

Autonomic reflexes and non-allergic rhinitis

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Functions traditionally ascribed to the nose include warming, humidification, and filtration of inspired air prior to its passage to the lower respiratory tract. The nose thus conditions inspired air, making it suitable for pulmonary gas exchange. In order to carry out these functions, the nose is subject to a complex series of reflexes mediated via the autonomic nervous system. The effector tissues are the nasal blood vessels and glands. Perennial non-allergic rhinitis may be divided into two types based on the presence or absence of eosinophilia in nasal secretions. Much circumstantial evidence suggests that non-eosinophilic non-allergic rhinitis (NENAR) may be a disease of autonomic imbalance. In a series of studies carried out at the University of Liverpool, patients with perennial non-allergic rhinitis, and NENAR in particular, were found to have qualitative and quantitative abnormalities in their nasal response to various stimuli as manifested by changes in nasal patency. The nasal response to axillary pressure is much reduced in NENAR patients compared with normal controls, and the normal decrease in nasal resistance in response to standing is abrogated. Isometric exercise has little effect in normal subjects, but those with NENAR demonstrate an increase in nasal resistance. A similar effect is seen in response to the cold pressor test. Of great importance for therapy is the effect of topical fluticasone propionate in patients with NENAR. Treatment normalizes the damaged nasal reflexes seen in this condition, whereas placebo has no effect. However, abnormalities in other non-nasal autonomic reflexes (systemic parameters) are not affected by treatment.

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The nose is a phylogenetically ancient organ with two basic functions – olfactory and respiratory. Nasal cavities are found not only in mammals, but also in fish, amphibious reptiles, and birds (1). Rhinitis and obstruction of the nasal cavities affect several types of mammals other than man, including cats, dogs, horses and pigs.

Nasal disease has long been a common problem, the earliest report being from ancient Egypt, found as an inscription on the tomb of the medical attendant to the pharaoh Sahura, transcribed as “he healed the King’s nostrils” (2, 3). Indeed, hypertrophic inferior turbinates, nasal polyps, and other obstructive conditions are all believed to have been recognized by the ancient Egyptians (4). Over the centuries, therapy for rhinological conditions has ranged from removal of nasal polyps by a sponge attached to a thread, as described by Hippocrates, to herbal medicine, diet modification, cautery, surgery, and magic! Although nasal surgery in general has improved considerably over the last two centuries, until very recently surgery for rhinitic disease was largely unsuccessful.

Respiratory function of the nose

The main respiratory function of the nose and nasal cavities is to provide a conduit for transportation of air to the lungs. However, it also has other important functions, including air conditioning (warming, cooling and humidification), it provides a resistance to airflow, filters inspired air, as well as subserving an immunological function.

In order to perform these functions, the nasal cavity has a complex structure. The lateral nasal wall consists of three turbinates, with a mucosal surface, each associated with a respective meatus. Inspired air is directed towards the middle turbinate by the nasal valve (5). While the irregular structure enhances the resistive function of the nose, most of the resistance occurs at the piriform aperture (6). Furthermore, an additional factor in increasing resistance is that most nasal airflow is turbulent in nature (7).

The nasal cavity has a mucosal lining beyond the mid-nasal vestibule, as well as mucous glands, goblet cells, and cilia. The mucosa is capable of

swelling and decongestion, and can therefore have a profound effect on nasal resistance to airflow. In fact, nasal resistance may vary from 0.2–0.7 kPa in the normal subject, while complete nasal obstruction may occur in a patient with rhinitis (8). Changes in nasal mucosal thickness are effected by a complex vascular system (9) regulated by autonomic reflex mechanisms. The nasal vasculature includes large venous sinusoids, with structures termed “cushion veins” at their distal end, which can expand and contract depending on the degree of sympathetic activity. High sympathetic outflow leads to low resistance within the cushion veins, collapse of the venous sinusoid, and shrinkage of the nasal mucosa, while a reduction in sympathetic tone causes swelling of the cushion veins, distension of venous sinusoids, and a corresponding increase in the thickness of the nasal mucosa.

