Airway Vascular Remodeling in Asthma

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Several characteristic changes occur in the bronchial wall in asthma, including specific changes to the vasculature. These result in an increase in vessel numbers per unit area, as well as increased vessel activity suggested by vasodilatation, vessel leakage, and cellular margination with transmigration to target tissues. This combined action in asthma leads to airway-wall thickening and reduced airflow. Each component of the vascular response has been shown to be controlled by a range of inflammatory mediators and growth factors. These factors are themselves regulated by a complex process initially involving gene expression, transcription, and translation at the molecular level, then subsequent protein release, binding to matrix elements, endothelial cell activation, and a proliferative endothelial response. Many commonly used airway medications are capable of modulating the vascular response to inflammatory stimuli. New therapies might improve airflow through better regulation of vessel growth, dilatation, and leakage in the airway wall.

Introduction

Once thought of as simple, but essential, conduits for nutrients, it is now clear that vessels have several highly significant roles in both normal homeostasis and obstructive airway disorders. Recent studies in adults have indicated that the extensive and complex vascular system of the human airway may play an important role in regulating airflow. Information gained largely from the use of bronchial biopsies and specific vessel stains has indicated that airway inflammation is highly dependent on the active role of the vasculature. Many current asthma therapies are active in regulating the bronchial vasculature, indicating that novel therapies may be directed at regulating vessel activation.

Significance of the Bronchial Vasculature

In the normal airway, the bronchial vasculature has several functions that are essential for maintaining homeostasis. These include provision of oxygen and nutrients, temperature regulation, and humidification of inspired air, as well as being the primary portal of the immune response to inspired organisms and antigens. In asthma, the bronchial vasculature might contribute to an alteration in bronchial-wall dynamic properties through increased vessel caliber (vasodilatation), increased vessel numbers (angioneogenesis), and the formation of interstitial edema within the airway wall (microvascular leak) [1]. Indirectly, submucosal vessels act as portals of entry for inflammatory cells, via upregulation of cell adhesion glycoproteins. They produce cytokine growth factors capable of autoregulation of endothelial function. Additionally, bronchial vessels respond to asthma therapy (Fig. 1). Typical airway vessels are identifiable with specific stains.

Deeper, interconnecting capacitance vessels may have smooth muscle in their walls that appears similar to venules. Increased pressure in this system, associated with vasodilatation, may cause substantial mucosal thickening [2]. The implication of this finding depends on (1) the site of any enhanced vascular response within the airway (depth within the wall, as well as airway caliber); (2) the number and density of vessels at that site; (3) underlying bronchial smooth muscle tone; (4) pre-existing mucosal thickening; and, possibly, (5) the degree of inspiration loading the capacitance vessels.

The detailed anatomy of the blood supply of the airways has been reviewed elsewhere [3,4•].

Tissue Angiogenesis

Nonreplicating vessels require trophic factors to maintain endothelial cell homeostasis. The endothelial cell is a metabolically active cell and is central to tissue vascularity. A wide range of factors have been found to have angiogenic ability (Table 1). To be capable of stimulation, resting endothelial cells must express receptors for angiogeneic factors [5]. For example, signal transduction pathways for the vascular endothelial growth factor (VEGF) receptors VEGFR-1 and VEGFR-2 involve specific tyrosine kinases Flt-1 (fms-like tyrosine kinase) and KDR (kinase domain region) [6,7]. Gene expression for these kinases has been shown to occur virtually exclusively within endothelial cells [8,9]. The regulation of receptor expression might be a crucial step in effective therapeutic interventions that control vascularity of the airway. The redundancy of growth factor activity allows many inflammatory cytokines, such

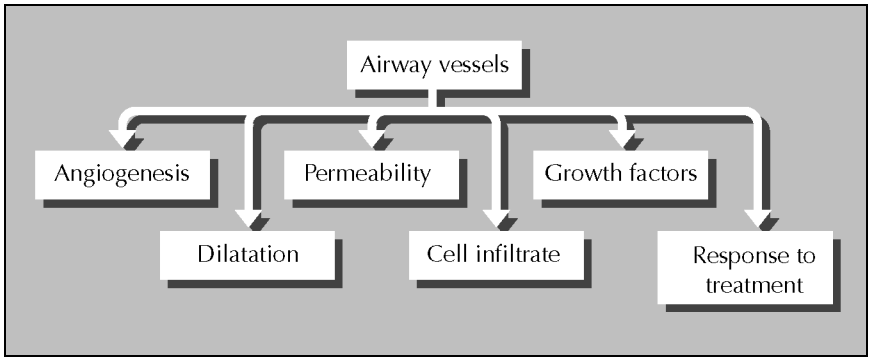

Figure 1. The role of bronchial vessels in asthma.

as interleukin-8 (IL-8), to exert overlapping angiogenic activity in the airway in asthma.

