Studies of Blood Flow in Human Nasal Mucosa with ^{133}Xe Washout Technique and Laser Doppler Flowmetry

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Lund 1986

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To Fredrik

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I A method for determination of blood flow with ^{133}Xe in human nasal mucosa.
Mats Bende, Knut Flisberg, Ingemar Larsson, Per Ohlin and Peter Olsson.
Acta Oto-Laryngologica (Stockholm) 96: 277-285, 1983.

II The laser doppler flowmeter for measuring micro-circulation in human nasal mucosa.
Peter Olsson, Mats Bende and Per Ohlin.
Acta Oto-Laryngologica (Stockholm) 99: 133-139, 1985.

III A comparison between the ^{133}Xe washout and laser doppler techniques for estimation of nasal mucosal blood flow in humans.
Peter Olsson.
Acta Oto-Laryngologica (Stockholm), accepted for publication.

IV Influence of environmental temperature on human nasal mucosa.
Peter Olsson and Mats Bende.
Annals of Otology, Rhinology and Laryngology 94: 153-155, 1985.

V The effect of leukotriene D_4 on nasal mucosal blood flow, nasal airway resistance and nasal secretion in humans.
Hans Bisgaard, Peter Olsson and Mats Bende.
Clinical Allergy, accepted for publication.

VI Sympathetic neurogenic control of blood flow in human nasal mucosa.
Peter Olsson and Mats Bende.
Acta Oto-Laryngologica (Stockholm), accepted for publication.

CONTENTS

INTRODUCTION

The human nasal airway is adapted to certain physiological functions that are part of the body's defense mechanisms. The vascular bed of the nasal mucosa is essential for these functions, and studies of nasal mucosal blood flow under various external conditions and under the influence of drugs are of theoretical as well as clinical interest.

General aspects on peripheral circulation

The vascular bed may be divided according to its functional specialization. Various 'parallel-coupled' circuits can be distinguished, e.g., coronary, muscular, skin and nasal vessels. Further, in any of these circuits functionally 'series-coupled' sections can be defined: 'Windkessel' vessels, pre- and postcapillary resistance vessels, precapillary sphincters, capillaries or exchange vessels, capacitance vessels, consisting mainly of veins and sinusoids, and in some tissues arteriovenous shunt vessels. Tissue blood flow is dependent on the state of the resistance vessels, of which the precapillary section normally is responsible for 80% of the total resistance to flow. Tissue blood volume or blood content is mainly dependent on the state of the capacitance vessels. Filtration or absorption of fluid in the exchange vessels is partly dependent on the relation between the pre- and the postcapillary resistance. Furthermore, blood may pass directly from arteries to veins by way of arteriovenous shunts. The individual vascular bed and its control is arranged in order to meet local nutritive demands as well as demands related to the organ function. E.g., the shunt vessels in skin are known to have a specific function related to regulation of body temperature (Folkow 1960, Mellander & Johansson 1968, Rosell 1980).

The vascular circuits are normally dynamically restricted by the vascular smooth muscles, which maintain a contractile activity called vascular tone. This tone is built up by myogenic activity and also by sympathetic vasoconstrictor activity and may be modified by local metabolic factors. Basal vascular tone is the state of vascular contraction that remains after the sympathetic neurogenic control has been eliminated under resting conditions. Vasodilatation due to sympathetic and parasympathetic nerve activity or axon reflex mechanisms may be present under certain circumstances in specific tissues but do not normally contribute to vascular tone. Neither does the hormonal component of the sympatho-adrenal complex contribute to vascular tone during resting conditions (Folkow 1960).

Regulation of the peripheral vascular bed is dependent on local factors and on remote control systems. Local control, i.e., myogenic and chemical-metabolic control, is mainly concerned with the nutritive demands of the individual tissue, while remote control, i.e., neurogenic activity and circulating vasoactive substances, basically are involved in regulation of vascular changes related to the organ function. Sympathetic vasoconstrictor activity is the most important factor in remote control of the vascular bed. Variations in the density of adrenergic innervation, various degrees of sensitivity to the constrictor mediator and differences in effector response to stimulation frequency make up a basis for centrally elicited redistribution of blood flow between vascular beds. The vasoconstrictor fibres mainly innervate the outer layer of the vessel wall while the inner muscles may be more sensitive to local control mechanisms and to circulating catecholamines. There is a continuous interaction between the control systems which becomes more evident under non-basal conditions, such as physical strain and hypovolemic situations (Folkow 1960, Mellander & Johansson 1968). Also local sympathetic reflex mechanisms (Henriksen 1977), and substances such as serotonin, histamine, arachidonic acid metabolites and neuropeptides may take part in adjustments of vascular tone (Mellander & Johansson 1968, Bisgaard & Kristensen 1984, Lundblad 1984).

The distribution of different types of adrenoceptors and their relative importance in mediating the effects of catecholamines varies not only with the vascular bed but also with the individual type of vessel. Blood flow through the capillaries, which lack smooth muscle cells, is regulated by asynchronic and rhythmic activity in small precapillary arterioles, i.e., the precapillary sphincters. These vessels are in close contact with the interstitial fluid and they are mainly dependent on local myogenic and metabolic control mechanisms. The sphincter section has only a sparse adrenergic innervation. The main precapillary resistance vessels are dependent on local control as well as sympathetic activity. The capacitance vessels are mainly under remote control. The tone of the arteriovenous anastomosis in the skin is mainly due to sympathetic vasoconstrictor activity elicited from hypothalamus. These shunts are also sensitive to an increase in circulating noradrenaline (Folkow 1960, Mellander & Johansson 1968).

The vascular smooth muscle response to noradrenaline released on sympathetic nerve stimulation as well as to circulating catecholamines is mediated by the adrenoceptors. There are two distinct types, alpha and beta, which may be further divided into $alpha_1$, $alpha_2$, $beta_1$ and $beta_2$. Activation of alpha- and beta-receptors on the effector cell leads in principle to a vasoconstriction and a vasodilatation, respectively. Several mechanisms regulate the release and re-uptake of noradrenaline at the nerve terminal, and various substances may more or less selectively stimulate or block the different receptor types (Mellander & Johansson 1968, Andersson 1980, McGrath 1981). The final response to noradrenaline may further be modified by the release of neuropeptide Y (Lundberg et al 1985). It should also be emphasized that adrenoceptors are present not only at nerve terminals and on smooth muscle cells (Andersson 1980).

