New perspectives on basic mechanisms in lung disease · 4

Why are the airways so vascular?

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The mucosa of the nose and of the tracheo-bronchial tree is highly vascular. In several species, blood flow at rest in both parts of the respiratory tract is about $0.3\text{--}1.0\text{ ml g}^{-1}\text{ min}^{-1}$.¹ In hyperthermic stress in the dog nasal flow may increase to $3\text{ ml g}^{-1}\text{ min}^{-1}$ and tracheal flow to over $7\text{ ml g}^{-1}\text{ min}^{-1}$.² These figures may be compared with blood flow in cardiac muscle (maximum $4\text{ ml g}^{-1}\text{ min}^{-1}$), skeletal muscle (maximum $1\text{ ml g}^{-1}\text{ min}^{-1}$), and secreting salivary glands ($3\text{ ml g}^{-1}\text{ min}^{-1}$); the kidney has a steady flow of about $4\text{ ml g}^{-1}\text{ min}^{-1}$.³

In the nose a large blood flow may be related to its role in air conditioning and in control of body temperature, but these roles are more difficult to understand for the tracheo-bronchial vasculature. A pathological condition of the vasculature is the main underlying defect in nasal diseases such as allergic and non-allergic rhinitis, where vascular congestion and oedema predominate in causing nasal blockage. For the lower airways, in

asthma the primary defect is increasingly considered to be mucosal inflammation, with secondary muscular effects; thus mucosal vascular changes and their sequelae are almost certainly important.

Vascular structure

For the nose and the lower airways the vasculature has two components, a copious subepithelial capillary network and a deeper system of venules and sinuses or sinusoids that constitutes a "capacitance system" (figs 1 and 2).⁴⁻⁷ There are, however, some striking differences.

SUBEPITHELIAL CAPILLARY NETWORK

The dense subepithelial capillary networks may be functionally related to a high metabolic rate of the epithelium, which, like glandular tissue, is very active in secretory processes. The oxygen consumption of sheets of tracheal epithelium (assumed $30\text{ }\mu\text{m}$ thick)

Figure 1 Low power scanning electron micrograph of the microvascular network of the dog for a 3 mm diameter bronchus that has been opened to expose the mucosa. The vessels were filled with anatomical corrosion compound and the soft tissue was digested away. The bronchus runs from upper left to lower right, and has been cut at both ends. The capillaries (C) are arranged longitudinally. A—arteriole; V—start of venule; bar represents $100\text{ }\mu\text{m}$. From Laitinen et al,⁵ reproduced by courtesy of the Journal of Anatomy.

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Figure 2 Low power scanning electron micrograph (montage) of the tracheal vasculature of the sheep: view from submucosal surface showing network of sinuses (S), with subepithelial capillaries lying deeper. Bar represents 300 μm . From Hill *et al.*,⁴ reproduced by courtesy of the *Journal of Anatomy*.

is $5\text{--}13 \mu\text{mol min}^{-1} \text{g}^{-1}$,⁸⁹ compared, for example, with $1.6 \mu\text{mol min}^{-1} \text{g}^{-1}$ for the liver and $4.5 \mu\text{mol min}^{-1} \text{g}^{-1}$ for the beating heart.¹⁰ The high metabolic rate of airway epithelia is presumably related to ciliary movement and to active transport processes. The rabbit has only a sparse capillary network; this may be related to a low mucosal metabolism since the rabbit lacks submucosal glands.

In the nose the subepithelial capillaries are fenestrated,¹¹ presumably facilitating extravasation of liquid and oedema formation, whereas in the tracheobronchial tree in most species, including healthy man, only the capillaries underlying neuroepithelial bodies are fenestrated, the rest having a continuous epithelium.¹² But in the rat, hamster and guinea pig the lower airway capillaries are fenestrated,¹³ and the same is true for asthmatic patients;¹² presumably in these patients liquid transudation and exudation are facilitated.

MUCOSAL CAPACITANCE SYSTEM

The role of the capacitance system in the nose has been postulated to control the conditioning powers of the nose.¹⁴ Thus vascular congestion would swell the mucosa and make the nose a more effective filter of inhaled particles and noxious chemicals; it might also improve the air conditioning function of the nose by increasing gas turbulence and water and heat exchange between lumen and tissue. These functions seem very plausible and are consistent with the physiology of the nose. In terms of a control system responding beneficially to environmental conditions, however, the subject has been little studied and there is not much good evidence on control mechanisms. The trachea of some species has a

prominent system of sinuses or capacitance vessels in the deeper layers of the mucosa and these are also found in the bronchi, though they are less conspicuous there.^{14,15} Thus the mucosa of both the nose and the lower airways is “erectile,” and vascular congestion may lead to its thickening.

