

REVIEW ARTICLES

Distribution of blood flow and ventilation in the lung: gravity is not the only factor

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Current textbooks in anaesthesia describe how gravity affects the regional distribution of ventilation and blood flow in the lung, in terms of vertical gradients of pleural pressure and pulmonary vascular pressures. This concept fails to explain some of the clinical features of disturbed lung function. Evidence now suggests that gravity has a less important role in the variation of regional distribution than structural features of the airways and blood vessels. We review more recent studies that used a variety of methods: external radioactive counters, measurements using inhaled and injected particles, and computer tomography scans. These give a higher spatial resolution of regional blood flow and ventilation. The matching between ventilation and blood flow in these small units of lung is considered; the effects of microgravity, increased gravity, and different postures are reviewed, and the application of these findings to conditions such as acute lung injury is discussed. Down to the scale of the acinus, there is considerable heterogeneity in the distribution of both ventilation and blood flow. However, the matching of blood flow with ventilation is well maintained and may result from a common pattern of asymmetric branching of the airways and blood vessels. Disruption of this pattern may explain impaired gas exchange after acute lung injury and explain how the prone position improves gas exchange.

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Understanding regional differences in ventilation and perfusion of the lung should assist understanding and management of respiratory failure. Several current textbooks state that gravity has either an exclusive or a predominant influence^{2 17 33 48 54} on pulmonary blood flow, although some texts present alternative accounts.^{7 18} Recent research has shown that factors such as the basic structure of the pulmonary vessels and airways may be as important as gravity in determining regional differences in blood flow and ventilation distribution. We review some of the other factors that can affect regional function, and consider the clinical implications of these effects.

The gravitational explanation for ventilation and perfusion distribution

Early studies using radio-labelled gases showed that regional ventilation was greater in the dependent part of

the lung.⁵³ The gradient in pulmonary ventilation was explained by the gradient of pleural pressure that was considered to be predominantly caused by the effects of gravity. In the upright position, there is a gradient in pressure from the apex to the base of the lung. In the resting state, the pleural pressure is less than the atmospheric pressure, but it is less sub-atmospheric at the base. These regional differences are attributed to two factors: the weight of the lung itself, which is considered to be semi-fluid, and differences between the shape of the lung tissue and the surrounding pleural space.²⁸ The transpulmonary pressure at the base of the lung is therefore less, and the lung tissue less expanded, than that at the apex. The less expanded basal lung tissue has a greater compliance and, consequently, has greater relative ventilation,²⁹ when inspiration starts from FRC and when these measurements are made under static or quasi-static conditions.²⁸

The effects of gravity on the distribution of blood flow in the lung are attributed to the hydrostatic pressure difference between the top and bottom of the pulmonary arterial system. At the uppermost parts of the lung, the pressure within the vessels may be less than the alveolar pressure. Therefore, these vessels collapse and the alveoli that these vessels traverse will receive little blood flow. This accounts for some 'wasted ventilation' or physiological dead space. In the gravitational middle zone, pulmonary arterial pressure is greater and pulmonary artery pressure exceeds the alveolar pressure, and, similarly, in the lower zone pulmonary venous pressure also exceeds alveolar pressure. West⁵² describes these regions as zones 1, 2, and 3. This well-established 'gravitational model' has shaped our understanding of differences in the matching of ventilation to blood flow in the lung, which affects the efficiency of gas exchange.⁵¹

Other factors that affect distribution of pulmonary ventilation and perfusion

Regional ventilation

Early studies of regional ventilation were done using radioactive gases, measured by external detectors that were directed at different lung regions. Xenon was used because it is almost insoluble and has a useful isotope, ¹³³Xe. However, the precision of these external detectors was limited, breath holds had to be imposed to allow sufficient time to acquire the data, and the original studies of regional ventilation were done with very slow manoeuvres. Theory predicted that the distribution of ventilation would be affected by greater flow rates.³¹ When the distribution of inspired gas was studied using greater inspiratory flows, the regional differences were less than with very slow inspiration³ (Fig. 1).