The nasal vasculature also includes radiator vessels near the surface of the nasal mucosa, as well as arteriovenous anastomoses which, in association with the large number of mucous glands, ensure efficiency in humidifying and warming inspired air. By the time the inspired air reaches the nasopharynx, its relative humidity will have increased to around 75% and it will have been warmed to body temperature (10), and by the time it reaches the upper trachea it will be fully saturated (11).

The nose also helps to prevent particulate matter from reaching the lungs; for example, it can remove pollen grains (20–30 μm in diameter) and 50% of house dust mite allergens (5 μm). These particles adhere to nasal mucus (assisted by turbulent airflow within the nose), are transported into the pharynx by the mucociliary system, and subsequently swallowed. Soluble chemicals may also be removed from inspired air by becoming dissolved in the nasal mucus, but poorly soluble air pollutants (e.g. hydrocarbons) are not affected and may therefore reach the lungs (12).

The nose also subserves a complex immunological function, trapping micro-organisms along with particulate matter, which may be destroyed by phagocytic cells and bactericidal substances, e.g. lysozyme. Immunoglobulins and antigen-presenting cells are also present in the nasal mucosa, and are central to the development of immunity. However, disorders of immunological function can result in a heightened response to inhaled particles, causing allergic rhinitis, though epidemiological evidence suggests that intrinsic (non-allergic) rhinitis is almost equally common.

Eosinophilia and non-allergic rhinitis

Perennial non-allergic rhinitis can be classified according to the presence or absence of eosinophils

in nasal secretions. Eosinophilia was first reported in 1927, though sampling of nasal secretions proved problematic (13). However, wide sampling techniques using a cytology brush have now been shown to minimize sampling errors (14). Most studies of eosinophilia have been undertaken in patients with nasal allergy, though characterization of non-allergic rhinitis on the basis of eosinophil counts has been well described (15, 16). Nasal secretion eosinophilia appears to be quite common – one study has reported elevated eosinophil levels in 20% of young adults (17). While these were not all symptomatic, there is evidence to suggest that symptomatic nasal secretion eosinophilia may predispose to the development of symptomatic rhinitis (18).

Nasal congestion, profuse rhinorrhoea, hyposmia, inferior turbinate hypertrophy, and mucoid nasal secretions are all characteristic clinical features of eosinophilic non-allergic rhinitis (19). Nasal polyposis is also frequently observed in these individuals (15, 19). In some (usually older) patients, rhinitis also represents a predominant symptom in the absence of eosinophilia (19, 20).

The role of the autonomic nervous system

Until recently, it was believed that the autonomic nervous system exerted its effect simply by secretion of adrenalin/noradrenaline and acetylcholine at sympathetic and parasympathetic nerve endings, respectively. However, the picture became more complicated with the discovery of many other neurotransmitters, such as vasoactive intestinal polypeptide and neuropeptide Y, both of which are associated with sympathetic nerve endings. In addition, stimulation of α - and β -adrenoceptors results in effects on the nasal vasculature – α -receptor stimulation causes constriction of nasal blood vessels (21), while little effect is observed upon β -receptor stimulation.

The role of the autonomic nervous system in regulating nasal secretion was elucidated by studies which examined the effect of interfering with sympathetic and parasympathetic inputs. Division of sympathetic nerves caused nasal obstruction (22), parasympathetic stimulation led to glandular hypersecretion (23), while division of the parasympathetic nerves caused a reduction in nasal secretion in patients with intractable rhinorrhoea (24). The sympathetic nerve supply to the nose originates in the hypothalamus, runs through the intermediolateral grey columns of the spinal cord, exiting in the cervical chain. It enters the nose as the deep petrosal nerve, while some sympathetic supply is also afforded by the vidian nerve. The parasympathetic nerve supply arises from the superior salivary

nucleus and is distributed via the nervous intermedius, to the greater superficial petrosal nerve, the vidian nerve, and finally to the pterygio palatine ganglion.