The functional differentiation between the blood vessels and the mechanisms that are involved in regulation of the vascular bed may well apply also to circulation in the nasal mucosa (Änggård 1974a, Malm 1974a, Eccles 1982, Bende 1983a). However, it must be stressed that vascular studies performed on experimental animals may not necessarily apply to humans, and studies performed on a specific human tissue may not be valid for other human tissues (Altura 1971, Ross 1971, Andersson 1980).

The vascular bed and circulation in the nasal mucosa

The human nasal mucosa receives branches from the maxillary, ophthalmic and facial arteries. From the periostal or perichondrial level the arteries ascend towards the surface in a helical manner, forming anastomoses along their course. The arteries ramify and give origin to arterioles which end in capillary networks mainly arranged in a subepithelial and a glandular zone. The capillaries join to form venules which drain into larger collecting veins. In turn, these veins drain into the deeper situated sinusoids, which are especially well developed in the mucosa of the turbinates. Also arterial blood may reach the sinusoids by way of arteriovenous anastomoses. Under normal conditions the thickness of the mucosa covering the inferior turbinate may exceed 5 mm, but there are considerable variations due to shifts in blood content of the mucosa (Cauna 1982) (see also Fig. 1).

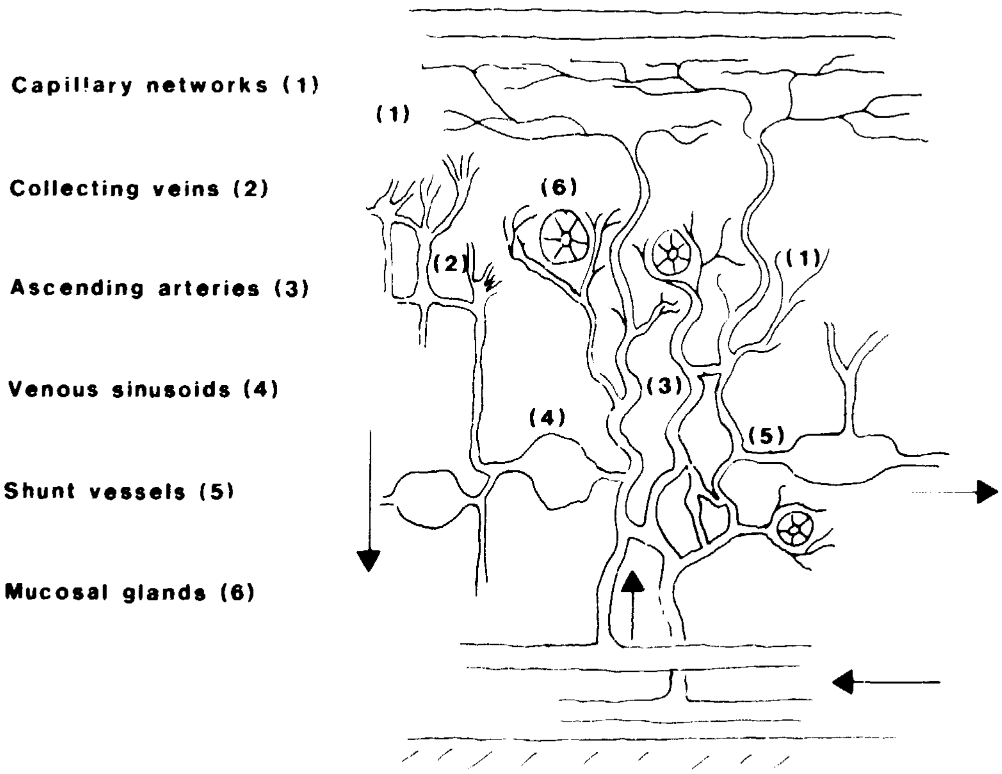

Fig. 1. A schematic drawing of the vascular bed in the nasal mucosa of the inferior turbinate in humans (after the description given by Cauna 1982).

Different functions of the mucosa and the complexity of the vascular bed require an extensive system of regulatory mechanisms. Changes in the vascular bed as well as factors mediating these changes have been studied in humans and in animals. Some of the methods that have been applied for such investigations in humans are listed in Table I.

TABLE I. *Some methods that have been applied for studies of vascular reactions in the human nasal mucosa*

	Methods	References
Blood flow	Rhinoscopy	Bernheimer 1934
	Temperature registration	Mudd et al 1921 Spiesman 1936 Ralston & Kerr 1945 Cole 1954 Drettner 1961
	Photoelectric plethysmography (septum)	Davis & Hertzman 1957
	Thermal conductivity (septum)	Drettner 1961
	Hydrogen clearance	Konno et al 1982a
	Fluorescence (septum)	Kumlien & Perbeck 1986
Blood volume	Rhinoscopy (degree of mucosal swelling)	Heetderks 1927 Steinmann 1948
	Intranasal balloons (changes in swelling of the mucosa)	Ralston & Kerr 1945
	Photoelectric plethysmography (hyperemia)	Davis & Hertzman 1957
	Rhinomanometry (resistance to air flow)	Aschan et al 1958 Miles Foxen et al 1971 Broms 1980 Clement & Hirsch 1984
	Peak flowmetry (resistance to air flow)	Taylor et al 1973 Wihl 1983
	Optical method (changes in swelling of the mucosa)	Juto & Lundberg 1982

Changes in local blood volume do not necessarily affect the resistance to flow, why the state of the capacitance and the resistance vessels should be studied separately (Mellander & Johansson 1968). If the amount of extracellular fluid and nasal secretion is not changed, variations in mucosal swelling and nasal airway resistance may be considered to indirectly reflect changes in the blood volume in the mucosa. Of the methods applied for blood flow studies in the human nasal mucosa (Table I), rhinoscopy, temperature registration, photoelectrical and thermal conductivity techniques may be considered to indirectly reflect the blood flow. The hydrogen clearance technique allows direct studies of blood flow but it is dependent on insertion of an electrode into the mucosa throughout the registration. The fluorescence technique has recently been applied for studies of blood flow in the mucosa over the septum.