Such studies were done in upright normal humans. The flow dependence found in the upright position was more marked than when the subjects were supine.⁴⁵ This suggests that there are differences in pleural pressure swings between

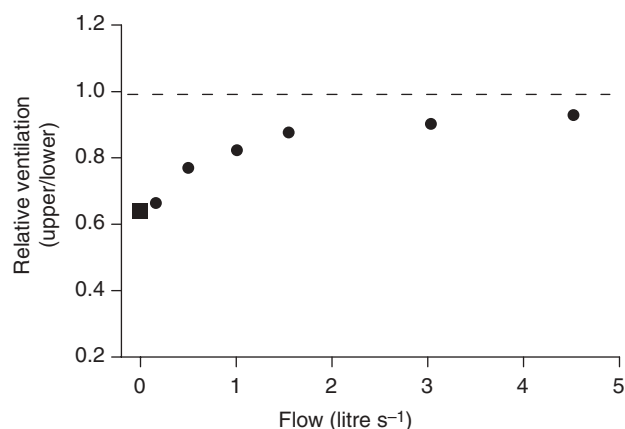


Fig 1 Change in distribution of ventilation (upper to lower ratio) caused by changes in inspiratory flow rate. The filled square shows the quasi-static value. Data from Bake and colleagues.³ Adapted with permission from the American Physiological Society.

the different regions, and such differences can affect regional ventilation and its dependence on the inspiratory flow.⁴⁴ Indeed, voluntary changes in breathing movements⁴³ and diaphragm activity⁴² clearly affect regional ventilation and reduce the differences between lung regions.

Measurements made with more precision show more variation in regional ventilation. Computed tomography (CT) allows measurements to be made of small regional differences in lung tissue expansion. Enhancement of CT measurements with xenon showed that ventilation was greater in the central lung than in the peripheral lung of mechanically ventilated dogs placed in the supine position.²⁶ In a careful study of exsanguinated lung, where CT density was used to measure the relative air and tissue content of each voxel, Rodarte and colleagues³⁸ confirmed earlier studies using radio-opaque markers. With both methods, they found considerable heterogeneity in expansion, which was not attributable to anatomical or gravitational gradients, at a scale of 1.5 mm³. At a slightly larger scale, two independent methods of measurement, using CT and aerosolized microspheres, showed good agreement. With both methods, there was considerable heterogeneity within each lung region, as much as between regions, and ventilation was greater in the central lung regions and less in the periphery.³⁷

Regional blood flow

The implication of the effects of gravity is that blood flow to regions of the lung at the same vertical height (iso-heights) should be equal. The consequences of the vertical flow gradient might apply irrespective of posture. Under conditions of zero gravity or weightlessness, variations in ventilation and perfusion should be abolished. These predictions are not supported by investigations.

Blood flow distribution at iso-heights

In upright human, there is a cephalad to caudal gradient of blood and gas flow distribution. The early studies used radio-labelled indicators and external counters of radioactivity that gave an averaged value for each horizontal level within the lung.^{4 8 53} At best, such methods gave a two-dimensional picture of what is in fact a complex three-dimensional structure. Evidence that blood flow was not uniformly distributed within horizontal planes emerged from studies in the 1970s. Reed and Wood³⁵ and later Greenleaf and colleagues¹⁶ used radioactive microspheres to determine regional blood flow in dogs placed in different positions. Microspheres were injected into the right ventricular outflow tract and lodged in the lung capillary beds in proportion to local blood flow. Analysis of the segments from the excised dried lung gave a three-dimensional record of blood flow distribution at the time of the injection of the tracer. These researchers found that blood flow varied within planes at the same vertical height and that there was a gradient of blood flow from apex to base, when

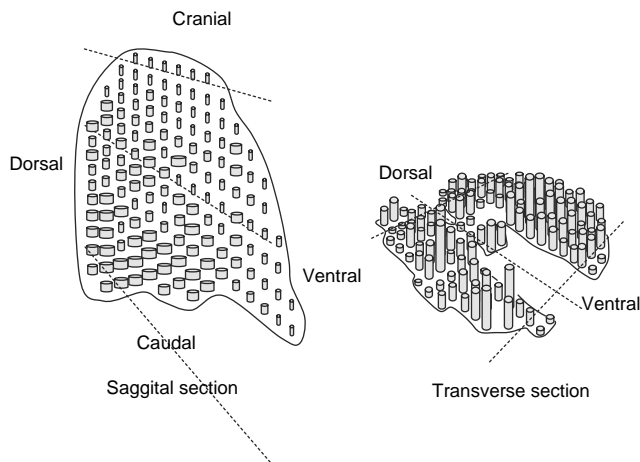


Fig 2 Relative blood flow in the saggital and transverse planes of upright baboon, measured using microsphere injection. The relative blood flow is shown in equal proportional steps, in relation to the mean, from 0.2 to 3 times. In the saggital plane, the flow is shown by increasing diameter, and in the transverse section, by increasing height. Data from Glenny and colleagues.² Adapted with permission from the American Physiological Society.