Circumstantial evidence suggests that non-eosinophilic non-allergic rhinitis (NENAR) may be a disease of autonomic imbalance (25, 26). The fact that anticholinergic agents can improve the condition (20) and division of the parasympathetic nerves may ameliorate symptoms (24) suggests that the autonomic nervous system is important. In addition, β -adrenoceptor blocking agents may cause a condition similar to NENAR (27). More recent work suggests that division of the nasal parasympathetic nerves not only normalizes symptoms, but also reduces histamine levels and mast cell numbers in the nasal mucosa (28).

Eosinophilic rhinitis, on the other hand, is perhaps a disease more associated with the nasal mucosa. Abnormalities in prostaglandin metabolism have been demonstrated in such patients, as well as an altered nasal resistance response to aspirin (14, 29). In addition, some studies suggest that patients with eosinophilic rhinitis may display subclinical allergy to house dust mite (30).

The picture is complicated by the fact that autonomic innervation and nasal mucosal inflammation are intimately interrelated (29). It is now well known that autonomic imbalance plays a role in airway hyperreactivity in asthma. The imbalance occurs between the moderating effect of β_2 -adrenoceptor responsiveness and the hyperreactivity effects of α -adrenoceptor and cholinergic receptors. Indeed, antibodies for β_2 -adrenoceptors have recently been found in asthma patients (31), and animal studies have shown that β -adrenoceptor function is disturbed in experimentally-induced nasal hypersensitivity (32).

The erectile tissue of the nasal mucosa exhibits regular cyclic congestion and decongestion, which is well documented in man and in animals (33, 34), and thus one tends to breathe through one side of the nose at a time. This nasal cycle occurs in approximately 80% of the population, yet most subjects are unaware of its existence since total nasal resistance remains unchanged (35). The reason for the nasal cycle is unclear – it may simply represent a variation in sympathetic outflow from the brain, reflecting some type of cerebral cyclical activity. Alternatively, it may be important in nasal physiology – one side of the nose may be resting from the damaging effects of inspired air, while the other side conditions incoming air. Nasal secretion may also alternate in phase with changes in airflow (36). Bamford and Eccles (37) have shown that electrical stimulation of the vasomotor area of the brain stem in cats can produce reciprocal changes

in sympathetic tone of the nasal blood vessels. The nasal cycle becomes clinically important in patients with rhinitis – since one side of the nose may be obstructed at any one time, rhinitic patients may report large variations in nasal patency.

Nasal reflexes

The nose is subject to a series of reflexes which improves its efficiency when, for example, carrying out exercise (38, 39). Isotonic exercise, up to a work rate of 120 watts, causes a gradual reduction in nasal resistance to around 50% of normal values (40), due to an increase in nasal sympathetic tone. However, a similar degree of isometric exercise does not affect nasal resistance (41, 42).

Nasal resistance is also affected by posture – moving from an erect to a supine position causes an increase in nasal resistance, possibly related to increased jugular venous pressure (43), and when lying on one side, nasal resistance is decreased on the lower side compared with the upper side (44). Interestingly, axillary pressure causes ipsilateral nasal obstruction and contralateral nasal decongestion (45).

All mammals, including man, exhibit the diving reflex, where nasal contact with water or facial contact with a cold wet cloth may induce apnoea and bradycardia with an associated increase in arterial blood pressure (known as the cold pressor effect). There is evidence to suggest that “cold” receptors are important in initiating this reflex (46–48). Chemical irritation of the nose by tobacco smoke, ammonia, sulphur dioxide etc. may produce a similar response. The afferent limb of this reflex is the trigeminal nerve, which when stimulated can cause sneezing (39); a similar response is observed upon stimulation of the vidian nerve (25).

The nasal response to changes in temperature is also complex. The influence of environmental temperature on human nasal mucosa has been studied by measuring nasal patency and nasal mucosal blood flow (49). On exposure to cold air there is a decrease in blood flow and nasal patency. Exposure to hot air results in an increase in nasal patency and no change in nasal blood flow (49, 50). Changes in humidity do not appear to influence nasal patency.