The isotope washout technique described by Kety (1949), and developed for ^{133}Xe by Lassen et al (1964), has been widely used for experimental as well as clinical investigations of regional blood flow in e.g. skin, intestine, subcutaneous adipose tissue, myometrium and cerebrum (Sejrsen 1971, Wilson et al 1975, Henriksen 1977, Haunsø et al 1979, Marcus et al 1981). With this technique, blood flow determinations are based on the elimination rate of the injected isotope, and blood flow is expressed in ml/min/100g tissue.

Laser doppler flowmetry admits continuous registrations of relative changes in tissue blood flow in a non-invasive manner, demonstrated e.g., in skin, muscle and intestine (Stern 1975, Holloway & Watkins 1977, Lewis et al 1979, Holloway 1980, Feld et al 1982, Rosenberg et al 1982, Tenland 1982). An attempt to determine nasal mucosal blood flow quantitatively has also been made (Druce et al 1984). The laser doppler method is based on the fact that light beams reflected in moving cells undergo a frequency shift, while beams scattered in static tissue remain unshifted in frequency (Tenland 1982). The blood flow index obtained from the output signal is expressed in arbitrary units or in volts.

The ^{133}Xe washout and laser doppler techniques might offer possibilities to study blood flow directly also in the human nasal mucosa.

The vascular bed in the human nasal mucosa seems to be built up in order to meet demands that by far exceed what is necessary for the nutrition of the mucosa. It is therefore natural to link the different parts of the vascular system to the organ functions of the mucosa. The fenestrated superficial capillaries have been suggested to be involved in the humidification of inhaled air by allowing transudation to the mucus blanket covering the mucosa (Cauna 1982). Nasal air flow volume, which is partly dependent on the state of the capacitance vessels, seems to be important for olfactory ability (Tatchell et al 1985), and the dimension of the vascular bed may be advantageous for nasal defense mechanisms against infection.

The resistance, capacitance and shunt vessels may further be of importance for exchange of heat over the nasal mucosa. It has been stated that the mucosa of the nose has two alternatives on exposure to cold air, either dilatation of arterioles and vascular spaces to provide heat and so to prevent chilling of the respiratory tract, or constriction of vessels to reduce heat loss, as in skin (Negus 1958). Negus was in favour of the latter alternative, while an increased blood flow was suggested by Slome (1956) on exposure to cold air. The function of the mucosa covering the turbinates has also been suggested to be more concerned with recovery of heat and water from the expiratory air and with general thermoregulation than with conditioning of inspiratory air (Scott 1954). Especially the arteriovenous shunts may be of importance for such heat transfer (Cole 1982a), analogous to the shunt vessels in skin (Mellander & Johansson 1968). Warming of the inspired air is partly dependent on heat supplied to the mucosa from the vascular bed and partly dependent on heat contributed to the nasal mucosa from the expiratory air. Heat and water losses via expiratory air increase when the mucosa is warmed while recovery of heat and water increases when the mucosa is chilled (Cole 1982a). Furthermore, a reduction of the nasal lumen by mucosal swelling improves the efficiency of air modification (Cole 1982b).

When both feet are placed in cold water, there is an initial transient widening of the nasal passage, which is followed by an increase in nasal airway resistance. There is also a transient reduction of the temperature on the mucosa of the turbinate and a transient decrease in thermal conductivity over the septum, indicating a decreased blood flow (Drettner 1961). On general cold exposure, a congestion of the nasal mucosa has been demonstrated with rhinomanometry (Drettner 1961). A decreased blood flow has been noticed in temperature, photoelectric plethysmographic and thermal conductivity measurements (Mudd et al 1921, Ralston & Kerr 1945, Cole 1954, Davis & Hertzman 1957, Drettner 1961). Cooling of the inspiratory air results in an increased nasal airway resistance (Drettner 1961, Salman et al 1971, Cole et al 1983) and a decrease in mucosal temperature, while thermal conductivity is probably not changed (Drettner 1961).

Changes in the vascular bed of the nasal mucosa on exposure to variations in environmental temperature have basically been considered either to take part in body temperature regulation or to be essential for conditioning of respiratory air. Furthermore, changes in blood flow have been studied with methods that might be less suitable for investigations of climate effects on blood flow (cf. Drettner 1963).

Vascular changes may also occur during various pathophysiological conditions in the mucosa. An increased blood flow has e.g. been noticed in infectious rhinitis (Bende 1983b) and in patients with vasomotor and allergic rhinitis (Özdem & Ercan 1984). An allergen challenge to the sensitized nasal mucosa has been seen to induce an increased blood flow (Konno et al 1982a) as well as a decreased blood flow (Bende et al 1984). An allergen challenge further produces irritative symptoms, nasal blockage, nasal secretion, local eosinophilia and increased reactivity (Mygind 1979, Griffin et al 1982). These changes can partly be accounted for by local release of histamine (Secher et al 1982), but also the leukotrienes (LT) C_4, D_4 and E_4 may be involved as they have been demonstrated in nasal lavage fluid after an allergen provocation to the nose (Creticos et al 1984, Shaw et al 1985).

Arteries, arterioles and veins in the animal nasal mucosa have a dense adrenergic innervation while small precapillary vessels and venules have only a few such fibres. There is a rich adrenergic plexus surrounding the thin muscle layer of the sinusoids (Dahlström & Fuxe 1965, Änggård & Densert 1974). The variation in adrenergic nerve distribution to the different sections of the vascular bed, and the possibility of different impulse flows and/or different turnover rates of the transmittor in these nerves indicate that various vascular circuits may be regulated in different ways (Dahlström & Fuxe 1965). In agreement with this assumption, functional studies on the cat nasal mucosa and on other vascular beds in animals have demonstrated a difference in vasoconstrictor response to sympathetic stimulation between different vascular sections (Folkow 1960, Änggård & Edwall 1974, Malm 1977). Morphological studies have also demonstrated the presence of adrenergic innervation in arteries, veins and in shunt vessels in human nasal mucosa (Cauna 1970, 1982). In this vascular bed, the alpha-adrenoceptors predominate while beta-adrenoceptors seem to be of minor functional importance (Svensson et al 1980, Andersson & Bende 1984). Blood volume in the human nasal mucosa seems to be controlled by $alpha_1$- and $alpha_2$-adrenoceptors, while nasal mucosal blood flow seems to be controlled mainly via $alpha_2$-adrenoceptors (Andersson & Bende 1984, Bende et al 1985).

