjects and others with asthma or with rhinitis and asthma,

concluding that the nasal response is not related to the bronchial response or the temperature and humidity of the air breathed in through the mouth during the exercise test.

In our study, we have demonstrated for the first time, using AR (volume and MCA), that in subjects with asthma and allergic rhinitis there is a very marked increase in nasal patency after exercise that persists at 50 min after its cessation, without finding any relationship between the intensity of the bronchial response and the increase in the volume of the nasal light, in either the overall evaluation of the subjects or with respect to positive or negative results in the exercise test. However, there is a greater percentage of increase in nasal patency at 15 min in subjects with a positive exercise test (61% vs 48%), although this was not statistically significant.

In most studies that have evaluated the nasal response to exercise by means of rhinomanometry, the nasal resistance returned to values similar to the baseline at 30–40 min after the exercise test. These findings contrast with our demonstration of the significant persistence of nasal dilatation with respect to the values prior to the exercise for at least 1 h after the completion of the exercise test (3–5, 22, 24). The origin of this persistent nasal dilatation is unknown. In our study, we found a significant reduction in nNO, although it could not be confirmed with any certainty that both facts are related and further research is required to verify this possibility.

There have been descriptions of a 'rebound effect' in nasal resistance after exercise in healthy subjects and patients with rhinitis and asthma, involving a period of reduced resistance following another with an increased resistance higher than the preexercise baseline value (3, 25). In our study, we have not been able to confirm this rebound effect, at least in the first hour after exercise, although this does not rule out the possibility that it could occur later on.

In conclusion, we have demonstrated, using AR, that there is an increase in nasal light, of at least an hour in duration, in subjects with asthma and rhinitis, that is unrelated to the intensity of the bronchial and nasal responses. We have not found any relationship between the preexercise and postexercise values of nasal and exhaled NO and the bronchial and nasal responses. The difference in the responses of the nose and the lower airways is an enigma that remains to be solved. The marked differences in the concentrations of NO (a vasoactive metabolite) in the nose and lower airways do not seem to contribute to this variation in response.

Acknowledgments

Supported by grants from: RedRespira-ISCIH.RTIC-03/11 and Generalitat de Catalunya (2001SGR 00384).

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