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Relationship between nasal nitric oxide concentration and nasal airway resistance*

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SUMMARY

In the present study the relationship between nasal nitric oxide (NO) concentration and nasal airway resistance (NAR) was investigated in healthy volunteers at rest. Endothelially derived NO is established as a potent vasodilator and as such may be involved in the regulation of the nasal vasculature. Nasal airway resistance is dependent upon the tone of the nasal vasculature. It is therefore suggested that NO may play a role in the regulation of nasal airway resistance. Nasal NO concentration and nasal airway resistance were measured in 123 healthy volunteers. Posterior rhinomanometry was used to obtain the total and unilateral nasal airway resistance. Nasal NO concentration was measured from both the left and the right nostrils, consecutively, during a 20-sec breath hold, using a chemiluminescence gas analyser. NO was measured by sealing a cannula into each nostril consecutively and drawing air through both nasal passages. The results demonstrated that there was no significant difference between the concentrations of NO from the left and the right nostrils (p=0.7). This indicated that the sampling technique provided a measure of nasal NO which was independent of the side of the nose used for sampling. The mean (±s.d) NO concentration sampled from the left nostril was 1,145±367 ppb. The mean NO concentration sampled from the right nostril was 1,163±401 ppb. There was a highly significant correlation between the right and left measurements (rho, corrected for ties=0.95, p<0.0001). The mean total NAR (±s.d) was 0.25±0.06 Pa/cm^3/s. The mean left NAR was 0.50±0.28 Pa/cm^3/s, whilst the mean right NAR was 0.48±0.31 Pa/cm^3/s. There was no significant correlation between total NAR and the left nasal NO concentration (rho=0.10) or total NAR and right nasal NO concentration (rho=0.05). Similarly, no correlation was found between the left or right unilateral NAR and left or right nasal NO concentration, respectively. The results of the present study on healthy volunteers demonstrate that the nasal concentration of NO is not related to the total NAR. However, the present study cannot eliminate the possibility that nasal NO may be involved in the regulation of unilateral NAR.

Keywords: nitric oxide, nasal airway resistance

INTRODUCTION

The purpose of this study was to determine whether any relationship exists between the concentration of the gas nitric oxide (NO) in the nasal airway and nasal airway resistance.

Air sampled from the nose contains a high concentration of NO which is believed to be produced by the epithelium lining the nasal passages (Furukawa et al., 1996) and the surrounding paranasal sinuses (Lundberg et al., 1995). Endothelial NO is an established vasodilator (Ignarro et al., 1987). Therefore, the NO produced by the nasal epithelium may influence nasal airway resistance by causing dilation of the nasal blood vessels and, in particular, by causing swelling of the venous sinusoids. Alternatively the swelling of the venous sinusoids, which have been referred to as "nasal venous erectile tissue" (Eccles, 1982) may occur by similar NO-mediated non-adrenergic, non-cholinergic (NANC) mechanisms which have been reported to be involved in the control of penile erectile tissue (for review, see Andersson, 1995). It is therefore speculated that the nasal concentration of NO may be related to the degree of congestion of the nasal venous erectile tissue and consequently related to nasal airway resistance.

In the present study, NO concentrations were measured from each nostril consecutively in order to confirm that NO is sampled equally from both nostrils and that the measurement

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therefore represents the total NO concentration in the nose. It is generally considered that, during sampling of nasal NO concentrations by the methods described above, air is drawn into the sample tube through both nostrils. It is therefore assumed that the NO concentration measured represents the total NO concentration in the nose. However, NO is a characteristically unstable free radical and it was thus felt that the NO in the nasal cavity might react during sampling. Because of this, and since NO from the contralateral nostril is drawn a greater distance during sampling than NO in the nostril ipsilateral to nosepiece insertion, it was felt that there may be a disproportionate contribution of NO in the sample air from the ipsilateral nostril.