Autonomic reflexes and non-allergic rhinitis

The comparative effects of a series of autonomic stimuli on nasal patency in patients with allergic and non-allergic rhinitis have been the subject of several studies. Tests used included isometric exercise, changes in posture and axillary pressure, as

well as the cold pressor response (or cold face test), which simulates the diving reflex (51). In most animals the decrease in nasal patency is very pronounced, but in humans it can only be measured by special techniques, e.g. rhinomanometry (48).

Isometric exercise is predominantly a sympathetic stimulus and has varying effects throughout the body. Unlike isotonic exercise, it tends to increase diastolic blood pressure and generally has different physiological effects (52). Isometric exercise in normal subjects produces little effect on nasal resistance, as measured by rhinomanometry, but a large increase occurs in those with non-allergic rhinitis, and a small increase in patients with allergic rhinitis. The normal response to standing is a reduction in nasal resistance, but no such response occurs in patients with allergic or non-allergic rhinitis. The cold pressor response in normal individuals (measured by rhinomanometry) also produces little change in nasal resistance, but in patients with NENAR a very large increase is observed (Fig. 1), while only a small increase is evident in allergic rhinitics.

These results suggest that patients with rhinitis have an altered nasal response to autonomic stimuli, and those with non-allergic rhinitis have an even greater derangement of response. This corresponds with our view regarding the two types of rhinitis, where nasal hyperreactivity is known to occur in the allergic group, but theoretically is expected to be greater in those with non-allergic rhinitis. The nasal response to standing is interesting, and appears difficult to explain. It is possible that standing is a weaker autonomic stimulus than the cold pressor response or isometric exercise, and thus it can be implied that nasal obstruction in patients with rhinitis (and perhaps underlying inflammation) may mask the effects of relatively small autonomic stimuli. Thus, an increase in sympathetic tone may occur, but may not be sufficient to override other factors giving rise to nasal obstruction.

Non-eosinophilic non-allergic rhinitis

Studies at the University of Liverpool have specifically examined the effects of autonomic stimuli in patients with NENAR. Again, the cold pressor test produced little effect on nasal resistance to airflow in normal subjects, but a 13% increase was observed in those with NENAR. A similar effect was seen in response to isometric exercise, with an 18% increase in nasal resistance in the NENAR group (Table 1). Axillary pressure produced an ipsilateral increase in nasal resistance in normal subjects but little effect in those with NENAR. Again, this result is interesting, but the same

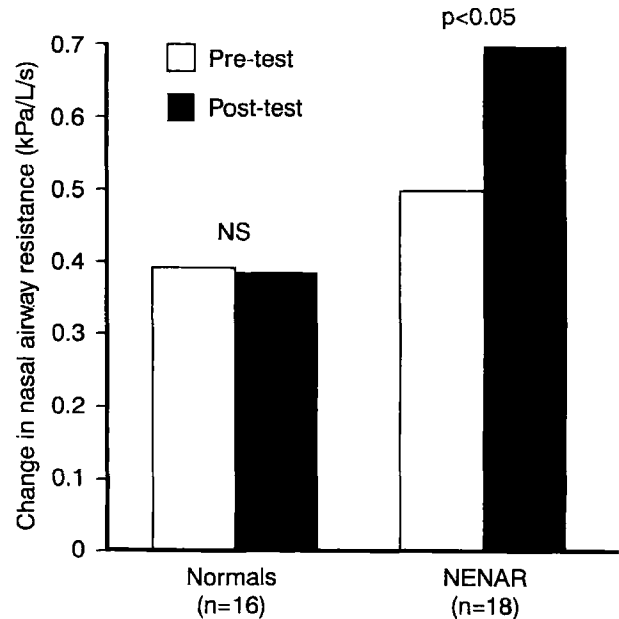


Fig. 1. Median change in respiratory nasal airway resistance in normal subjects and patients with non-eosinophilic non-allergic rhinitis (NENAR) in response to the cold pressor test.

explanation as for the response to standing may be invoked.