Endothelial Cell Activation

After binding of activating factors to specific endothelial receptors has occurred, replication and new vessel formation is dependent on a sequence of local events. Polarization of endothelial cells leads to interaction with matrix elements, including collagen IV, laminin, fibronectin, and vitronectin. This process is dependent on the cell-expressing integrins. The role of other adhesion molecules expressed during angiogenesis, such as CD34 and PECAM/CD31, is currently unknown. Importantly, endothelial expression of integrins has been antagonized by the action of antibodies directed at the adhesion molecule ICAM-1 to reduce eosinophil infiltration and successfully abrogate experimentally induced airway reactivity [10•]. Further induction of endothelial cell replication may occur because of sheer stress, cyclic strain, chronic inflammation, infection, and the action of drugs (including vasodilators). Vessel remodeling then occurs following endothelial cell proliferation, leading to the generation of new capillaries (Fig. 2).

An excessive angiogenic response to injury may potentially be regulated by several mechanisms including down-regulation of angiogenic factors or their receptors, or the later action of growth-limiting anti-angiogenic factors (Fig. 3). Currently known inhibitors of angiogenesis include angiopoietin-2 (antagonist of the tie-2 receptor) [11]; angiostatin (a fragment of plasminogen)[12]; thrombospondin (prevents heparin binding to growth factors such as basic fibroblast growth factor); tissue inhibitors of metalloproteinases [13], interferon (IFN)-α and IFN-γ; and IL-12 (by stimulating IFN-γ and inducible protein-10 [IP-10]) [14]. In addition, CXC chemokines that lack the ELR motif are also highly inhibitory and include IP-10 and PF4 [15•].

Quantitation of Airway Vessels

The airway in human asthma is accessible for study from three sources. Postmortem material affords the advantages of being potentially well characterized on clinical grounds and available in sufficient amounts for detailed studies [16]. Specimens from lung resection also afford the advantage of being available in reasonable quantities for study; however, they are available infrequently and may be complicated by other factors such as injury from cigarette smoking [17]. The use of fiberoptic bronchoscopy has allowed repeated interventions in well-characterized asthmatic volunteers, as well as the study of immunologic challenge and pharmacologic intervention [18].

Fiberoptic bronchoscopy has also allowed the study of relatively well-characterized, mild asthmatics. Kuwano *et al.* [17] used an antibody to factor VIII antigen to study vessel numbers and vascularity in asthmatic and control airways from resected lung and postmortem specimens [17]. They found an airway vascularity of 3.3% in subjects with asthma and 0.6% in control subjects. In a study of postmortem material from fatal asthma, nonfatal asthma, and controls, Carroll *et al.* [19] also used a monoclonal antibody to factor VIII antigen to measure vessels and their size. They found an increase in the number of larger factor VIII antigen-positive vessels in patients with fatal asthma, and concluded that increased vascularity must be a reflection of the increased wall thickness, rather than a causative factor.

The use of collagen IV antibodies to differentiate vessels in bronchial biopsies from mild asthma gave a better representation of true vascularity [20•]. In comparison with previous studies using factor VIII antigen, significantly more vessels were detected. Asthmatics have an increase in density of vessels compared with controls (738 mm^2 versus 539 mm^2), and airway vascularity was also increased in asthma compared with controls (17.2% vs 10.3%).

These findings indicate that the method of vessel identification is crucial to determination of airway vascularity and the likelihood of vessel proliferation in asthma. Angiogenesis in the asthmatic airway has been shown directly, using proliferating cell nuclear antigen as an indicator of replication in endothelial cells [21].