dogs were in both the supine and the lateral position. More recently, with higher resolution technology using fluorescent microspheres, Glenny and colleagues^{10,12} found considerable blood flow heterogeneity within planes at isovolume. In some studies, flow differences in lung samples at the same vertical height were 10 times greater than the flow differences at different heights.²³ The same methods gave high resolution of regional ventilation. Inhaled fluorescent microspheres show that regional ventilation in pigs varies considerably within the same vertical level.³⁶ Despite the varied distribution of pulmonary blood flow, variations in the blood flow patterns with time are remarkably small, with flow distribution patterns remaining relatively stable over days. The strongest determinant of flow to any region of the lung at any given time was the flow to that region at a previous or subsequent point in time.¹⁵ This suggests that under conditions of constant total blood flow (cardiac output) and perfusion pressure, variations in blood flow arise from the basic architecture of the pulmonary vessels. The underlying divisions of the bronchial/pulmonary vessels may have a fractal pattern. This is perhaps of limited clinical importance, but is of considerable physiological interest and will be discussed later.

Variation in blood flow in different postures

Studies of regional perfusion in dogs placed in different positions show that anatomy and gravity affect the distribution.⁶ Regional ventilation and blood flow were measured in the right and left lateral postures, using aerosolized and intravenous microspheres. A gravity-dependent gradient of flow was present in both postures, but the ventilation with gravity was greater in the right lateral position than in the left lateral position. A similar pattern was also

seen with ventilation, with an even greater difference in the vertical gradients in the two lateral postures. In fact, in the left lateral position, total blood flow and alveolar ventilation were less in the dependent left lung than in the non-dependant right lung. Adding 10 cm² PEEP reduced the differences in perfusion associated with gravity, in both postures. These differences in regional blood flow gradients between the two lateral positions do not accord with the concept that gravity alone determines blood flow distribution. The authors suggested that lung volume affected the vascular diameter and that vascular resistance was the primary determinant of blood flow distribution, with gravity playing a secondary role. Lung distortion by the weight of the heart and mediastinum is greater in the left lateral position than in the right lateral position. The dependent lung has a smaller volume and a greater pulmonary vascular resistance in the left lateral position, and this reduces the magnitude of the vertical gradient of flow. Even though moderate reduction in lung volume is usually associated with a reduction in pulmonary vascular resistance, the non-uniform distortion of the lung parenchyma in the left lateral position may increase pulmonary vascular resistance and reduce blood flow to the dependent lung in the left lateral position. PEEP reduced pulmonary vascular resistance by increasing ventilated lung volume, so that the \dot{V}/\dot{Q} ratio increased in the dependent left lung, and decreased in the non-dependent right lung, and hence the overall \dot{V}/\dot{Q} matching improved.⁶ The influence of gravity on flow distribution may be more important in bipeds than in the quadrupeds, so that the dog studies, such as the one discussed above, may not be applicable to the variations in ventilation and perfusion in humans.²³ Consequently, similar experiments were done in baboons, who spend most of their time upright.¹² Only 7, 5, and 25% of variation in perfusion heterogeneity was attributable to gravity in the supine, prone, and erect postures, respectively.¹² As the pulmonary vascular anatomy, including the serial distribution of vascular resistances (the proportion of resistance offered by the arterioles, capillaries and venules) is similar, the authors concluded that similar considerations would apply to humans (Fig. 3).

What are the effects of gravity?