Stimulation of the sympathetic nerves that innervate the nose decongest the nasal mucosa in animals (Tschalussow 1913, Malcomson 1959, Rooker & Jackson 1969, Malm 1973, Änggård & Edwall 1974, Asakura et al 1985). A corresponding reaction, mediated by a general increase in sympathetic nerve activity, is seen in the human nasal mucosa in exercise (Konno et al 1982b). The decongestion of the mucosa is due to a constriction of the capacitance vessels (Malm 1973, Änggård & Edwall 1974, Konno et al 1982b). Stimulation of sympathetic nerves in animals reduce nasal mucosal blood flow, indicating a constriction of the resistance vessels (Malm 1973, Änggård & Edwall 1974). In humans, Drettner (1961) found that the initial reduction in nasal mucosal blood flow elicited by local skin cooling appeared to be mediated via the cervical sympathetics. However, exercise did not change nasal mucosal blood flow in healthy subjects (Paulsson et al 1985). In the cat nasal mucosa, sympathetic stimulation results in a greater reduction in shunt blood flow than in capillary flow, "indicating that increases in sympathetic nerve activity will result in a redistribution of flow from shunt to exchange vessels" (Änggård 1974b).

Inhibition of sympathetic nerve activity by a stellate ganglion blockade or by transection of the sympathetic nerves result in a congestion of the nasal mucosa in animals as well as in humans (Millonig et al 1950, Stoksted & Thomsen 1953, Malcomson 195[illegible], Richerson & Seebohm 1968, Malm 1974b, Änggård & Edwall 1974, Simon & Schmidt-Kloiber 1985). The congestion of the mucosa has been ascribed to dilatation of the capacitance vessels (Malm 1974b, Änggård & Edwall 1974, Simon & Schmidt-Kloiber 1985). When the sympathetic neurogenic control is eliminated, blood flow increases up to 16% in the cat nasal mucosa (Änggård & Edwall 1974), and an increased thermal conductivity on the human nasal septum has been demonstrated (Drettner 1961).

Studies of the acute effects of a sympathetic nerve block on nasal mucosal blood flow are sparse why further investigations seemto be of interest.

AIMS OF THE STUDY

The present investigations were performed in order to

- evaluate the ^{133}Xe washout technique and laser doppler flowmetry as means for measuring blood flow in the human nasal mucosa (I, II, III),
- study the effect of environmental temperature on nasal mucosal blood flow and blood volume (IV),
- evaluate the possible role of leukotriene D_4 in the pathophysiological events of nasal allergy (V),
- study sympathetic neurogenic control of blood flow in the human nasal mucosa (VI).

THE PRESENT INVESTIGATIONS

The studies were performed on healthy volunteers (I-V) and on patients (I and VI). The subjects denied any history of airway allergy and they had no symptoms of nasal disease at the time of registration. Prior to each registration the nasal mucosa was inspected by means of anterior rhinoscopy. Studies were also performed on corpses (I).

EVALUATION OF THE ^{133}XE WASHOUT TECHNIQUE AND LASER DOPPLER FLOWMETRY AS MEANS FOR MEASURING BLOOD FLOW IN THE HUMAN NASAL MUCOSA (I, II, III).

The disappearance of ^{133}Xe injected into the mucosa of the inferior turbinate was studied with a scintillation detector before and after local administration of oxymetazoline (Nezeril®) and histamine. Blood flow was calculated in ml/min/100g tissue according to Lassen et al (1964) from the washout curve of the isotope between 1-5 min. The elimination rate of the isotope under these circumstances was compared to the elimination of ^{133}Xe injected into the nasal mucosa on corpses, which was assumed to represent passive elimination of ^{133}Xe. Since ^{133}Xe is almost completely eliminated from the blood in one lung passage (Alpert et al 1968), the disappearance of ^{133}Xe by blood flow and by leakage to the nasal air was evaluated with a scintillation camera on laryngectomees, where the expiratory air could be collected from the tracheostoma. Spreading of the injected isotope within the nasal mucosa was also evaluated.

The laser doppler flowmeter Periflux PF 1d and the measuring probe PF 103d (Perimed, Sweden) was applied for evaluation of blood flow changes in the mucoca of the inferior turbinate under resting conditions, and during a peripheral cold provocation simultaneously with registration of mucosal temperature. The measuring probe was fixed in a position with the tip of the probe close to the mucosal surface. The thermodetector was located in the contralateral nasal cavity. After blood flow and temperature registrations had stabilized, the feet were momentarily exposed to cold water (10 $\pm$ 1^{o}C) for 5 min.

Footnote: All subjects gave their informed consent to take part in the studies according to the Helsinki Declaration. The use of ^{133}Xe for blood flow measurements was approved by the Isotope Committee, University Hospital, Lund, Sweden. The studies were approved by the Ethics Committee, Faculty of Medicine, University of Lund, Sweden.

In separate registrations, the influence of the distance between the measuring probe and the tissue surface on the output signal was evaluated, and the coefficient of variation for the laser doppler method was determined from repeated measurements of blood flow changes induced by topical xylometazoline on different days.

To evaluate if the ^{133}Xe washout and laser doppler techniques reflect similar aspects of nasal mucosal blood flow, the effect on nasal mucosal blood flow from topical application of saline and the alpha-adrenoceptor agonists xylometazoline and noradrenaline were estimated with both techniques. In order to evaluate the effect of the injection trauma associated with the ^{133}Xe washout technique, a needle was pricked into the mucosa during registration of blood flow with the laser doppler.

Results

Blood flow decreased after oxymetazoline and it increased after histamine with the ^{133}Xe washout technique. A very slow elimination of ^{133}Xe was seen in corpses (Fig. 2).