Inflammation and Bronchial Vasculature

Characteristic changes of airway injury are associated with the inflammatory response in asthma. The capillary bed of the bronchial wall may respond to inflammatory products

Table 1. Factors that regulate the airway vascular response

Angiogenesis	Vasodilation	Microvascular leakage
VEGF	Histamine	O_2^-
aFGF	Tryptase	Adenosine
bFGF	Heparin	Histamine
TGF-β	Angiogenin	Bradykinin
HGF	TNF-α	SP
TNF-α	TGF-α	CGRP
IGF-I	TGF-β	NKA
Angiogenins	VEGF	LTB4
Angiopoietin-1	bFGF	LTC4
Histamine	aFGF	LTD4
NO	IL-4	PAF
LTC2	EGF	TNF-α
PGD2	EC matrix	VEGF/VPF
PGI2		ET-1
PAF		
SP		
CGRP		
NKA		
VIP		
IL-1		
IL-6		
IL-8		
IL-13		
Heparan sulfate		
collagen type I		
VCAM-1		

CGRP—calcitonin gene-related peptide; EC—endothelial cell; EGF—epidermal growth factor; ET—enothelin; FGF—fibroblast growth factor; HGF—human growth factor; IGF—insulin-like growth factor; IL—interleukin; LTC—leukotriene C; NKA—neurokinin A; NO—nitric oxide; PAF—platelet activating factor; PG—prostaglandin; SP—surfactant protein; TGF—tumor growth factor; TNF—tumor necrosis factor; VCAM—vascular cell adhesion molecule; VEGF—vascular endothelial growth factor; VPF—vascular permeability factor.

including soluble mediators and growth factors through a combination of vasodilatation, angiogenesis, and microvascular leakage.

Many vasoactive mediators, cytokines, and physical factors are known to induce vascular responses, many of which are directly relevant to active asthma (Table 1). Interpretation of the specific role of many of these factors is often indirect, given that original descriptions apply to animal models, in vitro conditions, sites other than the airway, and usually in isolation from important synergistic influences that may be relevant to human asthma.

The major pre-formed mast cell mediator histamine may exert potent effects on the airway wall including contraction of bronchial smooth muscle, increased mucus production, vasodilatation, and increased vascular permeability [22]. The vasoactive role of histamine assumes importance because of the close proximity of mast cells to vessels in the airway microcirculation. The potential for tissue expansion attributable to histamine is well demonstrated by the dermal response seen after the use of histamine as a positive control in skin prick testing.

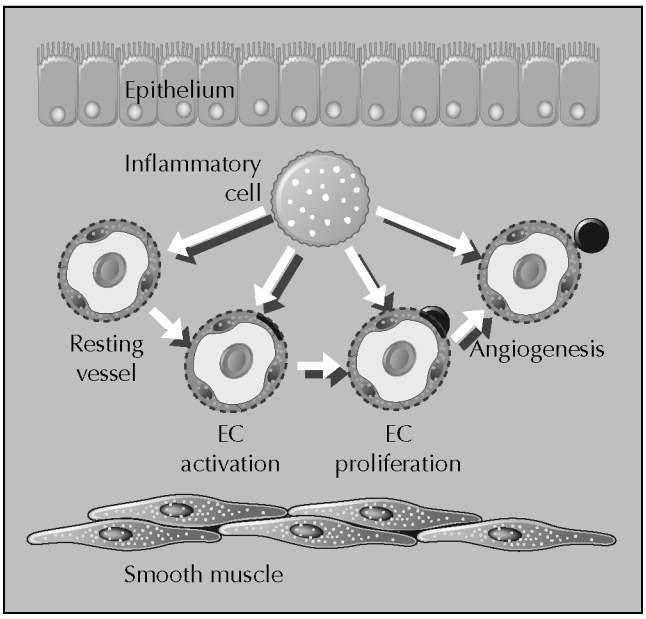

Figure 2. The role of the endothelial cell in airway inflammation.

Of the newly-generated prostanoid mediators produced by mast cells after allergen challenge, PGI_2, PGD_2, and LTC_2 are all known to be capable of causing vasodilatation. They are potent contributors to the classic type I response to allergen in the asthmatic airway through several mechanisms [23].

