Is Asthma a Vascular Disorder?*

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There are several possible mechanisms by which vascular disorders might lead to airway obstruction. This article will not address any specific vascular pathologic defect, but rather focus on the potential effects of such defects in general. Experiments will be described that demonstrate the effect on airways of pulmonary and bronchial vascular engorgement and edema.

Investigations of how vascular engorgement affects lung elasticity date back to the studies of von Basch, more than a century ago.1 Von Basch was concerned with the dyspnea associated with cardiac asthma, and did several innovative experimental studies in dogs measuring lung volume and compliance after inflating a balloon in the left atrium. Since left atrial pressure (Pla) is the downstream pressure for both the pulmonary and bronchial circulations, elevation of Pla serves to engorge both of these vasculatures. Interestingly, despite his focus on asthma, von Basch believed that lung volume restrictions caused by increased thoracic blood volume were of prime importance, and thus expressed little interest in the airways. The role of vascular engorgement on the dimensions of the airways is a relatively recent topic within the realm of pulmonary physiology. The first interest in the effect of such engorgement on airways appears to be a report in 1957 by Borst et al.2 These investigators presented data showing that brief (10 s) increases of Pla up to 50 mm Hg had no effect on lung resistance. In 1972, Hogg et al3 published a still often cited article partially supporting these results of Borst et al.2 Hogg et al3 found that acute elevations of Pla had no significant effects on central airway resistance. However, Pla increases did cause reversible increases in the peripheral airway resistance (Raw), as long as the increases were less than 15 mm Hg. For larger increases in Pla, there was an irreversible increase in peripheral Raw, which the authors attributed to interstitial edema. However, their explanation of how this edema would act was confused by their histologic images that failed to show any cuffing of interstitial fluid around the bronchi. The interstitial fluid was observed only around the pulmonary arteries.

Some years later, Lai-Fook et al4 presented theoretical and experimental work to show that increases in pulmonary vascular pressure will cause distortions in the shape of the airways. That is, as the pulmonary arteries were engorged and stresses in the peribronchovascular spaces became more uniform, the airways would deform to become less elliptical. Such changes in shape would be expected to increase the airway resistance, so these results are not consistent with the previous results of Hogg et al3 and Borst et al.2

The potential importance of the airway blood flow in altering Raw or obstruction also has a relatively brief history in the physiologic literature. The first consideration of this interaction probably stems from the book of von Hayek,5 first published in 1953 in German and translated into English in 1960. In this book, he stated the hypothesis that in order for the airways in the lung to contract, some space outside the airways must enlarge. Although contemporary models attribute this enlargement to a distributed expansion of the surrounding parenchyma, von Hayek believed that the blood vessels in the adventitia of the airway wall served this function. Thus, in his view, there was a strong link between the extent of vascularization and the extent to which the smooth muscle could shorten. In support of this theory, he shows a histologic section of a severely contracted airway with numerous and extremely large adventitial vessels. Von Hayek’s conjecture is related to what we are presently considering, that is, that vascular engorgement in the wall could be a direct cause of luminal constriction.

In this regard, many investigators in this field find it intuitively attractive to assume that vascular engorgement or swelling of the airway wall would lead to airway obstruction. The intuition for this is often based on an implicit analogy with airflow through the nose. In the nose, it is well known that acute vascular engorgement can very rapidly lead to airflow obstruction. Furthermore, the fact that the nose has no equivalent to the “airway” smooth muscle has strengthened the idea that smooth muscle might not even be important in the airway obstruction of asthma. That is, that the engorgement associated with acute inflammation might be sufficient by itself to obstruct the airways. However, it should be obvious to even the most casual observer that there are significant differences between the structure of the nasal passages and the parenchymal airways. The nasal mucosa is densely vascularized, and this vascular structure sits on a continuous cartilaginous backbone.6 The venous tree has throttling veins with extensive smooth muscle that can rapidly contract and engorge the mucosa, in the manner of erectile tissue. In contrast, the small parenchymal airways have a much less dense vascularization, and the structure allows vascular expansion to occur outward into the parenchyma. Indeed this is the preferential direction. Smith and Mitzner7 analyzed the relative distortions of the arteries and surrounding parenchyma when perivascular edema expanded the interstitial space. They found that at functional residual capacity more than 70%
of the distortion would occur in the surrounding lung parenchyma. The mechanism was based on the relative stiffness of the vascular and parenchymal boundaries. If we consider the airways to be of similar stiffness as the arteries, this theoretical prediction would suggest that with bronchial vascular engorgement and edema, the outward expansion of the surrounding parenchyma would likely be considerably greater than the direct inward compression of the airway. Thus, the nasal model is entirely inappropriate for the parenchymal airways.