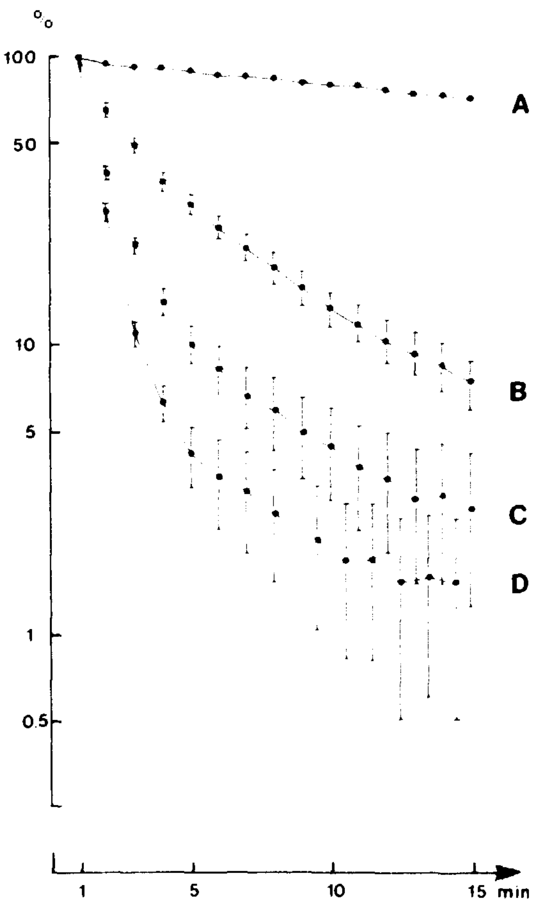

Fig. 2. ^{133}Xe washout curves from human nasal mucosa in corpses (A), after oxymetazoline chloride administration (B), without drug influence (C), and after histamine dihydrochloride administration (D).

In laryngectomees, about 95% of the ^{133}Xe activity in the nasal mucosa at 1 min was found either in the air expired via the tracheostoma or retained in the mucosa after 5 min. The leakage direct to the nasal air was about 5%. Apart from elimination by blood flow and by leakage to the air, the isotope did not spread outside the mucosa of the inferior turbinate.

The laser doppler output signal showed a steady value under resting conditions, apart from small spontaneous oscillations. Cooling of the feet elicited a decrease in blood flow for 2 min and a decrease in mucosal temperature for 4 min. The signal did not change with a varying distance between the probe and the mucosa up to 3.5 mm. If the probe was further removed, the signal disappeared abruptly. When the probe was pressed against the mucosa, a decreased output signal was obtained. The coefficient of variation for the laser doppler registrations was determined to 10%.

When related to the effect of topical saline, blood flow was found to decrease dose-dependently after topical xylometazoline, as registered with laser doppler flowmetry and with washout of ^{133}Xe. After topical noradrenaline, the blood flow was reduced as registered with the laser doppler, while no change was seen in the elimination rate of ^{133}Xe. The injection trauma induced an immediate decrease in blood flow, which was followed by an increased flow for 2 min.

Comments

The injected ^{133}Xe is eliminated from the nasal mucosa mainly by the blood flow. Leakage to the nasal air is small, and the isotope does not spread within the nasal mucosa outside the area covered by the scintillation detector. With the ^{133}Xe washout technique, differences in local blood flow can be distinguished under various circumstances, as calculated from the washout curve of the isotope between 1-5 min. The tissue trauma induced by injection of the isotope seems to be of minor importance in the highly vascularized nasal mucosa.

The laser doppler flowmeter admits continuous registrations of relative changes in blood flow induced by physical and by pharmacological stimuli. Possible changes in mucosal thickness during the registration do not interfere with the blood flow recording, unless the probe presses against the mucosa.

The ^{133}Xe washout and laser doppler techniques are complementary to each other in that they presumably reflect blood flow in different parts of the vascular bed in the human nasal mucosa. This is concluded from the finding of different results with the two techniques after topical application of noradrenaline.

VASCULAR CHANGES IN THE NASAL MUCOSA ON EXPOSURE TO VARIOUS ENVIRONMENTAL TEMPERATURES (IV).

Nasal mucosal blood flow and nasal patency were studied at room temperature (+23°C), and after 20 min of general exposure to a cold (+6°C) and a warm (+40°C) environment. Blood flow was measured with the ^{133}Xe washout technique, and nasal patency was determined with a peak flowmeter.

Results

There was a decrease in blood flow and in nasal patency after general exposure to cold. Nasal patency increased after general exposure to warmth, while blood flow was unchanged as compared to control registrations at room temperature. (A schematic drawing of the changes observed in each individual is presented in Fig. 3.)

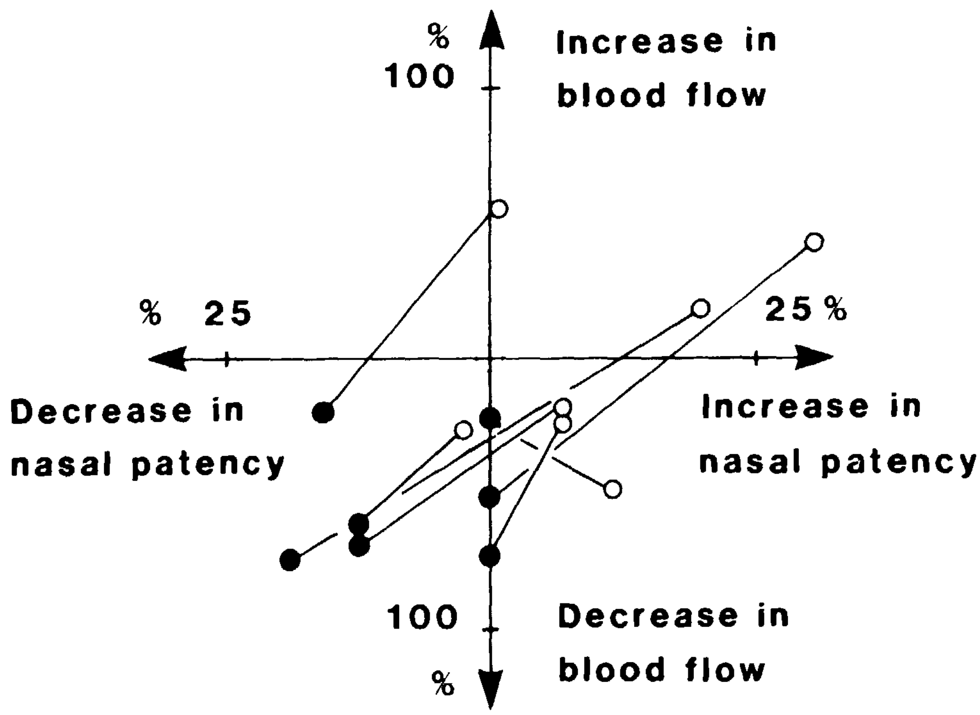

Fig. 3. Relative changes in nasal mucosal blood flow and nasal patency on general exposure to cold (+6°C, ●) and heat (+40°C, ○) in 7 subjects as compared to registrations at room temperature (+23°C, origo). The calculations are based on the figures given in the table p 154 (IV). Blood flow was studied with the ^{133}Xe washout technique and nasal patency was studied indirectly with a peak flowmeter.