The pro-inflammatory cytokines IL-1, IL-6, and tumor necrosis factor-α (TNF-α) are produced by stimulated monocyte/macrophages and are associated with an acute phase response to infection [24]. Increased production of these factors in the asthmatic airway [25] and the production of IL-6 and TNF-α by mast cells [25] in stable asthma might indicate a more long-term role, rather than the accepted classic early and late asthmatic responses (EAR and LAR) alone.

The human mast cell protease tryptase, which binds to protease-activated receptors (PAR) on cells, might also be angiogenic. Many other growth factors recently found to be present in asthma have angiogenic capacity [26]. VEGF is a heparin-binding protein that is relatively specific for the stimulation of endothelial cells [27]. In addition, VEGF may regulate cell adhesion molecule expression on endothelial cells and vascular permeability, suggesting a mechanistic link.

Physical factors, including mechanical stress, applied to vessels may act either directly to enhance vessel growth or indirectly through the release of growth factors to enhance endothelial cell replication. The airway wall in asthma is subject to stress and sheer forces associated with mucosal swelling and smooth muscle contraction. Stress forces, stronger than those present in the normal airway, might well be a stimulus for vessel proliferation.

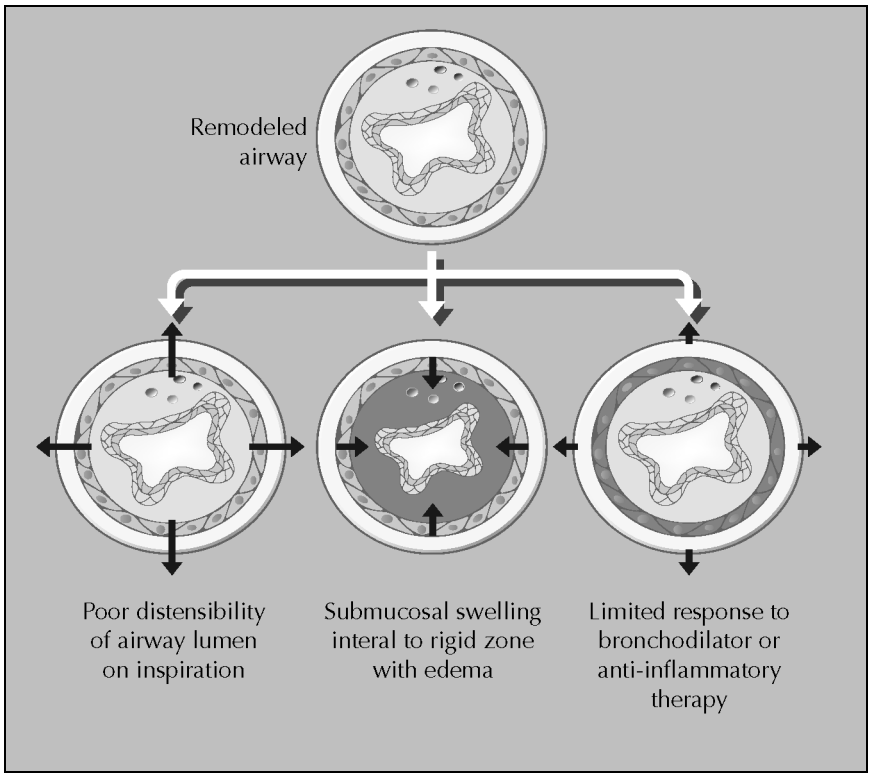

Figure 3. Controlling factors in regulating the angiogenic response.

Microvascular Leakage

Despite early descriptions of airway wall edema in fatal asthma [28], this aspect of airway inflammation remains one of the most important yet most difficult to study. Recently, new techniques have become available to quantify vessel leakage [29]. Some insight into the relationship between inflammation and capillary leakage has been provided by McDonald [30] using a rat model of airway infection. In a review of microvascular leakage within the airway, he identified a range of methods for assessing plasma leakage, including labeling with dyes and fluorescent microspheres [31]. Qualitative assessment of tissue spaces has found little difference between mucosal edema in asthma, chronic bronchitis, or normal subjects.

Airflow and Bronchial Vasculature

Evidence for the role of the bronchial circulation in airflow obstruction has come from histopathologic studies in asthmatics, animal models, and the example of left ventricular failure. The specific importance of the vasculature in airflow obstruction may depend on stimulus for bronchoconstriction and the site of microvascular dilatation or leakage.

