ORIGINAL CONTRIBUTION

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The role of Nervus Intermedius in side specific nasal responses*

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SUMMARY

Background: *Nervus intermedius (NI) dysfunction is common in patients who have had vestibular schwannoma (VS) surgery. Such patients have a unilateral parasympathetic-denervated nasal cavity. A number of side-specific nasal reflexes have been demonstrated in normal individuals, including hand cold-water immersion. It is not understood whether these reflexes have parasympathetic or sympathic efferent pathways. We aimed to evaluate the side specific nasal reflex to cold-water immersion in post-operative VS patients with NI dysfunction, in order to determine the nature of the efferent pathway of these reflexes.*

Method: *Side specific responses to cold-water immersion were tested by acoustic rhinometry in 10 normal individuals and 18 patients with NI dysfunction (proven by Schirmer's test) after VS surgery.*

Results: *A consistent pattern of ipsilateral congestion and contralateral decongestion after the cold-water immersion was seen in normal individuals ($p < 0.001$). We found no consistent response in VS patients both ipsilateral and contralateral to the side of NI dysfunction.*

Conclusions: *We confirm the consistent side-specific nasal reflexes to cold-water hand immersion in normal individuals. This is disturbed in patients with NI dysfunction. We have also shown unexpectantly that the contralateral side-specific reflex is disturbed in these patients. These data suggest that the reflex is parasympathetic and crosses the midline.*

Key words: nervus intermedius, parasympathetic innervation, autonomic innervation, vasomotor rhinitis, nasal reflex

INTRODUCTION

Rhinitis is a common disease with a number of underlying pathophysiological causes. There is a subset of patients with rhinitis, in whom it has been postulated that the underlying pathophysiology is disruption in the balance of the autonomic innervation of the nose (between the parasympathetic and sympathetic innervation). This is known traditionally as "Vasomotor Rhinitis" and has also been termed as "Non Eosinophillic Non Allergic Rhinitis" (NENAR) [(1)].

The autonomic innervation of the nose is complex and not well understood. The parasympathetic nerve supply to the nose arises from the superior salivary nucleus as the nervus intermedius, which passes along with the facial nerve and reaches the nasal mucosa through the greater superficial petrosal nerve. The sympathetic nerves arise from the superior cervical ganglion and form the deep petrosal nerve, which, along with greater superficial petrosal nerve, forms the vidian nerve. Parasympathetic stimulation results in congestion of the nasal mucosa [(1)] and sympathetic stimulation in decongestion [(2)].

It has been shown that the diving reflex causes nasal congestion, and that this is exaggerated in patients with NENAR [(3)]. It is assumed that this is a parasympathetic phenomenon on the basis of the end effect and known parasympathetic cardiovascular response to diving.

There are a number of side-specific nasal responses, thought to be autonomic, that have been demonstrated. The following unilateral stimuli have been shown to cause ipsilateral congestion with contralateral decongestion: axillary pressure [(4)]; hand cold-water immersion [(5)]; and handgrip (isometric exercise) [(6)]. These have been thought to be, again, parasympathetic responses, on the basis of the ipsilateral end-effect, although they cause systemic cardiovascular sympathetic responses [(4-6)].

An understanding of the mechanism of these, presumed parasympathetic effects, may help in the understanding of NENAR / Vasomotor Rhinitis.

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Trauma to nervus intermedius (NI) is relatively common in patients who have had a unilateral vestibular schwannoma excised [7]. Hence these patients, in terms of parasympathetic innervation, have a denervated nasal cavity on one side, with a normal parasympathetic innervation on the other. By elucidating any difference in nasal reflexes between these patients, we may be able to determine whether or not these reflexes are parasympathetically mediated.

The aim of this study was to determine the role of nasal parasympathetic innervation in patients who have NI dysfunction following removal of a vestibular schwannoma using cold-water immersion as the side specific stimulus and acoustic rhinometry to measure nasal congestion/decongestion.

METHOD

Study design and patients

A cohort observational study with internal controls was designed to evaluate the role of nasal parasympathetic innervation. The null hypothesis was that there is no difference in side-specific nasal response between the operated side and contralateral side (internal control) of post-operative vestibular schwannoma patients. This study was approved by the Central Manchester Local Research Ethics Committee. Patients who had vestibular schwannoma surgery were given a patient information sheet about the trial at the time of their discharge from the hospital. At 4 week follow up visit they were given a chance to participate in this study. Patients who agreed to participate in the study were recruited and an informed consent was obtained. All patients recruited into the trial underwent Schirmer's test to confirm unilateral NI dysfunction. This involves holding a small strip of filter paper inside the lower eyelid for 5 minutes. Both eyes normally secrete the same amount of tears. Less than 10 mm of moisture on the filter paper or asymmetry on both sides (less than 50% difference of the test side as compared to the normal) was assumed to indicate a positive test [8].

