Capillary Recruitment in the Pulmonary Microcirculation

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At the first Aspen Lung Conference on the pulmonary circulation in 1962, a hotly debated topic concerned which pulmonary vessels constrict during airway hypoxia. Those favoring a precapillary site argued that it was only the arteries which had sufficient smooth muscle in their walls to constrict, that it was the arterial muscle which hypertrophied at high altitude, and, finally, that the precapillary site was the most suitable location for regulating ventilation/perfusion balance, since arterial constriction would direct blood flow to better ventilated parts of the lung before it reached hypoxic alveoli. The venoconstriction camp contended that the veins were the only vessels that could possibly sample the oxygen levels in blood leaving underventilated alveolar regions, and therefore the postcapillary vessels had to be the site of hypoxic vasoconstriction. Since then, a variety of evidence has made it apparent that it is arteries of 200-300 μm in diameter that constrict during hypoxia and that the arteries themselves are capable of directly sensing airway oxygen tension.

Twenty-five years ago, however, these matters were far from clear. To study this issue, Giles Filley instigated work in his laboratory in Denver to make direct microscopic observations of the surface of the living lung, reasoning that if the technique could be developed, it would be easy to determine the site of hypoxic vasoconstriction. Krah and deAlva et al. made progress with the development of a thoracic window that, once implanted, permitted the pneumothorax to be aspirated so that the lung moved flush against the window pane and enabled the animal to breathe spontaneously. Unfortunately, their observations were hampered by lung movement. With each breath the lung slid across the window pane and, to make matters worse, the field oscillated rapidly with each heartbeat. The microscope, of course, magnified the movement. These problems were not unique to the Denver group; tissue movement has plagued all microcirculationists since Malpighi’s time.

Dr. Filley and I began working together in the early 1960s on this project and had the good fortune of discovering a location on the surface of the lung lying under the second rib that moved only slightly with respiration. Later, a suction manifold was added to the bottom of the window frame so that movement was reduced to 10 μm or less with each breath. This permitted us to make observations of the same field over many hours and thereby to use the same arterioles, capillaries, and venules as their own controls. The stage seemed set to discover the site of hypoxic vasoconstriction. Had we done sufficient preliminary theoretic work, we would have realized that the arterioles and venules on the surface of the lung rarely exceed 50μm in diameter, and that in the dog, which was our experimental animal, smooth muscle is uncommon in vessels smaller than 100μm. This combination made it unlikely that we would detect vasomotion. We did not reason this out ahead of time, however, with the result that despite 25 years of attacking the canine pulmonary circulation with every sort of vasoconstrictive abuse we could imagine, we have yet to see a microvessel on the surface of the lung constrict and so have made no direct contribution to our original goal of understanding which vessels constrict with hypoxia.

On the other hand, we had developed the ability to observe directly the pulmonary gas exchange vessels in a still field using high magnification in an animal with normal blood gas values, cardiac output, blood pressures, and, as best we can determine, an undamaged microvasculature. This has enabled us to make a number of studies of how the pulmonary capillaries respond to changes in pressure and flow. These observations form the basis of this report.

The majority of our observations have been made on the surface of the left lower lobe with the animal lying in the right lateral decubitus position so that observations are made downward on the uppermost surface of the lung. This position places the field in zone 2 hydrostatic conditions, where Ppa > Padv > Ppv in Zone 2 is an interesting part of the pulmonary circulation, because it is where much of the gas exchange reserve lies, both in terms of capillaries that can be recruited and capillary transit times that are very

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![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22163/)
long and so can be speeded up without risk of causing hypoxemia.16

In our early studies we noticed that RBCs consistently perfused more capillaries when the animals inspired hypoxic gas mixtures.14 To quantify this recruitment, we made drawings of all capillaries that were perfused by RBCs in a given field during normoxia and hypoxia. By measuring the total length of those capillaries, we demonstrated that capillary recruitment increased as oxygen tension fell (Fig 1).