The observation of bronchial vascular swelling in severe asthma has been documented in postmortem studies and at bronchoscopy [19,20•,28]. The interpretation of these observations, taking into account recent experimental studies, has lead to various interpretations of the way airway wall thickening contributes to airflow obstruction [32,33•]. Vascular engorgement may occur within the confines of a poorly distensible airway [34], a denser submucosal collagen network [35], and a thickened muscularis [36]. Whether the tissue expansion attributable to edema in the airway wall leads to an outward expansion or an inward expansion obstructing the lumen is highly dependent both on the initial size of the airway (with smaller airways being less vascular) and the degree of surrounding airway remodeling [37] (Fig. 3).

The phenomenon of airflow obstruction in left ventricular failure serves as an example of the potential role of bronchial circulation in airflow obstruction [38]. In addition to airflow obstruction, the bronchial wall has been shown to be radiologically thicker in left ventricular failure [39]. In addition, airway reactivity to methacholine is known to be enhanced in left ventricular failure [40]. Additional work examining airflow and bronchial responsiveness after fluid loading has found a causal relationship

Of interest is the finding that either saline or blood infusion could cause vascular congestion and exudation, leading to increased airway wall thickness [33•]. Saline caused considerably more airway-wall thickening than blood, presumably because of a component of edema formation associated with crystalloid infusion. Wagner and Mitzner [41] have examined airflow and responsiveness to methacholine, and correlated them with luminal area and airway-wall thickness using high resolution CT scanning [42,43]. Although hyperperfusion of the bronchial circulation resulted in no change in baseline airway resistance or methacholine responsiveness, there were considerable reductions in airway luminal area associ-

ated with increasing airway-wall thickness. With these results, it is tempting to speculate that airway-wall thickness secondary to vascular engorgement is a significant cause of airflow obstruction.

It is clear, however, that vascular responses alone do not seem to account for asthma [33•]. In addition to wall thickness, other factors, including distribution of airflow (longitudinal and cross-sectional), activation of sensory nerve endings, and structural changes in the airway wall, as well as clearance of inflammatory mediators are confounding factors likely to act in concert with vascular changes [44].

Current techniques of investigation of the airway in asthmatic volunteers have not allowed an accurate estimation of the contribution of the airway circulation in acute or chronic airflow obstruction. However, given that adequate circumstantial evidence exists for a role in asthma through at least five mechanisms, it is possible that future studies will link the immunologic stimuli for vascular remodeling with bronchial-wall thickening and clinical asthma.

Effect of Treatment

Initial estimations found that the vasculature in asthma was significantly increased in subjects who had used only β–agonist therapy for mild symptoms [20•]. There is little evidence to describe the short-term responsiveness of airway vessels in humans; however β-adrenergic agonists can cause vasodilation in canine tracheal vessels [45]. Interestingly, this effect was similar to that of histamine and methacholine, but weaker than VIP, bradykinin, and substance P. Based on this observation, the use of long-acting β agonists might be expected to cause vasodilatation and reduce edema, hence causing an increase in observed airway vascularity. In a further biopsy study, asthmatics treated with inhaled fluticasone and salmeterol had a reduction in the density of vessels, with no change in vascularity [46]. Possibly, much of this effect was due to the effect of the corticosteroid component as indicated by an earlier cross-sectional study [47]. Prospective studies are required to further assess the potential role of the bronchial vasculature as a target for therapy in asthma. Information regarding the short-term actions of β agonists and corticosteroids will assist with the interpretation of the vascular response.

Conclusions

The bronchial wall in asthma has been shown to be more vascular than normal airway, with an increase in density of vessels and a greater population of larger vessels than is seen in controls. The bronchial vessels may contribute to airflow obstruction through angiogenesis, vasodilatation, vascular leak, cell influx, and cytokine production. The effect of increased vascularity is accentuated by other remodeled elements of the airway, leading to rigidity with internal swelling and luminal occlusion. Biopsy studies have shown that pharmacologic intervention in asthma can lead to a reduction in airway vessel density in parallel with a reduction in asthmatic inflammation.

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