Patients with a positive test result were included in the study. The inclusion and exclusion criteria were as follows:

Inclusion criteria:

1. 18 Years of age
2. Confirmed unilateral NI dysfunction.

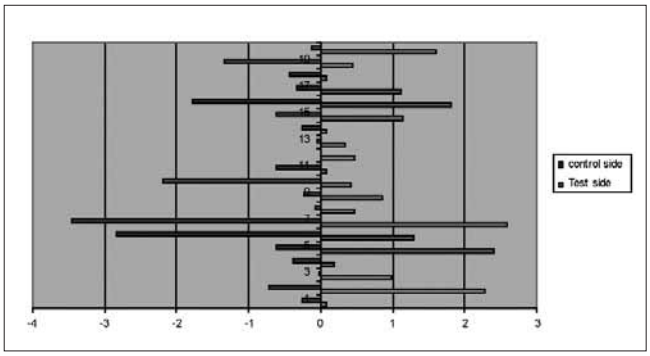

Figure 1. Change in nasal volume following cold-water immersion test in normal individuals.

Exclusion criteria:

1. Patient on sympathomimetic, sympatholytic, parasympathomimetic or parasympatholytic medication.
2. Patient with unstable cardiac conditions such as unstable angina, poorly controlled arrythmias and poorly controlled cardiac failure.
3. Patients with peripheral vascular disorders such as peripheral arterial insufficiency and Raynauds syndrome.
4. Patients with known diabetic autonomic neuropathy.
5. Patients with bilateral vestibular schwannomas.

Side specific response to cold-water immersion was tested by acoustic rhinometry. Cold-water immersion has been chosen in favour of other responses, as previous studies have shown that it causes a maximal side specific response [4-6].

Baseline nasal volume was measured on both sides of the nose using Acoustic rhinometer A1 (GM Instruments Ltd, Kilwinning, Scotland). Four readings were averaged to produce a reliable reading. Nasal volume from 0-5 cm was measured on both sides. The hand and the forearm of the test side were immersed in a water bath held at 15°C for 5 minutes and then the nasal volume was recorded. The same procedure was then repeated on the other side after a 30-minute rest period.

We also performed the cold-water immersion test on 10 normal individuals, to reproduce the results produced by Wilde et al. [5] and validate this test. In the controls both sides (left and right) were tested to double the number of results. Individuals with nasal symptoms were excluded from this study.

Table 1. Summary data.

Group	Ipsilateral baseline volume	Ipsilateral volume after stimulus	p	Contralateral baseline volume	Contralateral volume after stimulus	p
Normal	4.60 (3.96-5.90)	3.89 (3.32-4.50)	$p < 0.001$	4.24 (3.77-4.90)	4.82 (4.08-6.70)	$p < 0.001$
Patient: NID side	7.77 (5.46-10.00)	7.95 (5.62-11.41)	$p = 0.62$	7.69 (6.26-12.11)	6.89 (5.75-8.81)	$p = 0.42$
Patient: control side	7.88 (5.12-9.29)	9.30 (6.47-12.20)	$p = 0.039$	7.54 (6.04-12.07)	7.36 (5.77-10.01)	$p = 0.094$

NID: Nervus Intermedius Dysfunction; Volume: median (IQR)

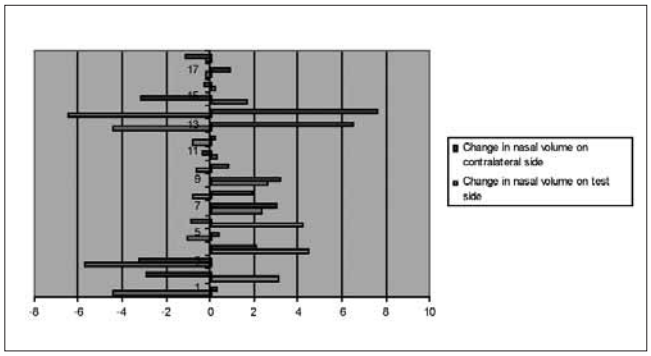

Figure 2. Change in nasal volume following cold-water immersion test on the test side.

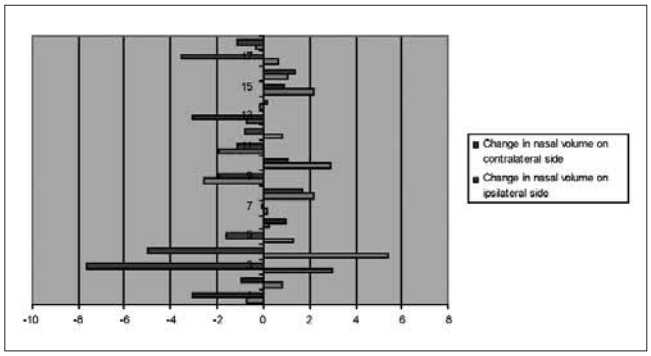

Figure 3. Change in nasal volume following cold-water immersion test on control side.