In dogs, ventilation and perfusion were greater in the dependent lung in the lateral position. However, after correction for absolute lung weight, the total blood flow and ventilation were greater in the right, non-dependent lung when the animal was placed in the left lateral position. This finding cannot easily be reconciled with the gravitational model. Total blood flow is the product of mean regional blood flow and lung volume, whereas total ventilation is the product of regional ventilation and alveolar

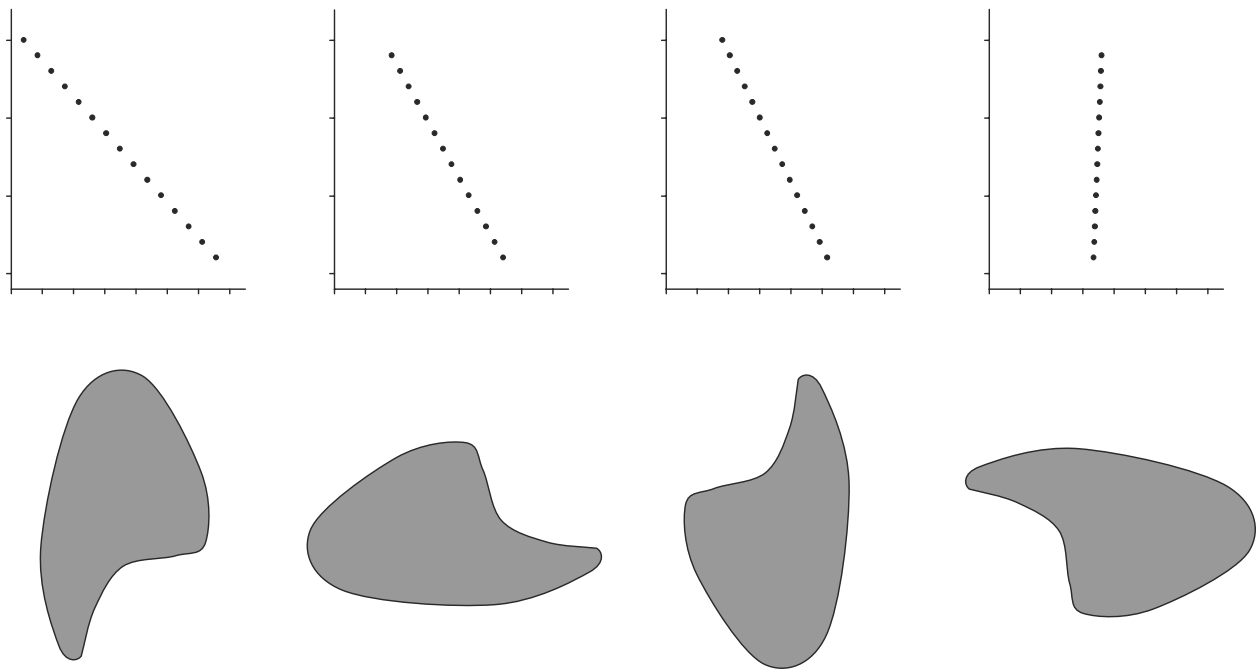


Fig 3 The vertical gradient of blood flow in baboons anaesthetized with ketamine and mechanically ventilated in four different postures. Measurements were made using microsphere injections. Data are from Table 2 of Glenny and colleagues, reprinted with permission from the American Physiological Society. In the upper panels, the linear regression of blood flow (expressed as a fraction of the overall flow) in relation to the vertical height is shown. This depiction resembles conventional diagrams, but it is important to note that height is the independent variable. The lo diagram indicates the orientation of the lung in relation to gravity. The influence of gravity on blood flow is greatest in the head up position and least in the prone position. However, it should be noted that the confidence limits of these relationships (not shown) are very large.

regional volume. Both measurements therefore have the same scale of measurement. Indirect methods such as the direct relationship to lung volume. In the left lateral position the dependent lung has a smaller volume than in the right lateral position, and the magnitudes of the vertical gradients of blood flow and ventilation are less. The relationship between blood flow and ventilation is not linearly related, with better spatial resolution. Different gravitational forces (0 to 1.8 G) were used in a study of pulmonary perfusion. Perfusion remained relatively constant in this position. Thus, total blood flow and alveolar ventilation in the dependent lung is less than in the non-dependent lung in the left lateral position, because the decrease in lung volume outweighs any gravity dependent increase in ventilation and perfusion.