Comments

The ^{133}Xe washout technique may be considered a more suitable technique to study nasal mucosal blood flow under the influence of various environmental temperatures than earlier described techniques, as the blood flow is estimated in a direct way. Although the state of the capacitance vessels is mostly investigated by means of rhinomanometry, the more simple peak flowmeter was applied in this study for practical reasons. An increase in nasal airway resistance is equivalent to a decrease in nasal patency.

This study confirms the predominating opinion of the correlation between nasal vascular reactions and changes in environmental temperature based on results from recordings with other methods. Furthermore, it is shown that the resistance and the capacitance vessels may be regulated independently of each other, i.e., the resistance vessels may constrict although the capacitance vessels are dilated. On general cold exposure, constriction of the resistance vessels may be primarily related to body temperature control, and dilatation of the capacitance vessels may be more concerned with the exchange of heat between the nasal mucosa and the respiratory air.

A POSSIBLE ROLE OF LEUKOTRIENE D_4 IN THE PATHOPHYSIOLOGICAL EVENTS OF NASAL ALLERGY (V).

Blood flow was measured with laser doppler flowmetry. After a stable recording was achieved and a baseline value had been noted, the test substance was administered atraumatically to the nasal mucosa focused by the laser beam, and blood flow was continuously monitored. The effect of LTD_4 in relation to time, and the effects of LTD_4 and histamine in various concentrations were studied. The effect of saline and LTD_4 on nasal airway resistance was measured by active anterior rhinomanometry. The effect of saline, LTD_4 and histamine on nasal secretion was measured by a nasal lavage with a ^{99m}Tc-albumin solution (Bisgaard et al 1986), and the occurrence of irritative symptoms were noted.

Results

A dose-dependent increase in blood flow was seen after LTD_4 as well as after histamine. LTD_4 induced a dose-dependent increase in nasal airway resistance, while increased nasal secretion or irritative symptoms were not observed. Histamine induced a dose-dependent increase in nasal secretion, and also produced irritative symptoms.

Comments

Local release of histamine as well as LTD_4 in the human nasal mucosa in response to an allergen challenge might induce an increased blood flow. The effect of histamine on nasal airway resistance was not evaluated in the present study, but it has previously been shown that topical histamine induces nasal blockage (Secher et al 1982). The present results show that also LTD_4 produces nasal blockage, why LTD_4 as well as histamine might be involved in the pathophysiology of nasal blockage in nasal allergy. Irritative symptoms and an increased nasal secretion, on the other hand, do not seem to be mediated by LTD_4, but might be due to the release of histamine or other mediators.

SYMPATHETIC NEUROGENIC CONTROL OF BLOOD FLOW IN THE HUMAN NASAL MUCOSA (VI).

Blood flow was studied in the nasal mucosa with the ^{133}Xe washout technique before and after a unilateral blockade of the sympathetic nerves to the nasal mucosa. Blood flow changes induced by cooling of the subjects' feet were evaluated with laser doppler flowmetry before as well as after the blockade in order to evaluate the efferent pathway for the decrease in blood flow elicited by a peripheral cold provocation (cf. Drettner 1961, II). The spontaneous occurrence of small oscillations in blood flow was also studied with laser doppler flowmetry before and after the blockade in order to evaluate whether such oscillations are dependent on sympathetic neurogenic activity (cf. II).

Results

Blood flow, expressed in ml/min/100g, was not found to change in response to a sympathetic nerve blockade. Before the blockade, cooling of the feet elicited a transient relative reduction in blood flow. This reduction was not elicited after the nerve blockade. The frequency of spontaneous oscillations decreased after the blockade as compared to before the blockade.

Comments

The absence of an increased blood flow after a sympathetic nerve blockade indicates that the tone of the resistance vessels during resting conditions is not built up by sympathetic nerve activity to any great extent. It is confirmed that the decreased blood flow elicited by a peripheral cold provocation is mediated by the cervical sympathetics, which, in turn, implies that sympathetic nerve activity is important for blood flow regulation under non-basal conditions. Vasomotion, which is illustrated by the spontaneous oscillations in the laser doppler output signal (Tenland 1982), is demonstrated in the nasal mucosa under resting conditions and it appears to be partly dependent on sympathetic neurogenic activity.

DISCUSSION

Vascular studies can be performed using different experimental models. Although investigations performed in animals often allow a better control of the experimental conditions, such studies may not necessarily apply to humans. The prime interest of the present study was to find out whether the well established ^{133}Xe washout and laser doppler techniques were suitable for direct investigations of blood flow also in the human nasal mucosa. For this purpose, these techniques were applied for studies of blood flow changes induced by factors with known vascular effects (I-III). Since the techniques were found useful, they were further applied for evaluation of some mechanisms in nasal physiology, nasal allergy and nasal vascular regulation (IV-VI).

Methodological considerations

The ^{133}Xe washout technique admits quantitative determinations of tissue blood flow (Lassen 1967, Sejrsen 1971). When this technique is applied in studies of nasal blood flow, however, some questions related to the complexity of the vascular bed should be recognized. Firstly, from which part of the washout curve should blood flow be calculated? Secondly, to what extent does elimination of ^{133}Xe reflect total blood flow, capillary blood flow or shunt blood flow?