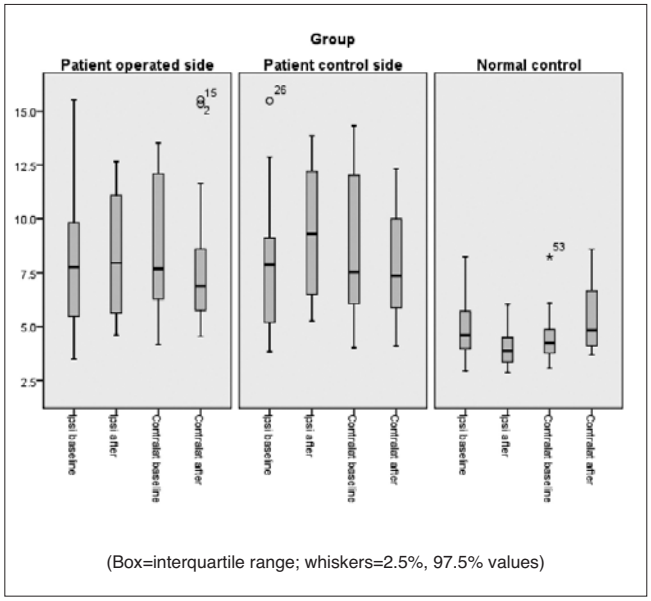

Figure 4. Box and whisker plots of baseline and post-stimulation nasal volumes.

Statistical analysis

The primary outcome measure was to detect a difference in nasal volume in parasympathetically dennervated nasal mucosa and normal nasal mucosa following cold-water immersion test. Fifteen patients with internal controls were required to detect 1 standard deviation difference between control and test side. This would give the study a power of 80%, with α probability at 0.05. Non-parametric tests were used for analysis as the data was not normally distributed (Wilcoxon rank sum; Mann-Whitney; Spearman's rank co-efficient).

RESULTS

In the normal control group, cold-water immersion led to an ipsilateral reduction in nasal volume (congestion) ($p < 0.001$) and contralateral decongestion ($p < 0.001$) (See Figures 1 and 4, Table 1).

Following vestibular schwannoma surgery, patients were seen four weeks post-operatively. Schirmers test was performed at this stage and was negative in 2 patients and positive in the rest. Eighteen patients were recruited into the study. Baseline nasal volume was recorded on the operated side (test) and the contralateral side (internal control). Cold-water immersion test was first applied to the operated (test) side. Figure 2 shows the change in the nasal volume in the ipsilateral and contralateral side following the test. This shows, following vestibular schwannoma surgery, the pattern of ipsilateral congestion and contralateral decongestion after the cold water immersion test as seen in normal subjects is disturbed in many. Only 5 patients had the expected response; 8, the opposite response; 3, bilateral decongestion; and 2 with bilateral congestion. There was no significant overall change in ipsilateral ($p = 0.62$) or contralateral ($p = 0.42$) nasal volume (Figure 4, Table 1).

The cold-water immersion test was then performed on the non-operated side (internal control). Figure 3 shows the change in the nasal volume in the ipsilateral and contralateral side. Again the side specific nasal response seen in normal subjects is disrupted in most: 6 had the expected response; 1, the opposite response; 6 bilateral decongestion; and 5 with bilateral congestion. There was no significant overall change in contralateral ($p = 0.094$) nasal volume and, whilst the change in ipsilateral nasal volume was significant ($p = 0.039$), it was in the opposite direction to the expected response (decongestion, not congestion) (Figure 4, Table 1).

Of the patients with normal responses when testing either side ipsilateral or contralateral to NI dysfunction, in only 1 patient were both sides normal.

There was no difference in change in nasal volume in post-operative patients between side specific responses on stimulating the operated side (test) and the contralateral side (internal control) ($p = 0.184$ ipsilateral response; $p = 0.791$ contralteral response).

There was no interaction between age and change in nasal volume within the normal control group ($p = 0.61$ (ipsilateral); $p = 0.79$ (contralateral)); nor within the post-operative group (($p = 0.51$ (ipsilateral); $p = 0.29$ (contralateral)). There was no

interaction between sex and change in nasal volume (($p = 0.21$ (ipsilateral); $p = 0.87$ (contralateral)).

DISCUSSION

In this study, we had a unique cohort of patients with confirmed unilateral NI dysfunction. Four weeks after vestibular schwannoma surgery NI dysfunction was confirmed by Schirmer's test. As the test was done 4 weeks postoperatively, regeneration was not an issue. With no evidence of disruption of sympathetic innervation in these individuals we had a group of subjects with parasympathetic nasal dennervation on one side and normal contralateral innervation in the same individual.

