

Vessels: new targets for asthma treatment

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Are airway vessels really important in asthma? This question has become more relevant since the finding of increased vessel numbers and vascularity in the submucosa of patients with relatively mild asthma.¹ It has been confirmed again by Salvato in this issue of *Thorax*.² The description of asthmatic bronchial vessels has been extended beyond traditional views of vessel function. As well as supplying nutrients to the vessel wall, temperature regulation, and facilitating humidification of the airway environment, vessels have several other important functions in the asthmatic response that may contribute to airflow obstruction. The study by Salvato² comments on each of these components.

Firstly, angiogenesis has been described in airway sections, identifying more vessels in asthma when anti-collagen IV antibodies were used to detect vascular basement membrane.^{1,3,4} Interestingly, collagen IV has been shown to be essential for the development of new endothelial cell tubes.⁵ Studies using anti-factor VIII Ag antibodies have consistently found fewer vessels or have not shown significant differences in asthmatic airway vascularity.^{6,7} Vessel numbers are predominantly regulated by factor dependent endothelial cell proliferation. The initial stimulus is more commonly hypoxia, tumour invasion, or wall stress followed by the release of fibroblast growth factors (FGFs, typically bFGF or FGF-2), vascular endothelial growth factor (VEGF, existing as equipotent isoforms), transforming growth factor β (TGF β), and platelet derived growth factor (PDGF-B).⁸ Increased vessel numbers resulting from angiogenesis in the airway wall contribute to thickening of the airway wall in asthma.

Secondly, airway vessels are capable of vasodilatation. The index of vascularity relates to the percentage of an airway section covered by vessels. Providing vessels have been adequately visualised, the vascularity will be a function of number (density) and size of vessel (vasodilatation). Using modern methods of image analysis, vessel areas can be ascertained with some accuracy and vessel enlargement can be quantified.¹ In active skeletal muscle, where blood flow can increase up to 100-fold to 1 ml/g/min, the “pump” can be significant with substantive increase in bulk. This remains small compared with hyperthermic canine tracheal blood flow at up to 7 ml/g/min.^{9,10} Coined “erectile” tissue by Widdicombe,⁹ the distensibility of the airway wall and its response to bronchodilators may well be reduced under these conditions.¹¹ The vasoactive determinants of bronchial vessel tone are generally well described inflammatory mediators, familiar players in the asthmatic airway response. Vasodilatory mediators include histamine, bradykinin, platelet activating factor, prostaglandins and serotonin.^{9,12} Assessment of the vascular compartment may potentially be complicated by the possible role of bronchodilators that cause bronchial vascular dilatation¹² or anti-inflammatory agents that cause vasoconstriction.¹³

In addition to the microscopically visible changes in vessels, there is as yet an unquantified contribution to human

airway wall thickening due to oedema.¹⁴ Although not stated in many works aimed at quantifying cell numbers or density of structures in the bronchial wall, the presence or absence of oedema may be crucial. As in the paper by Salvato,² many authors correctly describe density as cells per mm². The denominator may be expanded considerably in oedematous tissues leading to a falsely reduced count in the target tissue, minimising any true difference.

A fourth function of vessels is to act as the portal of entry of inflammatory cells to the bronchial microenvironment. The cellular response has been a convenient index of inflammation in in vivo studies, but the route of this response has received relatively little attention by researchers. One landmark study serves to remind us of the role of the eosinophil and adhesion glycoproteins in asthma.¹⁵ Antagonism of ICAM-1 in sensitised monkeys abrogated the cellular and airway response to allergen challenge. A crucial link in the inflammatory events in asthma appears to be the adhesion of inflammatory cells to the bronchial vessel wall. This complex process involves several stages of activation, adhesion, and transmigration—all dependent on intact adhesion mechanisms.¹⁶ While inflammatory cellular ICAM may be steroid sensitive, endothelial adhesion molecules are known to be expressed in asthma¹⁷ but are insensitive to the effects of corticosteroids and may therefore be a future target for novel treatment.¹⁸

With the mounting case for the importance of airway vessels in asthma, is the vascular bed of any clinical significance in airflow obstruction? Mitzner and colleagues have produced significant evidence linking cardiac failure to asthma,¹⁹ fluid loading to increased bronchial reactivity,²⁰ and increased bronchial blood flow to asthma.²¹ A renaissance in thinking about bronchial vessels may not be the first, as Leonardo Da Vinci might have been there before us.²²

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