The first description of how interstitial edema might affect the airways was by Gleason and Steiner\textsuperscript{9} in 1966. Using a lateral roentgenogram, they observed that the bronchial walls of lobar bronchi were thickened in patients with left heart failure. With resolution of the failure or with diuretics the wall was thinner and the lumen enlarged. They also coined the term “peribronchial cuffing.” One year later, Staub and colleagues\textsuperscript{6} first described the sequence of events in the formation of interstitial edema and the events that might lead to this peribronchial cuffing. The notion that vascular engorgement of the airway wall would lead to airway obstruction in asthma has become popular in recent years. Specifically, it has been proposed that exercise-induced asthma results from vascular hyperemia in the airway wall following exercise. Gilbert et al\textsuperscript{10} measured airway temperatures before and after a 4-min period of exercise breathing frigid air. Their results showed that asthmatics had a significantly more rapid rewarming of their airways following the exercise. They argued that this more rapid warming indicated an increased airway blood flow. Unfortunately, their theoretical model is not precise enough to provide quantitative estimates of how much of an increased flow occurred nor how much the vascular volume actually increased. This idea that engorgement of the bronchial vasculature is important in airway reactivity was supported by Cabanes and associates.\textsuperscript{11} They showed first that patients with left heart failure had increased airway reactivity, and second that this increased reactivity could be eliminated by giving the patients methoxamine (an \(\alpha\)-adrenergic blocker). They thus argued that \(\alpha\)-adrenergic blockade constricted the bronchial vasculature, and thereby increased airway size. In a later study, Gilbert, et al\textsuperscript{12} also showed that in asthmatics, the airway obstruction in response to saline solution infusions was decreased following drugs that are thought to constrict the airway circulation. In all of these studies, the mechanism remained entirely speculative, since no measurements were made of the bronchial blood flow.

**Experimental Studies**

To address this question more directly, we have used two different experimental preparations. The first uses an experimental preparation in sheep developed a number of years ago by Wagner and Mitzner\textsuperscript{13} that allows direct control of bronchial blood flow—details of the method are described in that paper. The protocol was to measure the changes in peripheral and central airway resistance and reactivity before, during, and after a 3-h period of hyperperfusion of the bronchial vasculature. The hyperperfusion was set at 300\% of the control bronchial blood flow at an average perfusion pressure of 192 mm Hg. Histologic studies showed that this level of hyperperfusion was sufficient to cause both bronchial vascular engorgement and airway wall edema, such that the average airway wall area increased by 18\% by the end of the 3-h period.\textsuperscript{14} Physiologic results from this study were negative with regard to any changes in either baseline Raw or reactivity. Thus, results from this study showed that substantial hyperperfusion of the bronchial circulation caused no detectable changes in baseline central or peripheral Raw. Furthermore, there were no significant changes in airway responsiveness to aerosol challenges with methacholine (MCh). More recent studies presented at this conference using the same experimental model have shown similar negative findings following engorgement of the pulmonary and bronchial vasculatures by left atrial pressure elevation.\textsuperscript{15} Based on these findings, it seems reasonable to conclude that unless the increase in airway area caused by bronchial
engorgement is much greater in asthmatic subjects, the notion that the physical effects of acute airway vascular engorgement could play a major role in an asthmatic attack is not tenable.

However, there remain questions regarding how much thickening can actually occur in *vivo*, is there a limit to how thick the wall can get, and more specifically, how much engorgement would one need to cause an airway to decrease its lumen? Part of the difficulty in answering these questions is the fact that the means to assess the effect of vascular engorgement are themselves fraught with uncertainties. Lung resistance and spirometry are global measurements that average all airway pathways in series and parallel. Spirometric indices include components of lung elasticity and tissue resistance, in addition to airway properties. Morphometric studies may involve uncertain fixation and processing artifacts, difficulties regarding statistical sampling, and one must use different lungs for control and experimental conditions.