Regarding what part of the washout curve to be used for blood flow calculations, the following aspects may be taken into consideration: the facts that 90% of the isotope activity is eliminated between 1-5 min after the injection in normal subjects (I), that washout of ^{133}Xe from the mucosa is not linear (I) and that the injection trauma might influence blood flow. The recording was started 1 min after the injection of the isotope, partly to allow a "stabilizing" period, and partly because it took some time to get the experimental set-up ready. Although the injection trauma was seen to affect the blood flow from 0 to 2 min (III) and a "stabilizing" period of 2 min would be correct from this point of view, the changes appeared to be minor. Also in other studies, an injection trauma has been shown to have only slight effects on blood flow recordings in highly perfused tissues (Holloway 1980, Ottesen 1980). The upper limit of 5 min was chosen because the first component of the washout curve was seen to end after 5-7 min (I). Although the absolute value of the blood flow may not coincide exactly with the blood flow calculated in this way, calculations based on the isotope elimination between 1 and 5 min can be used as a semiquantitative measure of blood flow in the mucosa. It should be noted that blood flow in the mucosa of the inferior turbinate may differ from blood flow in other parts of the nasal cavity, which has been shown in dogs (Abe & Jackson 1972).

As to the amount of ^{133}Xe eliminated via different vascular segments, ^{133}Xe is freely diffusable in the tissue, why it may be eliminated both via the exchange and via the shunt vessels (Sejrsen 1971), as well as by diffusion directly to postcapillary vessels. The latter has been estimated to about 10% in skeletal muscle (Sejrsen & Tønnesen 1972). Regarding the shunt flow, only a small fraction has been assumed to be reflected with the ^{133}Xe washout technique in skin (Engelhardt & Kristensen 1983). Since the arteriovenous shunts in the nasal mucosa have been considered comparable to shunt vessels in the skin (Änggård 1974b, Cole 1982a), they would be expected to dilate in exercise, on general exposure to heat and after a blockade of the stellate ganglion (cf. Mellander & Johansson 1968). However, under none of these circumstances is the blood flow changed in the human nasal mucosa as registered with the ^{133}Xe washout technique (Paulsson et al 1985, IV, VI). Thus, when injected into the nasal mucosa, the ^{133}Xe seems not to be eliminated via the shunt vessels. Although there are differences between various radioactive tracers, this is in accordance with the statement of Kety (1960) that "radioactive sodium and nitrous oxide techniques neglect the flow through arteriovenous shunts and estimate only capillary flow". Calculations of capillary blood flow based on the ^{133}Xe tracer disappearance rate will therefore not be invalidated by a redistribution of flow between the exchange and the shunt vessels within the mucosa. In turn, this implies that the calculated values do not reflect total mucosal blood flow (cf. Änggård & Edwall 1974). On the other hand, when ^{133}Xe is injected 'deeply' into the mucosa, the washout technique seems to reflect blood flow mainly at this level (III).

The ^{133}Xe washout technique admits semiquantitative determinations of blood flow in the human nasal mucosa. The drawbacks are related to the radiation dose, although it is small, and to the invasive nature of the technique.

According to Tenland (1982), the laser doppler flowmeter Periflux PF 1 (Perimed, Sweden) constitutes a fast-reacting and longterm stable method for continuous registrations of relative blood flow changes. Furthermore, in vitro studies have shown the laser doppler signal to be linearly related to the number of moving red cells times their mean velocity, and it has been stated that a linear relationship would be expected in tissues with a low or moderate fraction of red cells and with no large vessels in the measured tissue volume (Tenland 1982). The fraction of red cells is not known a priori for a specific tissue, but the flux of cells in mucous membranes has lately been suggested to be underestimated with the Periflux PF 1 (Nilsson 1984). A more sophisticated equipment has therefore been designed (Periflux PF 2, Perimed, Sweden) which will give a linear relation between the actual flux of cells and the output signal also in tissues with a high fraction of red cells (Nilsson 1984). The Periflux PF 2 was not available when the present study was performed and the blood flow changes recorded with the Periflux PF 1 might have been underestimated, especially in case of an increased blood flow. This does not invalidate relative determinations of blood flow changes, however.

The penetration depth for the laser light has been estimated to be about 1 mm in human skin (Bonner & Nossal 1981). The lack of an epidermis in the nasal mucosa means that the light may well penetrate deeper in this tissue. On the other hand, the penetration depth is assumed to be reduced in richly vascularized tissues (Tenland 1982). Although the exact penetration depth cannot be determined for the nasal mucosa, it seems likely that the laser doppler flowmeter reflects mainly the superficial blood flow in the mucosa (III). The arteriovenous shunts and the sinusoids are situated in the deeper parts of the human nasal mucosa (Cauna 1982), why flow in these vessels may not contribute to the output signal to any great degree.

An additional factor to be considered is related to a possible influence of a changed distance between the probe and the tissue surface during the recording. With the probe used, variations within 3.5 mm from the mucosa did not affect the output signal (II). On the other hand, the probe must not press against the mucosa, as this will reduce the blood flow. The reproducibility of laser doppler registrations imply that this technique, like the ^{133}Xe washout technique (cf. Bende 1983c), may be used for comparisons of blood flow studies performed on different occasions even on small groups (III).

Laser doppler flowmetry admits continuous registrations of blood flow in an atraumatic manner. The main limitations are related to the variation in penetration of the laser light in different tissues, which means that it is not quite known from which part of the tissue the blood flow is measured, and to the relative nature of the blood flow determinations.

Aspects on blood flow in the human nasal mucosa

The present study shows that a dissociation can occur between changes in the resistance and the capacitance vessels on variations in the environmental temperature (IV). This may be very important when discussing the role of nasal vascular changes for body temperature regulation and for conditioning of respiratory air. This opinion has not been emphasized previously (cf. Negus 1958, Drettner 1961, Cole 1982a).

On general exposure to cold, heat-saving mechanisms are needed. The present finding of a diminished blood flow in the nasal mucosa at cold exposure (IV) might be part of such mechanisms. The decreased blood flow may contribute to the reduced mucosal temperature (Drettner 1961), which will increase recovery of heat and water from the expiratory air (Cole 1982a). The present finding of an increased blood volume in the mucosa (IV) means that recovery of heat and water may be further enhanced by narrowing of the nasal passages (Cole 1982b). As for conditioning of inspired air in cold, warming as well as moistening of the air is also facilitated by a congestion of the mucosa (Cole 1982b). Although there is a slight reduction in mucosal temperature (Drettner 1961), the temperature difference between the inspired air and the mucosa may well admit warming of the cold air. Thus, in cold, body temperature control and conditioning of respiratory air could be achieved by the described mechanisms.