In the light of these findings, the following questions can be posed:

Reduced gravity

During the 9-day mission of the space shuttle Columbia on the Spacelab Life Sciences-1 (SLS-1) mission, regional variation in pulmonary perfusion was studied. Volunteers hyperventilated, held their breath, and then the amplitude of the cardiogenic oscillations and the height of phase-4 in expired CO₂ were recorded in a single expired breath.

These measurements indicate variations in intrapulmonary perfusion. There was a significant reduction in perfusion heterogeneity, consistent with the traditional gravitational model. Unfortunately, the single breath exhalation technique does not provide satisfactory spatial resolution for an accurate quantitative analysis of pulmonary blood flow distribution. In structures with an underlying fractal geometry, the ability to demonstrate heterogeneity depends on

- (a) What factors influence distribution of ventilation and perfusion in the lung?
- (b) Is the gravitational model obsolete?
- (c) What are the clinical implications?

What factors influence distribution of ventilation and perfusion in the lung?

The spatial distribution of ventilation and pulmonary blood flow remains relatively fixed over time, and the shape and structure of the bronchioles and pulmonary arterioles/veins are important determinants of flow distribution. The branching series of bifurcations (Fig. 4). On average, the airways

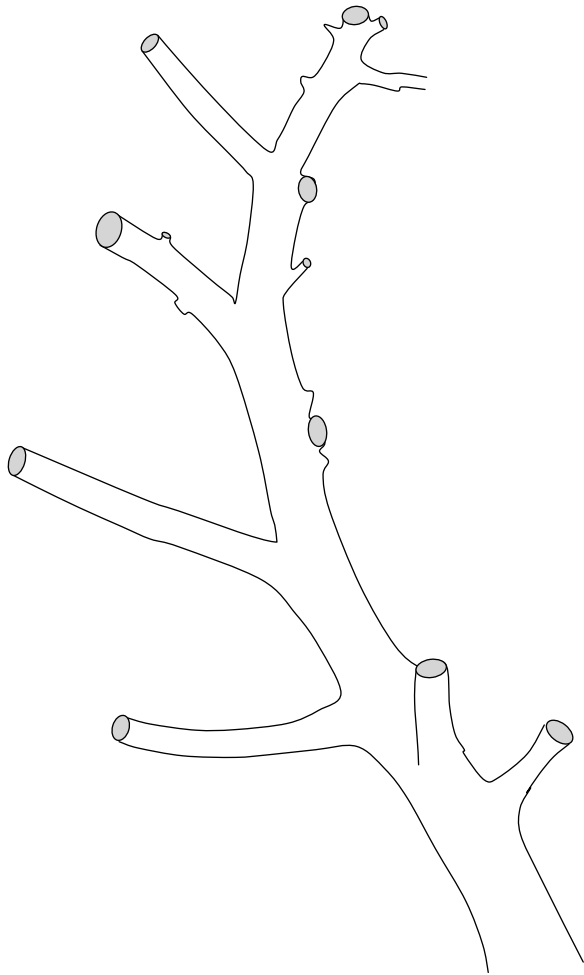


Fig 4 A bronchial cast showing the asymmetric branching structure typical of both airway and vascular branching in the lung.

branch about 23 times. Alveoli are present after about the 14th branch point. The pulmonary arteries follow the airways closely and have a similar branching pattern. However, the arteries continue to branch for several more generations, as the vessels penetrate further into the alveoli. Consequently, the pulmonary arterial system has an average of 28 generations of branches. The branching of the pulmonary veins resembles that of the arteries.

The pattern of branching is asymmetric and follows consistent rules. At each bifurcation, the diameter and lengths of the daughter branches are reduced by a constant factor (Fig. 5). This process of repeated branching can be described by a relatively simple set of rules (or a mathematical function). The repeated branching results in complex multi-dimensional structures, and examples of such structures are widely distributed in nature. In the lung, it provides an efficient mechanism to yield a vast surface area of approximately 130 m^2 within a limited volume of $5 \text{ D}6$ litres. Benoit Mandelbrot, a Polish mathematician, described fractal geometry, which was required for the accurate mathematical description of these objects (see http://wikipedia.org/wiki/Beno%C3%AEt_Mandelbrot accessed