Over the past several years, we have made use of high-resolution CT (HRCT) to directly measure reactivity of individual airways. Recently we have addressed specific questions related to vascular engorgement in the lung using this high-resolution method in dogs. In this study, we sought answers to the following questions: (1) What is the airway response to intravascular engorgement, and (2) What is the response to airway edema? To address these questions, we compared the effect of rapid volume loading with saline solution or blood at comparable pulmonary vascular pressures. Because the saline solution can readily leak from the vessels, differences from the blood infusion are interpreted as a result of the lung edema. Our protocol was the following. On a given experimental day, dogs were anesthetized with thiopental, paralyzed, and ventilated and placed in the HRCT scanner. For the saline solution infusion, animals were subjected to three successive 1,000-mL saline solution loads. Each volume was given over the course of 5 to 10 min and followed immediately by a sequence of HRCT images (see below). When one image acquisition was completed, the next volume load was given. The entire saline solution sequence took about 35 min. On another day, the same dogs were similarly prepared, but the challenge consisted of two successive 500-mL loads of whole blood. These volumes of blood were selected because they resulted in pulmonary artery pressures comparable to those following saline solution challenge. Figure 1 shows these changes in *P*pa measured at baseline and at the end of each volume increment. Finally on subsequent experimental days we challenged the same animals with intravenous infusions of MCh and histamine at levels sufficient to reduce the average airway area by about 50%.

To measure the airways, we took 50 overlapping 2-mm-thick HRCT (Siemens Somatom Plus) slices at functional residual capacity during a breath hold. Details of the scan parameters and image analysis software are described elsewhere. In each animal, we measured airway wall thickness and lumenal area in 12 to 15 airways, ranging in size from 2.6 to 21 mm in diameter. Using anatomic landmarks, we were always able to find the same airways in a given animal for each of the different experimental

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**Figure 2.** Representative HRCT images of the same airways at baseline and following either A, two sequential infusions of 500 mL blood (labeled 500 and 1,000), or B, three sequential infusions of 1,000 mL normal saline solution (labeled 1,000, 2,000, and 3,000). On each figure, C indicates the control scan. Blood vessels appear white and airways appear as black spaces surrounded by a thin light wall. With either infusion, the pulmonary arteries can be clearly seen to increase in area. Notice the increasing distortion of the airway shape with increased amounts of volume infused and engorgement of the adjacent pulmonary arteries. Note also the substantially greater overall effect on airway lumen and wall thickness with the saline solution infusions (reproduced with permission).
protocols. Figure 2 shows representative HRCT images following blood and saline solution loading from a single animal. With blood loading, there is clear evidence of vascular engorgement, as shown by the large increases in vascular dimensions. However, with this blood engorgement, there seems to be little change in either the wall thickness or lumenal area. There is, however, clear evidence of some direct vascular distortion of the airway, similar to what was predicted by Lai-Fook et al.\textsuperscript{4} With saline solution engorgement, there is also a similar distortion, but in addition there are more dramatic effects on the airway caused by the edema in or around the airway wall. One can clearly see both a markedly decreased lumen and a thickened wall. The mean changes from airways in all dogs are summarized in Figure 3. This figure shows that extreme vascular engorgement with blood (to a Ppa of 40 mm Hg) has only a slight effect on airway dimensions. We believe that the small changes in airway lumenal area result from the above-mentioned direct effect of the engorged pulmonary arteries on the adjacent airway. With saline solution loading, there was a significant wall thickening and reduction in airway cross-sectional area. Since this was not found with the blood infusion to comparable pulmonary artery pressure, we interpret these results as indicating a significant amount of fluid leakage.

The question of whether this fluid leakage with saline solution engorgement can be a major cause of airway obstruction depends on one's perspective. Is the proverbial glass half full or half empty? We interpret these results not by looking at this moderate degree of obstruction (30%), but rather by looking at the much larger retention of patency (70%). From this perspective, we consider the data as supporting the idea that airway edema per se cannot be the primary cause of airway obstruction. Our reasoning is that a short-term volume load of 3 L of saline solution in a dog is about as massive a challenge as could be achieved, without getting alveolar flooding and gross pulmonary edema. Yet even with this massive amount of loading, the airways were only moderately obstructed. It is also worth emphasizing that even with gross pulmonary edema, the degree of airway obstruction reaches a limit not much beyond what we have found in this study. That is, once the peribronchovascular cuffing has reached a critical level, alveolar flooding begins. Further edema serves only to add fluid to more alveoli, but the cuffs do not increase further.\textsuperscript{20} Based on these considerations, it thus does not seem reasonable to ascribe a primary role of airway engorgement in airway obstruction.

