Scientific knowledge develops through the evolution of new concepts. This process is usually driven by new methodologies that provide observations not previously available. Understanding of pulmonary blood flow determinants advanced significantly in the 1960s and is now changing rapidly again, because of increased spatial resolution of regional pulmonary blood flow measurements.

Before the late 1950s, the lung was thought to be uniform in its gas exchange properties. New technologies, using radiolabeled gases, provided higher-resolution information about the vertical distribution of PBF. The observation was made that oxygen and carbon dioxide exchange differed between upper and lower lung regions. The zone model evolved as an explanation for the observed vertical differences and provided a framework that guided both research and clinical medicine for over three decades.

New methods with even higher resolution have led to equally surprising observations and new insights. It is now apparent that although gravity does have a measurable influence on PBF distribution, the anatomic structure of the arterial tree plays a prominent role in the distribution of PBF. For more details of the factors that lead to heterogeneity in the lungs, the reader is referred to Complexity in Structure and Function of the Lung (11).
Gravity-dependent vascular mechanisms

Early work with the concept of vertical dependence of PBF began in the 1950s with the efforts of Richard Riley and colleagues. These authors first examined the changes in dead space by measuring gas exchange in subjects placed in various postures. Riley et al. (13) reported that in the erect position, alveoli in the apex of the lung were not perfused. They presented the idea that alveolar and vascular pressures determine blood flow changes with lung volume (alveolar pressure) in the whole lung.

This concept was advanced by the introduction of the waterfall concept by Permutt and colleagues at the Fifth Annual Conference on Research in Emphysema (also called the Aspen Conference) in 1962 (12). They pointed out that pulmonary capillary flow was determined by the relationship between alveolar pressure and intravascular pressure. This comprehensive article outlined the equations to describe the relationships among alveolar, arterial, and venous pressures. They considered the pulmonary circulation to be the equivalent of a series of Starling resistors but did not discuss the possible vertical distribution of these relationships.

Similar work was carried out at the same time in Great Britain. Banister and Torrance (2) described the influence of airway pressure in PBF and the concept that height in the lung influences the effective transmural pressure of the blood vessels. They explained the effect by referring to a “sluice,” a channel for flow of water with a gate at the head of the channel to control flow. This is a very different concept than that of the Starling resistor.

The original description of the vertical dependence of PBF was put forth by West, Dollery, and Naimark (15). This group used an isolated perfused dog lung, mounted in the upright position, set up so that the arterial and venous pressures could be controlled relative to alveolar pressure. $^{133}$Xe was injected in the blood, and the vertical distribution of average blood flow was measured by scintillation counters. In this preparation, blood flow was greater near the lower (caudal) part of the lung and less near the upper (cranial) part of the lung. Using the presumption that the vertical distribution of arterial and venous pressure is determined primarily by hydrostatic mechanisms, these authors proposed the zone model (Fig. 1) to explain the vertical distribution of blood flow. Intravascular pressure is thought to decrease linearly with vertical height. In zone 1 near the top of the lung, alveolar pressure exceeds arterial pressure and the collapsible blood vessels close, stopping flow. In zone 2, arterial pressure exceeds alveolar pressure, which exceeds venous pressure. At any given height, the flow is determined by the difference between arterial and alveolar pressure. In zone 3, both arterial and venous pressures exceed alveolar pressure. Although the driving (arterial–venous) pressure is equal with vertical position, the increase in flow down the lung was explained by vessel distension, decreasing vascular resistance, going down the lung. In the initial zone presentation (15), a model was proposed with three zones. A fourth zone was added later to deal with the decreased flow near the bottom of the lung. This has been explained by perivascular cuffing due to the excessive vascular pressures and consequent edema formation. However, the presence of similar values of flow in the same region when the animal is inverted to the opposing posture argues against this gravity-dependent mechanism.