SUBJECTS AND METHODS

Subjects

The study recruited 123 healthy volunteers (73 females and 50 males, mean age 22 years). Subjects underwent medical screening prior to inclusion to assess their suitability for participation in the study. Volunteers were excluded if they: (1) suffered from asthma or hay fever; (2) reported a history of common cold within the previous 4 weeks; (3) had taken any prescribed medication, other than the contraceptive pill; (4) had any clinically significant respiratory or cardiovascular disease; or (5) had taken any menthol product in the previous 12 h.

Methods

Nasal airway resistance was measured by posterior rhinomanometry (NR6-2; GM Instruments Ltd., United Kingdom). The rhinomanometer pressure and flow were calibrated prior to use. Total nasal airway resistance was obtained against a reference pressure of 75 Pa. Two measurements were obtained, with a coefficient of variation <10% between measurements. The face mask was repositioned between measurements. The mean of these two measurements was recorded as the tNAR. Unilateral NAR was then obtained in the same manner, using surgical tape to occlude the contralateral nostril.

On completion of NAR measurements, the nasal NO concentration was sampled using a chemiluminescence gas analyser (LR2000; Logan Research Ltd., United Kingdom) at a flow rate of 250 ml/min. The analyser was calibrated prior to use at 3,000 parts per billion/ppb (BOC Spectra-seal). The gas analyser sample tube was connected to a Teflon nasal olive. The nasal olive was then positioned gently into the vestibule of the left nostril to ensure a satisfactory seal. The contralateral nostril remained unobstructed throughout sampling. Sampling then took place during a 20-sec breath hold. This technique has been confirmed, by oral fibroscopy (Imada et al., 1996), to raise the soft palate and thus isolate the upper airways ensuring air of nasal origin only is sampled. Carbon dioxide levels were also monitored throughout sampling as a indication of satisfactory breath hold. The NO concentration reached a stable plateau during this sampling period. The mean NO concentration in ppb over the final 2 s of sampling was recorded. Following measurement of the nasal NO concentration from the left nostril, the nasal olive was removed and positioned in the vestibule of the right nostril. The sampling procedure was then repeated using the right nostril.

The study was approved by the Local Ethics Committee.

Statistical analysis

Nasal airway resistances and nasal NO concentration were expressed as the mean±standard deviation. NO concentrations were normally distributed, thus the paired Student's t-test was employed to assess the statistical significance between the mean NO concentration sampled from the left nostril and the mean NO concentration sampled from the right nostril. A p-value <0.05 was considered statistically significant. The parametric Fisher's r-z correlation test was applied to examine the relationship between the left and right nasal NO concentration. Total NAR was correlated with the NO concentration sampled from the left nostril and the right nostril using the non-parametric Spearman rank-correlation test. The Spearman rank-correlation test was also employed to correlate unilateral NAR measurements with the NO concentration sampled from the corresponding nostril. Coefficients of correlation (rho, corrected for ties) >0.4 with tied p-values <0.05 were considered statistically significant correlations.

RESULTS

Measurements of NO typically reached a plateau within the 20-sec breath hold, as illustrated in Figure 1. The mean NO concentration over the final 2 s of this plateau was calculated. The mean NO concentration sampled from the left nostril was 1,145±367 ppb (range: 398-2,290 ppb), whilst the mean NO concentration sampled from the right nostril was 1,163±401 ppb (range: 428-2,632 ppb). No significant difference was found between the mean NO concentration sampled from the left and right nostrils ($p=0.1$). The frequency distribution curve of NO concentrations obtained from the left nostril is illustrated in Figure 2. The NO concentration from the left and right nostril exhibited a positive correlation (rho (corrected for ties)=0.95, $p<0.0001$).