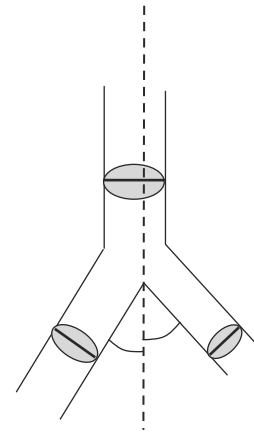


Fig 5 A method of quantifying asymmetry of branching. Both the branch angle and the relative diameters of the parent to the daughter branches can vary. The relative flow depends on these features, tube length, the nature of the flow, and considerations such as minimizing energy loss.

on February 18, 2007). One of the basic concepts of fractal geometry is that the overall structure should be self-similar at different scales of observation (Fig. 6).

The size relationships at each bifurcation determine flow distribution in the bronchial and arterial systems. If, for example, the ratio of the diameter of the branches at each bifurcation is not equal, but is 1:1.1, then the flow difference between these two branches (assuming laminar flow) will be $1.1^4:1$ (i.e. 1.46:1). When this process is repeated through several generations, considerable variation in flow

Asymmetric branching generates inhomogeneity

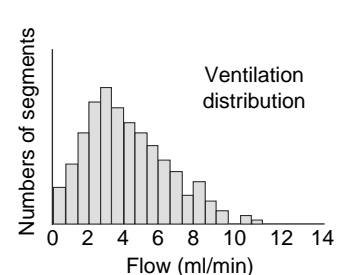
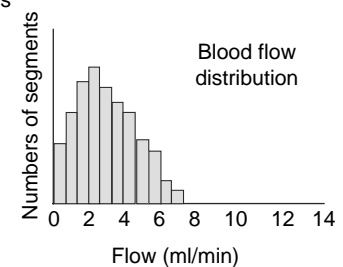


Fig 6 The consequence of asymmetry in branching. The total flow divides into two fractions in each of the branches. The greater fraction is g and hence the remaining fraction is $1-g$. When this asymmetrical pattern is continued for many generations of branches, this results in a distribution where different lung segments receive a wide range of flows (upper distribution histogram) and ventilations (lower distribution). The resultant blood flow and ventilation values in lung segments (samples) have a skewed normal distribution.

results within a small part of the lung (Fig. 6). To detect this heterogeneity, a measurement of local blood flow (or ventilation) will require good spatial resolution. Using graded centrifugal forces to mimic different gravitational conditions (1, 2, and 3 G), workers in Seattle have studied how gravity affects pulmonary perfusion in conscious animals.²¹ They found variations in perfusion in all three conditions, at the same gravitational plane, and this heterogeneity is the most convincing argument against gravity being responsible for blood flow variation. More than 75% of blood flow variation was attributable to factors related to the basic vascular architecture under all gravitational conditions.¹⁹ The increase in heterogeneity with greater centrifugal forces was attributed to the stretching of the more peripheral vessels and the consequent increase in vascular resistance. Over the last two decades, researchers have amassed an impressive body of evidence supporting the concept that pulmonary vascular (and bronchiolar) architecture is the most important factor to determine the distribution of ventilation and perfusion in the lungs. This is an important change in the concept of applied respiratory physiology, incompletely recorded in the current texts,^{5,4} and the clinical implication of these observations remains to be assessed.

What are the clinical implications?

Is the gravitational model obsolete?

Early studies used radioactive gases with collimated scintillation counters over the chest wall to detect the inhaled gases.^{4, 8, 53} Counts after a single breath of the radioactive gas were used to compare ventilation in different vertical zones, and the rate of removal of the isotope from the counting fields was used to measure the regional perfusion. Each counter measured at a single horizontal level and provided an averaged value for that level; hence, horizontal heterogeneity was not measured. These early studies reported ventilation and perfusion distribution only in the vertical dimension. With higher resolution methods, a more detailed three-dimensional picture of pulmonary perfusion has emerged. Fluorescent microspheres can show patterns of blood and gas flow within the lung. Given intravenously, they lodge in capillary beds in proportion to blood flow, and aerosol microspheres distribute themselves in the airways in proportion to gas flow. Different colours of microspheres can show differences in temporal, positional, or gravitational patterns.¹⁵ If smaller areas of lung are examined, the variation in blood flow between regions is found to be greater. Using an imaging cryomicrotome to determine the spatial distribution of fluorescent microspheres at a microscopic level, it appears that perfusion heterogeneity increases progressively and remains fractal down to the acinar level.¹³ In a study of the effects of Altmeier and colleagues¹ on pigs, a pattern of increasing and then decreasing blood flow down the lung was found by Glenn and colleagues.¹⁴ This observation correlated well with West's

How does this new concept relate the frequent clinical problems with pulmonary gas exchange and the management of respiratory failure? We will consider ventilation and perfusion matching in the normal and abnormal lungs, PEEP, prone ventilation, and the lateral position.