Finally we consider the mechanism that explains why the airway lumen is smaller with the blood and saline solution infusions. Figure 4 plots the relationship between airway wall thickness and luminal area. Results shown are for the saline solution and blood infusions and for the effect of independent aerosol challenges with histamine and MCh. The curved dashed line is a theoretical line showing how the wall would thicken as the airway contracted if the airway wall cross-sectional area remained constant. Although this assumption may be incorrect, it is a reasonable first approximation. What the graph shows is that both the agonist challenges and the blood engorgement all fall near the expected theoretical line. The saline solution engorgement, however, shows wall thicknesses much greater than any of the other challenges (shown is a linear regression through the saline solution points). This means that for comparable degrees of airway contraction, the wall is much thicker with saline solution engorgement. We interpret this observation as indicating that wall thickness per se is not an independent predictor of airway size. For example, one can get a 15 to 20\% decrease in luminal area with both blood and saline solution engorgement, despite the wall being significantly larger (20\%) with the saline solution.

For the agonist constrictions and the blood engorgement, the wall gets thicker because the airway is con-

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\includegraphics[width=\textwidth]{figure3.png}
\caption{Summary graph of the mean changes in airway lumen and wall thickness following saline solution and blood infusions.}
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stricted. In contrast, with the saline solution infusion, the airway is constricted because the wall gets thicker. The main reason why the airway area is decreased slightly with the blood infusion is the above-mentioned direct effect of the engorged pulmonary arteries pushing on the adjacent airways. Since our protocol caused substantial increases in vascular pressure in the bronchial circulation without much of an increase in the wall thickness (ie, above the theoretical line), we interpret these results as indicating that engorgement of this circulation has only a minimal effect on airway obstruction. This finding is consistent with the previously discussed experimental studies in the sheep.

With saline solution infusion, there is also an effect of the pulmonary arteries impinging on the airways, but in addition, the airway now can get even smaller because of the increased interstitial fluid that has leaked from the vessels. This added fluid, observed as a wall thickness well above the theoretical line, can cause a mechanical decoupling of the airways from the parenchyma, thereby allowing the airways to recoil inward, decreasing the lumenal area, and increasing wall thickness even further. Thus, with the saline solution infusion, the airway gets smaller by virtue of both the direct impingement of pulmonary arteries and because of edema.

**Conclusion**

Given these experimental results, what can we conclude is responsible for the extensive obstruction in human asthma? We believe that this responsibility falls on that specialized tissue in the airway wall that is missing from the nose, ie, the airway smooth muscle. Modeling has indicated that from purely geometric considerations, a thickened airway wall\(^1\text{21-23}\) should lead to a much greater response to agonist challenge. Thus, the combination of airway wall thickening and smooth muscle activation should be synergistic. Experiments are currently underway to examine this directly using HRCT. In conclusion, there seems little possibility that bronchial wall edema or interstitial pulmonary edema could by itself cause sufficient obstruction to be considered a primary cause of asthma. However, a thickened airway wall would be expected to cause exaggerated airway smooth muscle responses. Thus, vascular abnormalities can exacerbate the problem, but without airway smooth muscle contraction, there would be no asthma. And thus the answer to the question, "Is asthma a vascular disorder?" must be no. We believe that asthma would still be a problem even with a perfectly normal vasculature.

**References**

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Resistive Loading and Pulmonary Capillary Volume in Asthma*

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We recently observed that an inspiratory flow-resistive load can worsen airflow obstruction in supine asthmatic patients. As such loads reportedly augment intrapulmonary blood volume, we examined the effect of a prolonged inspiratory resistive load on pulmonary capillary volume (corrected for alveolar volume—VC/VA) in 15 asthmatic and 4 normal subjects. Subjects inspired continuously while supine through increasing resistances (hour 1, 9.0; hour 2, 17.0, and hours 3 and 4, 21.5 cm H2O/L/s).

*From the Veterans Administration Medical Center, Denver.

![Graph](image-url)

**Figure 1.** Capillary volume corrected for alveolar volume (VC/VA): normal subjects vs nonresponder vs responder asthmatics at upright baseline, supine baseline, and supine after 4 h of inspiratory resistive loading.