The zone model has been used to characterize behavior of the pulmonary circulation to establish experimental protocols and help in the interpretation of experimental observations. Several predictions can be made from the zone model. 1) Because the arterial and venous pressures are determined by vertical height, PBF should be uniform at any location within an isogravitational plane. 2) At any location in the lung, PBF in any posture should be negatively correlated with PBF in the opposing posture (prone vs. supine, erect vs. head down, left lateral decubitus vs. right lateral decubitus). 3) A vast majority of the variability of PBF among all regions of the lung should be explained by vertical position of the region. 4) Increasing pulmonary arterial pressure during exercise should lead to a more uniform PBF distribution. 5) Increasing gravitational force should increase the vertical height dependence of PBF in a proportional manner.

Resolution of methods

Resolution limitations of methodology depend on the available technology. The initial experiments defining the gravitational dependence of blood flow relied on the use of radioactive gases ($^{133}$Xe or labeled CO$_2$; Refs. 1, 14) and external counters of radioactivity. Radiolabeled gases were dissolved in venous blood. Appearance of label in the lung indicated the relative amount of blood flow in that lung slice. Collimated counters were placed horizontally adjacent to the chest at different vertical positions. Each counter integrated information across the lungs and chest, giving a single average value for the entire horizontal (isogravitational) slice of the lung. All potential horizontal heterogeneity was, therefore, lumped into a single averaged value. In these earlier experiments, one PBF value was...
used to represent the blood flow to any piece of lung at a given vertical height.

Labeled 15-μm-diameter microspheres and personal computers are the new technologies that provide for a markedly increased spatial resolution of PBF. Vascularly injected microspheres lodge in pulmonary capillaries within lung regions in proportion to the amount of blood flow to that region. The lungs are processed by drying during inflation to near total lung capacity and then cut into small (1.0–2.0 cm³) pieces, depending on the animal and degree of resolution desired. Radioactive counts or fluorescence labels are measured in each piece and recorded along with its spatial location. Thus the distribution of relative PBF is measured in small pieces.

**Isogravitational heterogeneity**

A strong test of the zone model was performed by Glenny et al. (7), who measured the PBF distribution using radiolabeled microspheres in anesthetized dogs placed in both the prone and supine positions (Fig. 2). In the supine animal, a clear dorsal (down) dominance of PBF is demonstrated (consistent with the zone model), but a considerable isogravitational heterogeneity is seen within each isogravitational plane (inconsistent with the zone model). In the prone animal, the degree of isogravitational heterogeneity remains, but now with an average blood flow that dominates in the upward direction. This dorsal dominance, regardless of posture, was also identified by Beck and Rehder (3) and is not predicted by the zone model.

A plot comparing prone and supine blood flow shows a positive slope with a high correlation. If the zone model dominates, a dependent region should have relatively high blood flow in the supine posture, and it should become a low-flow region when repositioned to the prone posture. Thus the zone model would predict a negative slope for a prone-supine flow comparison. The data of Glenny et al. (7) indicate a positive correlation between flow in a prone and a supine posture, with an $R^2$ of 0.725. Changing from the supine posture to the prone posture or vice versa, high-flow regions remain as high flow and low-flow regions remain as low flow. Simultaneous injections of two microsphere colors reveal a methodological measurement error of <1%.

Statistical analysis comparing flow in each piece as posture is changed shows that gravity accounts for only 4% of the variance (7). It should be remembered that not only do changes in posture affect the direction of the gravity vector, but changes also occur in chest wall and diaphragm position and local parenchymal stresses. Thus the calculated effects of gravity through the hydrodynamics stress, as outlined by the zone model, are actually overestimated by this approach.

The zone model would predict a positive relationship between PBF and height up the lung. This relationship should be greatest in animals with a large vertical lung size. However, data in resting thoroughbred horses, with a vertical lung size of ~50 cm, show no significant vertical gradient with a large degree of isogravitational heterogeneity comparable to other mammals (9). This finding is not consistent with the zone model.