The mean total NAR was 0.25±0.06 Pa/cm^3/s (range: 0.11-0.39 Pa/cm^3/s). The mean left NAR was 0.50±0.28 Pa/cm^3/s (range: 0.20-1.70 Pa/cm^3/s), whilst the mean right NAR was 0.48±0.31 Pa/cm^3/s (range: 0.17-2.27 Pa/cm^3/s). No correlation was shown

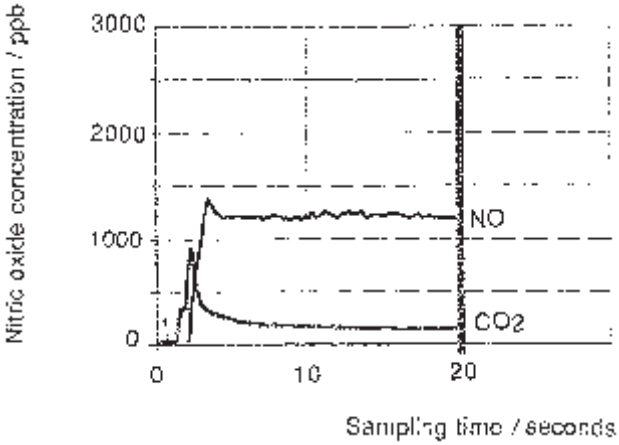

Figure 1. Typical NO curve obtained by sampling during a 20-sec breath hold. The figure clearly demonstrates the NO plateau which is believed to represent the continuous production of NO in the nose.

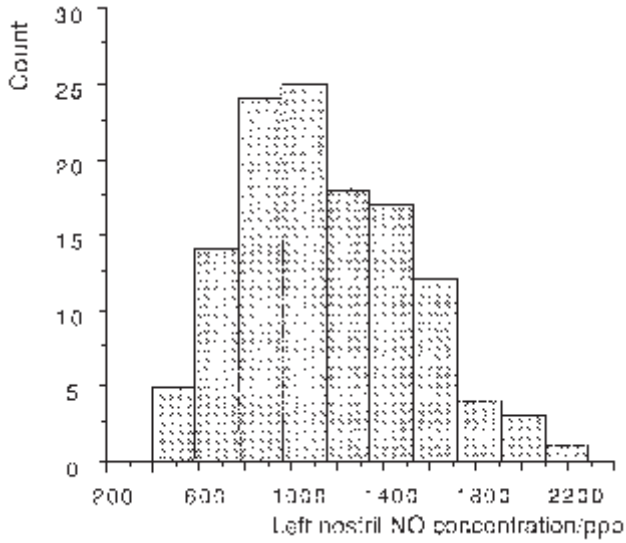

Figure 2. Frequency distribution of nasal NO concentration (ppb) sampled from the left nostril (n=123).

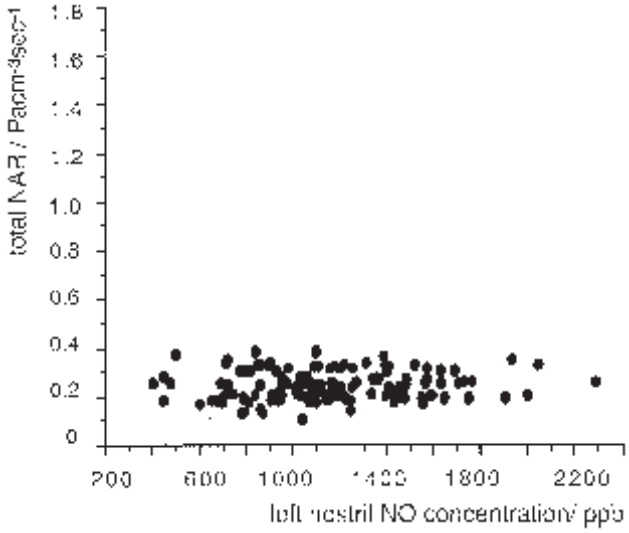

Figure 3. Scattergram illustrating the relationship between the NO concentration (ppb) sampled from the left nostril and total unilateral nasal airway resistance (NAR; in Pa/cm^3/s; rho (corrected for ties)=0.10, p=0.27; n=123).

to exist between tNAR measurements and the left nostril NO concentration (rho (corrected for ties)=0.10, p=0.27; Figure 3) and tNAR and right nostril NO concentration (rho (corrected for ties)=0.05, p=0.55). Unilateral NAR did not correlate with the NO concentration obtained from the corresponding nostril (left NAR/left nostril NO concentration: rho (corrected for ties)=0.17, p=0.07; right NAR/right nostril NO concentration: rho (corrected for ties)=0.16, p=0.08).