The physiological advantages of an “erectile” tracheobronchial mucosa are difficult to understand. In the tracheas of the dog and sheep direct measurements show that vascular congestion changes mucosal thickness only by about 100–300 μm , or less than 1–3% of the diameter of the tracheal lumen.^{16,17} It is difficult to see how this would affect the conditioning and filtering role of the trachea. At the level of the smaller, intrapulmonary airways the proportionate change in mucosal thickness would be greater (though it has not been measured), but at this level the capacitance system is less well developed and the conditioning role of the airways is less important. Possibly the capacitance vessels provide a source of heat or water that would lessen the cooling and evaporation associated with hyperventilation through the mouth and thought to be the cause of exercise induced bronchoconstriction. The most efficient vascular system for this function, however, would be arteriovenous anastomoses because both heat and water supplies depend on total blood flow rather than on blood volume as occurs in the nose and skin. Possibly a higher blood volume in the trachea is related more to transients of conditioning, as occur on a breath to breath basis. A large blood volume might buffer such transients.

Other roles of the tracheobronchial capacitance vessels might include acting as a short term reservoir of blood borne mediators, but

this is not consistent with the complex arrangement of tight junctions seen between the endothelial cells of the individual sinuses. Congestion of the bronchial mucosa decreases considerably the compliance of the airway walls,¹⁸ and this could be an important action of the capacitance system. They might also act as a mechanical shock absorbing system to minimise the high shearing forces in the larger airways associated with acts such as coughing and sneezing.¹⁹ All these suggestions are speculations, however, and we really have no answer about the role of the lower airway capacitance system.

One of the most puzzling aspects of the tracheobronchial capacitance system is the pronounced variation between species. If we take the most common laboratory animals, it is most prominent in the sheep and rabbit,^{14 15} poorly developed in the guinea pig and cat, and intermediate in the dog as well as in man. Furthermore, the two species with well developed systems differ in that the vessels in the sheep have no smooth muscle in their walls whereas those in the rabbit have an abundant supply. In man the sinuses have a muscular coat. It seems impossible to correlate these species differences with life style or breathing mechanisms.

ARTERIOVENOUS ANASTOMOSES

The nose, at least in its respiratory region, has a prominent system of arteriovenous anastomoses;²⁰ these may take at least half of the nasal blood flow^{21 22} and their role is presumably related to heat exchange, as with the arteriovenous anastomoses in the skin. They seem to be controlled by sympathetic nerves containing noradrenaline and neuropeptide Y.²⁰ In the dog mediators such as prostaglandin (PG) E₂ can increase mucosal blood flow at the same time as the mucosa shrinks, presumably as a result of the opening of arteriovenous anastomoses and the emptying of capacitance vessels.²³ This observation points to a possible therapeutic approach to vasomotor rhinitis. For the tracheobronchial tree there is no histological evidence of arteriovenous anastomoses. Functional studies with microspheres indicate that they are absent in the sheep but that some may be present in the rabbit²⁴ (also A Robson and J Widdicombe, unpublished observations).

Control of airway vasculature

Blood flow through the airway mucosa is controlled via its innervation and by the action of locally released mediators. Parasympathetic nerves dilate the blood vessels,²⁵⁻²⁷ an action that can be mimicked by the appropriate neurotransmitters acetylcholine and vasoactive intestinal polypeptide or peptide histidine isoleucine or methionine (PHI/PHM).^{28 29} Sympathetic nerves cause vasoconstriction,^{30 31} which can be mimicked by noradrenaline and neuropeptide Y, the sympathetic cotransmitters.^{32 33} These effects apply both to the nose and to the lower airways. The exact balance of motor nervous influences on the different

parts of the vasculature—arterioles, venules, sinuses, and arteriovenous anastomoses—has not been worked out.

VASCULAR REFLEXES

The neural motor input is in turn controlled reflexly in several ways. Of main interest in respiratory disease is the observation that stimulation of lung and airway C fibre receptors causes a reflex vasodilatation in the trachea, the bronchi, and the nose.³⁴⁻³⁶ The sensory receptors for this reflex are thought to be activated by mediators released in inflammatory and immunological reactions in the airways, and to underlie neurogenic inflammation (see below). The reflexes may contribute to the bronchoconstriction and mucus secretion seen in some forms of asthma.^{37 38} As the same afferent activation causes vasodilatation of the mucosa there will be thickening of the mucosa and an increased blood supply as part of the total inflammatory response.

Activation of lung nerve receptors in inflammation causes nasal vasodilatation; the physiological results of this response are not clear. Indeed, if there were to be nasal blockage and opening of the mouth for breathing this might be harmful in some forms of asthma. In the nose inflammation or irritation on one side leads to reflex vasodilatation on the other;³⁹ whether these reflexes from the nose also act on the tracheobronchial vasculature has not been determined.

The airway vasculature is unusual in that baroreceptor reflexes seem to have little action on it³⁴ (also K Dylewska and J Widdicombe, unpublished results), which may be advantageous as vascular congestion in the airways would not be reflexly influenced by body posture. Peripheral chemoreceptor reflexes cause vasoconstriction both in the nose and in the trachea,^{40 41} and the former may contribute to the nasal decongestion and increase in patency seen during exercise and after breath holding.⁴² The effect of chemoreceptor reflexes on the bronchial vasculature is less certain, different patterns of response having been described.⁴³ It is clear, however, that changes in blood gas tensions that may occur in pulmonary disease may reflexly contribute to the control of the circulation of the airway mucosa.