Can the structural model enhance our understanding of ventilation and perfusion matching in normal and abnormal lungs?

As the variation in ventilation and perfusion in normal lung is greater than that assumed previously, in both the horizontal and vertical planes, how are ventilation and perfusion matched to maintain efficient pulmonary gas exchange?

Consider a part of the lung in which the blood flow has branched asymmetrically so that the distribution of blood flow has become heterogeneous. If this portion of lung is divided into small equal samples, these samples will show a range of different blood flows, with a skewed distribution. If these blood flows and ventilations in each lung sample were matched in a random fashion, a very large range of ventilation to perfusion ratios would result, with a variance equal to the sum of the variances of ventilation and blood flow. However, this is not the case in practice. West¹ showed that although regional ventilation and perfusion are heterogeneous, they are closely correlated with each other, ensuring efficient gas exchange. High-resolution maps of regional ventilation in pigs show that the strongest determinant of regional

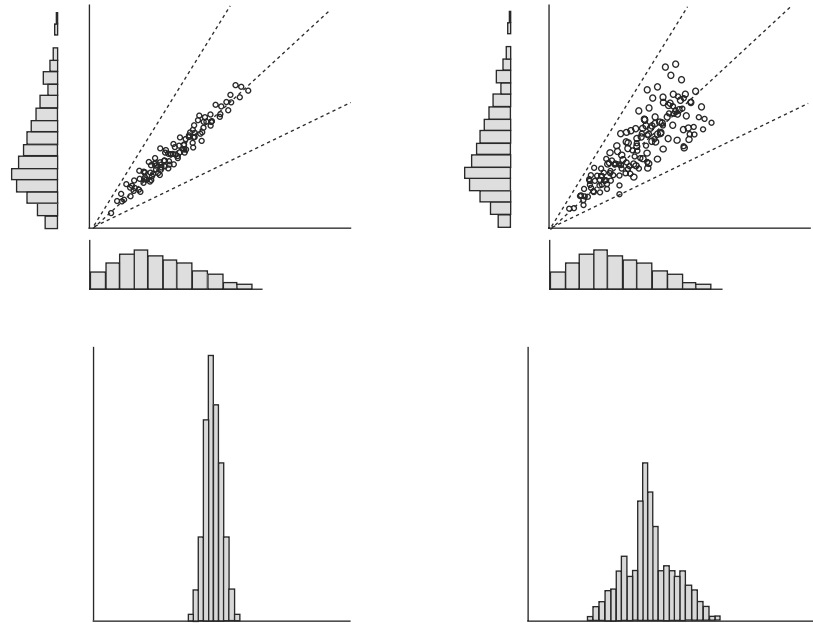


Fig 7 Two hypothetical models of correlation between ventilation and blood flow, using both the same number of lung samples and the same distribution of blood flow and ventilation (a) and (b), distributions shown parallel to the axes in each case. The correlation between blood flow and ventilation in each lung sample is close, and the resultant scatter of values in the samples is small (Gas exchange is efficient). (Despite the same overall distribution of ventilation and blood flow values, the correlation is less close and the resultant distribution of values is broader (b) and gas exchange less good.