Exercising horses (at 90% $V_{O_2\text{max}}$) increase pulmonary artery pressure from rest by approximately threefold (from 35 ± 6 to 107 ± 12 cmH₂O). The zone model would predict a marked increase in zone 2, resulting in a smaller vertical gradient in PBF and a more uniform PBF distribution. Bernard et al. (4) found that exercise resulted in a proportional increase in flow to all regions of the lungs with little change in coefficient of variation of het-
erogeneity, with no change in gravity dependence with exercise, despite the considerable increase in pulmonary artery pressure.

The role of increased inertial (gravitational) force on PBF distribution using high-resolution methods has been studied by our group on the human/animal centrifuge at Brooks Air Force Base (10). Increasing force from –1 G (dorsal to ventral direction) to –3 G resulted in an increase of the coefficient of variation of PBF from 0.38 to 0.72, a substantial decrease in PBF in both the ventral and dorsal regions of the lung, and an increase in PBF (mean and variation) in the mid-lung or hilar regions. Statistical analysis revealed that >81% of the variance in flow among the lung pieces is due to vascular structure, whereas <19% of the variance is due to changes in inertial force via acceleration. These latter findings are inconsistent with the predictions of the zone model.

Spatial and temporal correlation

Like many organs and tissues, the lungs exhibit a remarkable degree of heterogeneity of structure with a high degree of similarity of function. It has been speculated that this heterogeneity of structure is an important advantage that allows easy compensation in the face of disease and local perturbation of function. Even though a significant heterogeneity exists across isogravitational planes in the mammalian lung, there is a strong correlation among adjacent pieces (6) and a negative correlation among pieces that are very far apart (Fig. 3). High-flow pieces are next to high-flow pieces and low-flow regions neighbor other low-flow areas. The spatial pattern of PBF is not random and remains very stable over days (6). The ordered, nonrandom isogravitational heterogeneity of flow distribution is not consistent with the zone model.

Fractal geometry

Figure 4 demonstrates the relationship between the apparent heterogeneity of perfusion, expressed as the coefficient of variation, and size of pieces used to examine this heterogeneity. Apparent coefficient of variation increases as lung piece size decreases. The linear relationship shows that the observed heterogeneity depends on the resolution

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**FIGURE 2.** Weight-normalized pulmonary blood flow (PBF) vs. vertical height up the lung in dogs in either the prone or the supine posture. Modified from Ref. 7.

**FIGURE 3.** Correlogram of regional blood flow as a function of distance between the pieces. Pieces separated by 1.2 cm have similar flows (r = 0.676), and flows become less similar and eventually negatively correlated at larger distances. Filled circles indicate points with spatial correlation significantly different from 0.0 (P < 0.05). Modified from Ref. 6.
of the method. As the lung is examined with smaller and smaller pieces, the heterogeneity increases. This process continues until the heterogeneity does not increase. This occurs when the "functional unit" is reached where further reduction in size yields pieces with identical properties. A fractal system (8) is one in which the properties of the system at different scales are self-similar. In the pulmonary vasculature, the nature of a bifurcation is the same as either the parent or the daughter generation. The spatial correlation of flow and scale-dependent heterogeneity are consistent with pulmonary vascular anatomy being a dominant factor in causing the observed patterns of PBF distribution in mammals.

Conclusion

The gravitational hypothesis that attributes the distribution forces of both blood flow and ventilation to hydrostatic forces in the lung has been a cornerstone of pulmonary physiology. The gravitational model was advanced because higher spatial resolution methods revealed nonuniform blood flow. Our current understanding of PBF distribution has been further advanced with the development of methods allowing even higher resolution in the measurement of local PBF. These new observations are inconsistent with the zone model and the gravitational hypothesis. Rather, they offer a new perspective from which to explore determinants of regional blood flow. The gravitational model does not preclude the waterfall relationships proposed by Riley and Permutt. Rather, it predicts that multiple sets of conditions exist within isogravitational planes rather than being vertically stacked. New models are important to the scientific community; they influence interpretation of data and put forth new experimental ideas that may challenge or support commonly held beliefs.

References