We reproduced the results of Wilde et al. [5] in 10 normal individuals, confirming that ipsilateral cold-water hand immersion causes ipsilateral congestion ($p < 0.001$) with contralateral decongestion ($p < 0.001$).

We postulated that this ipsilateral congestion response would be altered in patients with NI (and therefore parasympathetic) dysfunction following surgery for VS, if the efferent arm of the reflex is parasympathetic.

When testing with the stimulus on the side of NI dysfunction, there was no consistent nasal response at all, both ipsilateral and contralateral to the stimulus. What was surprising, however, is the finding that there was also no consistent response when testing with the stimulus contralateral to the side of NI dysfunction. Again, this was both ipsilateral and contralateral to the stimulus. Overall, there was even a significant change in ipsilateral nasal volume ($p = 0.039$) but in the opposite direction (decongestion rather than congestion). Furthermore, in the post-operative group, only in a single patient were the responses normal when stimulating both sides.

This suggests that NI (and therefore parasympathetic) innervation plays an important role in these nasal responses. The disruption of the pattern of normal responses would be expected when stimulating the side ipsilateral to surgery, if one accepts that parasympathetic innervation plays a role in this response, probably as an efferent arm. However, the disruption when stimulating the opposite side is totally unexpected. This raises the possibility that there may be communication of the parasympathetic autonomic innervation across the midline, i.e. the unilateral NI dysfunction also effects parasympathetic innervation in the contralateral nasal cavity. A bilateral response was also noted incidentally by Golding-Wood in some of his patients following vidian neurectomy [9].

Various studies have tried to analyse the regulatory mechanism of autonomic innervation and its effect on the nasal vasculature. It is postulated that the spontaneous congestion and decongestion of the venous sinuses is under the control of the autonomic nervous system [10]. However, there is no evidence of an influence on the nasal cycle in patients with disturbance of the parasympathetic and sympathetic innervation of the nasal mucosa [11].

Abnormalities of the autonomic control of the nasal vasculature has been implicated in all forms of rhinitis [12], but more so in vasomotor rhinitis [1,13,14]. On the basis of the alteration of nasal responses to isometric exercise and diving reflex, it has been speculated that this could be due to a parasympathetic disorder in one paper [15] and a decrease in sympathetic tone in the other [16]. It has also been suggested that the inflammatory disorders of the upper airway may result in varying degree of autonomic dysfunction [17,18] and local neurogenic inflammation [19].

Much of what has been either postulated or evidenced has supported a role of variance in sympathetic tone as responsible for nasal congestion/decongestion. It has been shown that the sympathetic tone to nasal vasculature is influenced by the partial pressure of carbon dioxide, which suggests close connection between the respiratory centre in the brainstem and the control of the nasal airway resistance [20,21]. Changes in the nasal airflow due to a change in posture may also be due to reflex changes in sympathetic activity at the level of the brainstem [22,23].

Nerve stimulation/sacrifice studies in dogs have shown a predominance of sympathetic effect in the nasal cavity with respect to nasal congestion/decongestion leading to the conclusion that nasal congestion may be related more to a withdrawal of sympathetic discharge than to an overactivity of the parasympathetic nerves [24,25]. Loehrl et al. [26] in their experiments in patients with vasomotor rhinitis demonstrated the autonomic dysfunction to be due to sympathetic hypoactivity.

Parasympathetic stimulation has been postulated to be responsible for various nasal vascular responses. However there is very little evidence confirming this. Anggard [27] in his experiments in cat found parasympathetic nerve activation results in increase in nasal secretions and vasodilatation. He has also demonstrated that the maximal effect of graded stimulation results in a greater response to sympathetic stimulation [28,29]. He concluded that under physiological conditions a change in the parasympathetic tone results in only a minor change in the nasal patency.

Golding-Wood [9] postulated that the phenomenon of chronic vasomotor rhinitis is mediated purely by parasympathetic overactivity. He carried out vidian neurectomy/petrosal neurectomy in resistant cases of chronic vasomotor rhinitis with improvement in nasal obstruction as well as rhinorrhea. As alluded to above, he also found an unexpected bilateral response to unilateral petrosal or vidian neurectomy. These results and our findings are in contrast to the animal experi-

ments. There is no biological basis for any disruption of the sympathetic nervous system in our group of patients and the response seen has to be attributed to parasympathetic disruption.

CONCLUSION

We confirm the side-specific nasal reflex of ipsilateral congestion/contralateral decongestion to unilateral cold water hand immersion in normal individuals. This reflex is not present in most patients with proven NI dysfunction following surgery for vestibular schwannoma. It is also not present when the stimulus is applied to the contralateral side. We conclude that the nasal reflex to cold-water immersion is parasympathetic in nature, and we suggest that there is cross-innervation of parasympathic innervation over the midline.

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