In patients with NENAR, a derangement is also seen in the effect of autonomic stimuli on systemic parameters, including pulse rate, and systolic and diastolic blood pressure. In patients with non-eosinophilic intrinsic rhinitis, standing produced a decrease in systolic blood pressure compared with normal subjects. Isometric exercise resulted in an increase in pulse rate and diastolic blood pressure and a reduction in systolic blood pressure compared with normal subjects. With regard to the cold pressor response, a significantly reduced effect on pulse rate and systolic blood pressure was apparent compared with normal subjects (Table 1).

Table 1. Effect of autonomic stimuli on nasal resistance and systemic parameters in normal subjects and patients with non-eosinophilic non-allergic rhinitis (NENAR)

	Normal subjects	NENAR	ANOVA
Facial cooling			
Nasal resistance	No change	13% ↑	NS
Pulse rate	21% ↑	No change	P=0.014
Systolic blood pressure	52% ↑	11% ↑	P=0.02
Diastolic blood pressure	19% ↑	No change	NS
Isometric exercise			
Nasal resistance	No change	18% ↑	NS
Pulse rate	13% ↑	24% ↑	NS
Systolic blood pressure	15% ↑	No change	NS
Diastolic blood pressure	8% ↑	15% ↑	NS

Effect of topical corticosteroids

Of particular interest was the potential effect of topical intranasal corticosteroids on the response to autonomic stimuli in patients with NENAR. Change in nasal resistance was measured in response to a stimulus before and after treatment with fluticasone propionate. Although little change in nasal resistance was seen in response to standing, a large difference in nasal resistance values before and after intranasal fluticasone propionate was observed in response to isometric exercise (Fig. 2). In non-treated NENAR patients, a large increase in nasal resistance was noted on isometric exercise, but following treatment with fluticasone propionate, this effect was significantly ameliorated. A similar finding, but of much larger magnitude, was noted in response to the cold pressor test (53). Reassuringly, treatment with intranasal corticosteroids had no effect on systemic parameters, including blood pressure and pulse rate.

Conclusions

These studies demonstrate that the normal response to autonomic stimuli is altered in patients with rhinitis compared with normal subjects. Not only is the nasal vascular response qualitatively and quantitatively different, but general cardiovascular responses are also altered. The effect seems to be more pronounced in patients with non-allergic rhinitis, especially those with NENAR. This supports the view that non-allergic rhinitis is predominantly a disease of the autonomic nervous system and other circumstantial evidence supports this concept. The fact that some degree of inflammatory change seems to be present, even in intrinsic rhinitis, is interesting, and perhaps this explains why topical intranasal corticosteroids frequently provide

a beneficial effect in this condition. Apart from the anti-inflammatory effect of corticosteroids, they have many other properties including the stabilization of membranes and modification of autonomic reactivity via local neural effects.

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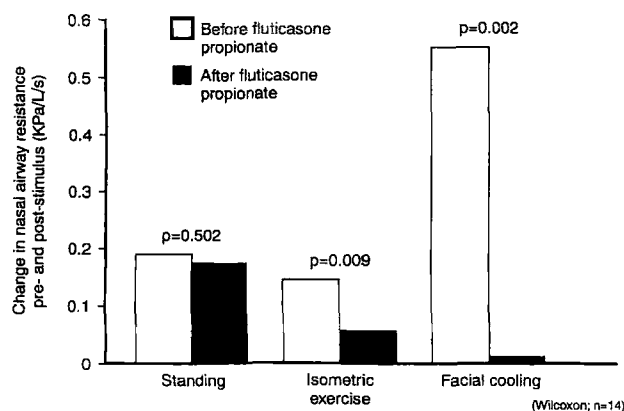


Fig. 2. The effect of intranasal fluticasone propionate on median change in nasal resistance in response to autonomic stimuli in patients with non-eosinophilic non-allergic rhinitis.

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