On general exposure to heat, elimination of body heat is needed. The temperature of the nasal mucosa may increase, leading to a decreased temperature difference between the mucosal surface and the expired air, which, in turn, results in a diminished recovery of heat and water from the expiratory air (Cole 1982a). A decreased blood volume in the mucosa (IV) means that elimination of heat and water may be further enhanced by the widening of the nasal passages (Cole 1982b). Warming of the inspired air in a warm climate is not needed, while moistening of the air is desirable. However, water is known to carry heat efficiently (Swift 1982), why a conflict arises between body temperature regulation and conditioning of inspiratory air on general exposure to heat. Temperature control may be considered more essential for the organism, why recovery of water from the expiratory air and moistening of inspiratory air will diminish.

The laser doppler flowmeter was applied for studies of blood flow changes induced by histamine and leukotriene D_4 (LTD_4) on non-atopic subjects (V). The substances were found to induce an increased blood flow in the nasal mucosa, as previously shown in human skin (Bisgaard et al 1982, Camp et al 1983, Bisgaard & Kristensen 1984). On the other hand, LTD_4 has been seen to initially constrict small vessels in the hamster cheek pouch (Dahlén et al 1981), and to reduce blood flow in guinea-pig skin (Peck et al 1981). An initial short-

-lasting vasoconstriction cannot be excluded for methodological reasons in the present study. However, a possible dual effect of LTD_4 or differences between species may also account for the diverging results. The findings in the present study indicate that a local release of LTD_4 as well as histamine in response to an allergen challenge to the sensitized human nasal mucosa may be responsible for an increase in local blood flow. Such an increase has been demonstrated in the acute allergic reaction with the hydrogen clearance technique (Konno et al 1982a) and with laser doppler flowmetry (unpublished observations).

Nasal blockage is a major symptom in nasal allergy, which may partly be accounted for by local release of LTD_4, as nasal blockage is induced by topical application of LTD_4. On the other hand, the same dose of LTD_4 that was seen to increase nasal airway resistance had no effect on nasal secretion and it did not produce any irritative symptoms. Although it cannot be excluded that a higher dose could induce an increased secretion and irritative symptoms, the present results indicate that hypersecretion, itching and sneezing induced by an allergen challenge to the sensitized human nasal mucosa are mediated by other substances than LTD_4.

Neurogenic control of a vascular bed may be studied either by stimulation or by inhibition of neurogenic activity. Stimulation of the sympathetic nerves innervating the human nasal mucosa is not possible to perform directly for ethical reasons. Indirectly induced increase in sympathetic nerve activity seems to be present when the feet are chilled with cold water and in exercise (Drettner 1961, Konno et al 1982b). However, studies during exercise might be compromised by contemporary demands on body heat elimination which may counteract the effects of the general sympathetic stimulation.

Inhibition of sympathetic neurogenic control of the vascular bed in the nasal mucosa can be studied in patients undergoing stellate ganglion blockades (VI). Such studies allow determination of the extent to which vascular tone during resting conditions in the specific tissue is built up by sympathetic neurogenic activity. It should be recalled that except for sympathetic neurogenic activity, the vascular tone is built up by myogenic activity that is independent of neurogenic control (Mellander & Johansson 1968), why a maximal dilatation of the vascular bed may not be achieved by a sympathetic nerve blockade. Earlier studies have demonstrated an unequivocal congestion of the nasal mucosa after a stellate ganglion blockade, which has been ascribed to a dilatation of the capacitance vessels (Konno et al 1982b, Simon & Schmidt-Kloiber 1985). Blood flow, which is dependent on the state of the resistance vessels, was not found to change in the present study under similar conditions (VI). Although a comparison between changes in vascular tone in the capacitance and the resistance vessels based on changes in nasal airway resistance and blood flow, respectively, may not be proper, the finding supports the opinion that differences exist in the regulation of the resistance and the capacitance vessels in the human nasal mucosa (cf. IV). This is in agreement with the earlier demonstrated relative difference in vasoconstrictor response to sympathetic stimulation between the capacitance and the resistance vessels in the cat nasal mucosa (Änggård & Edwall 1974, Malm 1977). The finding also demonstrates the well-known fact that the resistance vessels may be under different degrees of sympathetic tone in different tissues (Folkow 1960).

The effect of a peripheral cold water provocation has earlier been found to be dependent on nervous afferent signalling and not to be mediated by cooling of the blood (Drettner 1961). Drettner (1961) found that the efferent pathway appeared to be the cervical sympathetics, and this is confirmed in the present study (VI).

In conclusion, the ^{133}Xe washout and laser doppler techniques are useful for studies of blood flow in human nasal mucosa under various external conditions and under the influence of drugs.

SUMMARY

The overall aim of the present study was to evaluate whether the ^{133}Xe washout and laser doppler techniques could be used for investigations of blood flow in the human nasal mucosa. Since they were found useful, the techniques were applied for studies of the influence of environmental temperature on the human nasal mucosa, for studies of mediators in nasal allergy and for studies of the sympathetic neurogenic control of blood flow in the nasal mucosa.

The results show that the two techniques are complementary to one another. The ^{133}Xe washout technique is useful for semi-quantitative estimations of blood flow in the deeper parts of the mucosa, while the laser doppler technique is especially suited for continuous recordings of relative blood flow changes in the superficial part of the mucosa. None of the techniques seem to measure shunt blood flow.

Vascular changes may take part in body temperature regulation as well as in conditioning of respiratory air. The results support the theories that changes in nasal mucosal blood flow are related to body temperature control, while conditioning of inspiratory air may be more dependent on mucosal blood content. The observed dissociation between changes in the resistance and the capacitance vessels also illustrates that these vascular segments are regulated in different ways.

Histamine is a well documented mediator in nasal allergy, but other mediators may as well be involved. The present results indicate that leukotriene D_4 might contribute to an increased blood flow in the nasal mucosa and to blockage of the nasal airway in the acute allergic reaction.

The sympathetic neurogenic influence on the resistance vessels in the human nasal mucosa is not marked during resting conditions. Vasomotion is demonstrated to be present in the nasal mucosa, and it appears to be partly dependent on sympathetic neurogenic activity, however. Furthermore increased sympathetic activity reduces blood flow in the mucosa.

The development of the present techniques, which allow studies of blood flow in the human nasal mucosa, means that vascular changes involved in normal nasal function and in nasal disease may be evaluated by a new approach.

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