Inflammatory vascular changes

Mediators released in mucosal inflammation or in antigen-antibody reactions may exert profound effects on the vasculature in the nose and lower airways. For example, histamine, bradykinin, platelet activating factor, prostaglandins, and 5-hydroxytryptamine all cause vasodilatation.⁴⁴⁻⁴⁹ This applies both to the resistance vessels, with an increase in blood flow as part of a general inflammatory response, and also to the postcapillary venules, which are the main site of plasma extravasation and oedema.⁵⁰⁻⁵² The increased vascular permeability will bring into the tissue plasma mediators, their precursors, and also

Figure 3 Possible neurogenic inflammation in asthmatic airways via retrograde release of peptides from sensory nerves via an axon reflex. Substance P (SP) causes vasodilatation, plasma exudation, and mucus secretion, whereas neurokinin A (NKA) causes bronchoconstriction and enhanced cholinergic reflexes, and calcitonin gene related peptide (CGRP) causes vasodilatation. From Barnes,⁷⁶ reproduced by courtesy of the Academic Press.

various enzymes. Further, the increased interstitial fluid volume may act mechanically on the epithelium, causing increase in permeability and leakage of plasma into the airway lumen. Antigen-antibody reactions in the airways may cause vasodilatation, mimicking the changes seen in asthma.⁵³⁻⁵⁴

Some mediators have actions more complex than simple vasodilatation. Histamine and 5-hydroxytryptamine, for example, may give rise to biphasic or triphasic responses, with a vasoconstrictor component.⁴⁴⁻⁴⁵ The response may reflect the anatomical complexity of the mucosal vasculature.

A second effect of inflammation is to stimulate sensory nerves in the mucosa, thus setting up neurogenic inflammation, which consists of vasodilatation, oedema, mucus secretion, and possibly contraction of tracheobronchial smooth muscle.⁵⁵⁻⁵⁸ These effects are mediated by axon reflexes in the sensory nerve terminals in the mucosa (fig 3) and are analogous to the triple response in the skin. The nerves are stimulated by a large range of mediators (including histamine, bradykinin, and prostaglandins) and by various exogenous irritants (such as cigarette smoke and capsaicin, the extract of hot peppers).⁵⁹⁻⁶¹ The sensory nerves contain several neuropeptides, such as substance P, calcitonin gene related peptide, and neurokinins A and B.⁶²⁻⁶³ All these neuropeptides cause vasodilatation and increase in blood flow through the tissue, and all except calcitonin gene related peptide increase the permeability of the postcapillary venules and therefore induce extravasation of protein and oedema. The vascular actions can be mimicked by exogenous application of individual sensory neuropeptides.

The vascular response in inflammation is clearly complex. For example, release of a mediator such as histamine or bradykinin will have a direct vasodilator action on blood vessels, will stimulate sensory nerves to set up

neurogenic vasodilatation by an axon reflex, and will set up central nervous reflexes, also leading to vasodilatation. Given that in inflammation many active mediators are released, all of which will act on these systems, the end picture becomes very complicated. It has not been adequately analysed.

A further action of the inflammatory mediators and neuropeptides is on the vascular endothelium, leading to adherence of neutrophils and their passage into the interstitium, which will contribute to the chain reaction of inflammation.⁶⁴⁻⁶⁶ In their turn the neuropeptides will be broken down by enzymes such as neutral endopeptidase, and much research is being done on ways to influence the activity of this enzyme and, in turn, the progress of mucosal inflammation.⁶⁷⁻⁶⁸ The vasodilator action of some inflammatory mediators—for example, bradykinin—is due to release of endothelium derived relaxant factor from capillary epithelium.⁶⁹

Other vascular changes in airways disease

In inflammatory diseases of the lower airways the vasculature is not only dilated but also hypertrophied.¹² This can be shown in viral infections of the airways in laboratory animals,⁷⁰ and in man biopsy material suggests that this also applies to chronic human inflammatory conditions, such as asthma.¹² Thus the pharmacological and physiological mechanisms studied in the healthy condition will be applied to quite a different baseline in airways disease.

The role of the airway vasculature in bronchoconstriction induced by cold, exercise, and hyperventilation is receiving considerable attention. These conditions cool the airways and make its lining liquid hypertonic.⁷¹⁻⁷² Cooling the tracheal mucosa causes vasodilatation, and a similar response is obtained by applying hypertonic saline solutions.⁷³⁻⁷⁴

What happens after the hyperventilation, however, is clearly more relevant to the human bronchoconstriction. It has been suggested that there may be a period of reactive hyperaemia, which is exaggerated in patients with asthma and which leads to bronchial obstruction.⁷⁵ Although removal of a cold evaporative stimulus does lead to increased mucosal blood flow in laboratory animals,⁷⁴ whether this would lead to contraction of airway smooth muscle and obstruction is uncertain; and the experimental change develops far more quickly than could account for exercise induced bronchoconstriction. Thus there are clues suggesting that the mucosal vasculature may have a role in airway responses to hyperventilation, exercise, and cold; but the picture is far from clear and more research needs to be carried out.

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