ventilation is regional blood flow.³⁶ The correlation between blood flow and ventilation is of the order of 0.8, where 1 would be perfect (Fig. 7). The way regional oedema formation in acute lung injury distorts the precise matching of ventilation with perfusion, however, is not clear. In embryogenesis, the development of bronchioles and pulmonary arterioles could be coupled, so that their relative branching and development of the two systems could be linked, so that both ventilation and perfusion show proportionate changes through successive generations. Such synchronous changes in gas and blood flow in the successive branches of the airways and pulmonary vessels. Even a small change in the division of flow in one of the proximal branches can be amplified in the subsequent generation of branches and generate considerable convective mixing of gas in the alveoli, which could compensate for differences in alveolar gas composition caused by mismatching between ventilation and perfusion. The non-linear process makes the system extremely sensitive to initial conditions. This could explain why the observed clinical signs or radiological changes in acute lung injury or aspiration pneumonia do not seem to be proportional to the extent of gas exchange impairment. Increased gravitational forces reduce P_{aO_2} and increase P_{ACO_2} .²¹ Increased gravitational forces also increase $P_{A2a} O_2$.¹⁴

Can the structural model enhance our understanding of therapies such as the prone positioning or PEEP in acute lung injury? The changes in the lung found in acute lung injury resemble, in many respects, the changes found with increased gravity. In both conditions, hydrostatic pressure gradients increase the bronchiolar and pulmonary arterial pressures dorsally and cranially, reduces the lung volume, and

moderately increases pulmonary vascular resistance, more so than in the prone position. Even in normal subjects, the prone position allows better conditions for pulmonary gas exchange. This is exaggerated in critically ill patients with acute lung injury and multiple organ failure. The increased volume of abdominal contents caused by oedema and ascites commonly present in these patients may aggravate the effects of the supine position. Rohdin and colleagues⁴¹ found that in human volunteers exposed to five times normal gravity, gas exchange was more efficient in the prone position. Pulmonary changes in these conditions mimic those seen in acute lung injury, and hypergravity has been used by several authors as a model of acute lung injury. In the supine position, vital capacity and diffusion capacity are reduced more, and there is a greater increase in V/Q mismatch than in the prone position.⁴⁰ The prone position protects against hypoxaemia during hyper-gravity (89.7 vs 84.6% when supine).³⁹ Studies in animals have also found more uniform distribution of alveolar ventilation in the prone position.^{5, 25, 30} In patients with acute lung injury the beneficial effect of the prone position is attributable to better alveolar ventilation in the dorsal regions of lung that preserves good V/Q matching. The fundamental structural features of the lung accord with evolution in which the upright position of the human race is a relatively recent event.

PEEP is an accepted manoeuvre to improve oxygenation in acute lung injury. Gattinoni and colleagues³² used CT to show a direct relationship between the PEEP needed to re-open collapsed lung units with the distance below the ventral-dorsal axis of the lung in supine patients.³² This observation was consistent with a greater gradient in hydrostatic pressure because of pulmonary oedema, with a greater effect in the dorsal and caudal regions of the lung. If gravity were the only important factor, then the beneficial effects of PEEP would be independent of posture. However, PEEP redistributes pulmonary perfusion to dependent lung regions in patients who are supine but not in patients when they are prone.⁴⁷ A simple model of alveolar recruitment, increased airway patency, and reduced pulmonary vascular resistance does not clearly explain why the effects of PEEP depend on posture.

What are the implications for the left lateral position? The traditional gravitational model suggests that in the lateral position, both blood flow and ventilation will be greater in the dependent lung. However, in the left lateral position, total ventilation, total blood flow, V/Q ratio, and regional oxygenation can be less in the dependent lung than in the non-dependent lung. Crucially, regional perfusion in the lower parts of the dependent left lung was found to be sufficient to trigger hypoxic pulmonary vasoconstriction,¹³ and the V/Q ratio for the whole lung was greater in the left as opposed to the right lateral position.⁶ This may have important implications for gas exchange in patients in the left lateral position.

Conclusion

The gravitational model of ventilation-perfusion distribution has held sway for decades, particularly in the frontline anaesthesia/critical care textbooks, and has been applied extensively to our understanding of pulmonary pathophysiology. However, it fails to explain adequately several important observations regarding the distribution of ventilation and perfusion: heterogeneity at the same vertical level, postural inequality, and the persistence of heterogeneity in the absence of gravity. The underlying structure of the bronchial and pulmonary vascular anatomy with non-symmetrical branching is now considered an important factor in causing heterogeneity in pulmonary perfusion and ventilation in both health and disease. Consequently, this new structural model should now replace the earlier gravitational model in our understanding of ventilation-perfusion inequalities in the lung: at least until a better explanation is forthcoming.

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