DISCUSSION

From the results of the present study we have found no relationship to exist between nasal NO concentration and total NAR. The data also confirms that no significant difference exists between the nasal NO concentrations sampled from the left nostril and those sampled from the right nostril during breath hold, each measurement therefore represents the total NO concentration in the nose which is independent of the side of the nose used for sampling.

The finding that in healthy volunteers no correlation exists between tNAR and nasal NO concentrations are in contrast to those of Imada et al. (1996), who proposed that nasal NO may be involved in the control of nasal airway resistance. Their theory, however, is based on the observation that changes in tNAR, occurring due to exercise, correlate with a reduction in nasal NO. No data is shown in their paper to suggest that an attempt was made to correlate pre-exercise resting NAR with the pre-exercise NO concentration.

It remains uncertain why no relationship should be observed between resting NAR and nasal NO concentration, whilst a change in NAR is seen to be associated with a change in nasal NO concentration (Imada et al., 1996). Further evidence of this pattern is demonstrated by a previous study on patients with acute upper respiratory tract infection (Ferguson and Eccles, 1997), in which no relationship can be found between the resting tNAR and nasal NO concentration. Yet, in the same sample population, the decrease in tNAR following treatment with a topical nasal decongestant was associated with a decrease in nasal NO concentration. It now seems unlikely that the volume of the nasal cavity significantly influences nasal NO concentrations, originally suggested as a possible explanation for the concomitant fall in NO concentration following vasoconstriction, as one would then also expect a correlation between resting tNAR and nasal NO concentration. Interestingly, recent work by Rinder (1996) has been unable to find any significant correlation between nasal cavity volume determined by acoustic rhinometry, and nasal NO concentration, following a period of exercise.

It is acknowledged that, since measures of nasal NO obtained in the present study have been shown to represent the total NO concentration of the nose, any effect of asymmetrical unilateral NAR on the NO concentration of each nostril would not be detectable in the present study. Indeed, no correlation was observed between unilateral NAR and the NO concentration obtained from the corresponding nostril. To determine if unilateral changes in NAR do affect the NO concentration in that nostril, or vice versa, it would be necessary to isolate the nostril and thus measure ipsilateral nasal NO concentrations only. Total isolation of one nostril would require sealing of the posterior nares which was not undertaken in the present study.

During sampling it was noted that the NO concentration reached a plateau, rather than declining, as shown in Figure 1. Since NO is drawn through both nostrils in series during sampling, this plateau presumably represents the continuous production of NO by the epithelial lining of the nose and/or the paranasal sinuses. The rate of this continuous production of NO (V'NO) is quantified when using nl/min to express the NO in the sample air. Assuming V'NO = [NO] x V'E, where [NO] is the concentration of NO (ppb) and V'E is the ventilatory flow rate (l/min; Iwamoto et al., 1994), the mean rate of production of NO in the present study was calculated to be: 1,145 ppb x 0.25 l/min = 286 nl/min. The need to take into account the flow rate of sampling is evident as ppb cannot simply be compared. The

results of the present study compare well with those documented by Imada et al. (1996). Using a flow rate of 1 l/min, Imada et al. (1996) obtained a rate of NO production of 323 nl/min.

In conclusion, we have shown that there is no relationship between the measure of nasal NO obtained and total NAR in healthy volunteers, but from the results of the present study alone it is not possible to eliminate any relationship between nasal NO and unilateral NAR. In addition, we can conclude that the present method of sampling nasal NO may give a measure of the nasal NO rate of production and that, with the present sampling procedure, the same measurements are obtained from both left and right sides of the nose.

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