This observation led to a series of studies designed to determine what caused the capillary recruitment. The obvious extrapulmonary causes, increased left atrial pressure and cardiac output, were eliminated because left atrial pressure was unchanged by hypoxia, and cardiac output fell in some instances of hypoxia, yet there was substantial recruitment present during those times.16 In later work, we held output constant from control to hypoxia and found that recruitment occurred independent of total pulmonary blood flow.18 Thus, an intrapulmonary mechanism seemed likely to be the cause of the recruitment. Venoconstriction could certainly cause a retrograde rise in capillary pressure that would lead to recruitment. The well-known elevation of pulmonary arterial pressure during hypoxia might also account for the recruitment by redistributing blood flow upward to our zone 2 observation site. To differentiate between these potential causes, we directly measured pressure in both small pulmonary veins and arteries, made the animal hypoxic, and measured capillary recruitment. Then, while continuing the hypoxic challenge, a vasodilator, prostaglandin \( E_1 \), was infused to relieve whatever vasoconstriction had occurred.17 The vasodilator caused a large reduction in the number of perfused capillaries. We could not measure any increase in pulmonary venous pressure during hypoxia, nor detect any effect of the vasodilator on vein pressure. Pulmonary artery pressure, however, fell to near control levels during vasodilator infusion. The plots of pressure vs recruitment (Fig 2) showed no correlation with vein pressure.

**Figure 2.** Correlation between capillary recruitment index and pulmonary venous pressure was not significant \( (p=0.9) \), but was highly significantly correlated with pulmonary arterial pressure \( (p<0.001) \) for this group of 10 dogs. (After Wagner et al.17)

**Figure 3.** In this model the apartment house represents the lung and the shower heads the capillary bed. Capillary recruitment is analogous to recruitment of holes in shower head. Under normal conditions, the shower heads are not fully recruited in the upper stories, and flow is brisk in the lower stories (left panel). During hypoxia, arterial vasoconstriction (represented by the partially closed control valves in the right panel) causes pressure to be elevated and flow to be redistributed to the upper shower heads where recruitment occurs.
but an impressive correlation with artery pressure.

Therefore, capillary recruitment during hypoxia did not correlate with cardiac output, pulmonary venous, or left atrial pressure, but did correlate with pulmonary arterial pressure. If recruitment is caused by a rise in capillary pressure, which it certainly must be, how could the pressure rise in the capillaries which are located downstream of an upstream constrictor? It seemed more plausible that constriction of an artery feeding a capillary bed would have to be associated with reduced flow and derecruitment.

To help visualize the pressure, flow, and resistance relationships in the pulmonary circulation, we developed a model that in some ways is undeniably too simple, but it is compatible with our data and has suggested several further experiments. The model is based on an apartment building and what happens when the tenants all try to take a shower at 7 AM (Fig 3, left). When everyone opens his shower control valve simultaneously, the dwellers on the lower floors benefit from a rapid flow of water through a fully recruited shower head (analogous to the capillary bed in zone 3, where \( Ppa > Ppv > Palv \)). The upper-floor tenants are confounded by a derecruited shower head. To this point, the model reproduces in part the elegant pulmonary capillary hydrostatic zone model developed by Permutt et al. and West to describe the hydrodynamic distribution of blood flow under normal conditions.

To extend the apartment house model, suppose that there is a meeting in which the tenants all agree to open their control valves only partially (Fig 3, right). This condition represents generalized pulmonary arterial vasoconstriiction. With higher pressure available, water is redistributed to the upper floors, and holes in the shower heads are recruited. The paradox is solved of how capillaries can be recruited downstream from an upstream constriction, because some water is available to flow past the constriction in the control valves to the upper floors (Fig 3, right), whereas no water had been available to flow past the wide open control valve (Fig 3, left) under control conditions.

The model predicts, with conditions of steady total flow (analogous to lack of the cardiac output changes during hypoxia) and even constriction in all control valves, that there will be upward redistribution of flow, which could result in an overall gain in the number of holes in the shower heads via recruitment. Under these conditions, the extra flow to the upper shower heads must come from the lower apartments. The lesser flow in the lower apartments, however, need not lead to local derecruitment; rather, the extra water could come from a reduction in the velocity of the water passing through the lower shower heads (analogous to slower transit times). If this reasoning is correct, the model predicts that in the lung there should be an increase in capillary volume during the increased pulmonary arterial pressure associated with airway hypoxia.

To test this prediction, it was necessary to determine the effect of hypoxia on total pulmonary capillary volume. To do this, we measured the diffusing capacity of the lung for carbon monoxide at two widely different alveolar oxygen tensions, both \( \geq 100 \text{ mm Hg} \), and computed the capillary volume occupied by RBCs. The diffusing capacity for carbon monoxide is known to increase during hypoxia. This change could reflect either increased capillary volume, less competition from oxygen for hemoglobin binding sites (which would alter the reaction rate between CO and hemoglobin [\( \theta \)]), or some combination of the two. To determine the effect of recruitment alone, the vasodilator prostaglandin \( E_1 \) was infused while airway hypoxia was held at a constant level. The resultant decrease in pulmonary artery pressure caused, as expected from earlier work, capillary derecruitment (Fig 4, left). Diffusing capacity also decreased (Fig 4, right). By assuming no change in membrane diffusing capacity, and by having held \( \theta \) constant by keeping the level of hypoxia constant, the experiment showed that there was a net gain in capillary volume, most likely through capillary recruitment. Such an increase in gas exchange surface area would be advantageous during whole lung hypoxia.

The apartment house model predicts upward redistribution of flow with constriction and downward redistribution with dilution. There is evidence that hypoxia causes upward redistribution of pulmonary blood flow both acutely in anesthetized dogs and in man native to high altitude. To determine what vasodilation did to blood flow distribution in our preparation, we injected radiolabeled 15 \( \mu \)m microspheres into the right atrium and measured the location of the wedged spheres in the lungs during hypoxia and hypoxia plus prostaglandin \( E_1 \). As expected, hypoxia caused microparticle distribution to be relatively even from top to bottom (Fig 5). The vasodilator caused the curve to rotate (Fig 5), indicating that blood flow diminished in the upper lung and returned to high levels in the lower lung. This seems convincing evidence that upward redistribution of blood flow existed in our preparations and is a likely explanation for capillary recruitment in the upper lung during hypoxia.

From these data, the response of the pulmonary circulation can be summarized as follows: hypoxia \( \rightarrow \) pulmonary arterial constriction \( \rightarrow \) increased pulmonary arterial pressure \( \rightarrow \) upward redistribution of blood flow \( \rightarrow \) capillary recruitment \( \rightarrow \) increased surface area for gas exchange. It is not certain how much improvement in arterial oxygen tension might occur from the increase in gas exchange surface area provided by the recruited capillaries. As best we can calculate it might...
not exceed 5 mm Hg in a normal lung, although it could be substantially more in a heterogeneously diseased lung. In any case, whenever arterial oxygen tension is below 30 or 40 mm Hg, any addition would be welcome.

There are other conclusions that can be drawn from this series of studies. This and other work suggests that capillary recruitment is a passive event resulting from increased pressure in the capillary bed. Presumably the pressure rise can be from any source. For example, a downstream increase in resistance causing a retrograde rise in capillary pressure would be expected to cause recruitment just as readily as an upward redistribution of blood flow causes recruitment in the case of whole lung hypoxia. We find no evidence that venoconstriction, even if it does exist during hypoxia in small veins between the capillaries and the 2-mm catheter we used to make measurements, has any detectable effect on the pulmonary capillaries. Thus, in a circuitous way, we have produced some data that bear on the question, charged to us 25 years ago by Professor Filley, concerning which vessels constrict during airway hypoxia.

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Pulmonary Vascular Reactivity*
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