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Point:Counterpoint: Gravity is/is not the major factor determining the distribution of blood flow in the human lung

POINT: GRAVITY IS THE MAJOR FACTOR DETERMINING THE DISTRIBUTION OF BLOOD FLOW IN THE HUMAN LUNG

In 1944 the first recordings of pulmonary artery pressure (Ppa) in normal humans were published (6a). Dock (7), a Brooklyn physician, foresaw that in the upright position, with such a low Ppa, the upper quarter of the lung would be relatively ischemic in most people. He linked this notion to the apical (cranial) location of tuberculous lesions in humans in contrast to its caudal and dorsal distribution in quadrupeds and bats (8). Dock in 1947 did not consider a gradient of increasing blood flow below the bloodless apical regions; in 1960, West and Dollery (25) found a systematic increase in blood flow per unit volume from apex to base in the erect lung with a tenfold increase from top to bottom (Fig. 1). Apical blood flow increases at the onset of exercise and decreases when exercise stops (14), in keeping with the known increases and decreases in pulmonary artery pressure—further confirmation of Dock's reasoning.

Postural changes. Subsequently, with a variety of radiotracers and detection systems and also contrast enhanced computed tomography [electron-beam CT or EBCT (16)], a vertical gradient of blood flow from upper to lower regions has been found in other postures [prone and/or supine (1, 5, 16–20), right and left lateral decubitus (1, 17, 20), supine anesthetized (23)] in keeping with a gravitationally determined gradient. Despite widely different methodologies and techniques such as *1*) single breath hold at TLC (17) or at midlung volumes (17, 18) or steady-state tidal breathing (1, 5, 20), *2*) front and back detector pairs (17) or gamma cameras (1) or single photon emission tomography (SPECT; Refs. 19, 20, 23) or positron emission tomography (PET; Refs. 5, 18) or EBCT (16), *3*) inert gas radiotracers (1, 5, 17–20) or radiolabel led albumin macroaggregates (MAA; Refs. 19, 23), the data in humans have been remarkably consistent. Interestingly, no vertical gradient was found in the dependent lung in lateral decubitus (1), where the lower lung is relatively compressed by the mediastinum above, in keeping with earlier studies (2, 15) showing loss of the vertical gradient in the erect position at low lung volumes. SPECT is the one technique that has at times been out of line. Hakim et al. (13) found in supine humans that, in any given sagittal slice, blood flow diminished from the center in a concentric fashion without a recognizable gravity gradient. This finding has not been confirmed. Another SPECT study (19) found no vertical blood flow gradient in the prone posture, but four other studies, using EBCT (16), PET (5, 18), and SPECT (20), disagree. Finally, a recent SPECT study (21) suggested that flow tracer distribution is determined by the posture during imaging, not the posture during the flow measurement, with a dorsal predominance of flow in prone (but imaged supine) identical to that in supine. The authors' postulate that vertical redistribution of tissue occurred when posture changed and that flow predominance seen in dorsal regions in both supine and prone was caused by a greater number of alveoli and blood vessels per unit volume dorsally rather than by gravity. However, the reconstruction algorithms are of such complexity that verification of these findings is needed using a different approach.

Changes in gravity. Acceleration of erect subjects [increasing the head to foot gravity vector (Gz) 3- or 4-fold] in a centrifuge increased in a systematic fashion the unperfused region [~zone 1 where alveolar pressure (Palv) exceeds Ppa] at the apex of the lung in line with a fall in pulmonary artery pressure (9); at the same time the gradient of increasing blood flow from apex to base became steeper (6, 9). No topographic measurements have been made in micro- or zero gravity (~weightlessness) but cardiogenic oscillations in CO_2, an indirect index of uneven blood flow, were reduced to 60% during and after exposure to microgravity in the Spacelab Life Sciences-1 Mission (22).

Gravity and the microvasculature. In addition to topographic differences between regions of lung 1–5 cm apart or 0.6–6 cm^3 in volume, gravity has an important role to play in terms of capillary recruitment and distension. The generally accepted zone I, II, III model is based on measurements of blood flow distribution in isolated perfused lungs and on the relationships between pulmonary artery, Palv, and venous (Pv) pressures (27). The driving pressure (ΔP) for flow in zone II is the Ppa−Palv difference (Palv is >Pv),

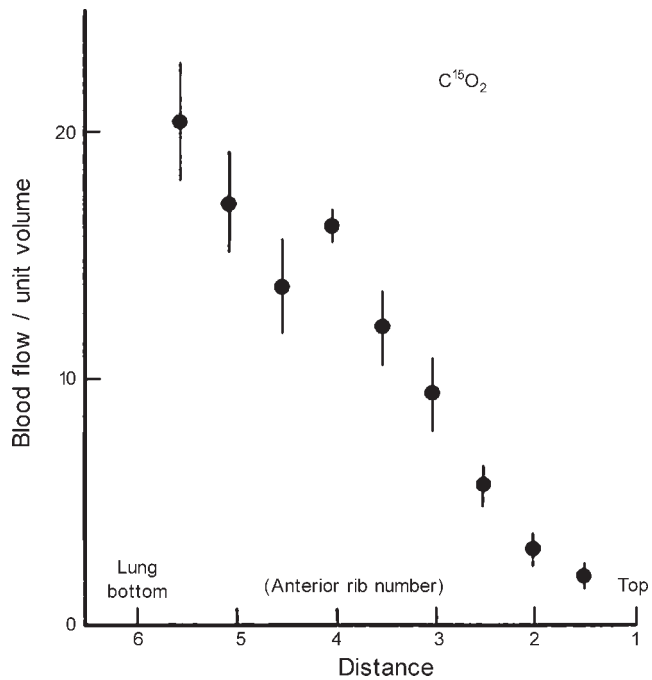

Fig. 1. Distribution of blood flow in the upright lung in 16 normal subjects, following single inhalation of radioactive CO2 ($C^{15}O_2$): mean and SD of clearance rates. Blood flow decreases systematically from lung base to apex along the axis of gravity. Redrawn from West (26).

and clearly ΔP increases by 1 cmH_2O/cm vertical distance down zone II. But why does blood flow increase down zone III, right to the bottom of the lung at high lung volumes (2, 15), or in decubitus postures, when ΔP (~Ppa − Pv) is constant down this zone? The reason is that mean microvascular pressure [~(Ppa + Pv)/2] increases by 1 cmH_2O/cm vertical distance leading to recruitment of septal vessels and distension of those already open, thus reducing microvascular resistance and increasing flow (10). This mechanism also contributes to the increase of flow with distance down zone II.

Human vs. animal lungs. Those who question the importance of gravity in determining flow distribution in the human lung refer extensively to experiments in animal lungs (12). Although such experiments assist our understanding of mechanisms, biped humans differ from quadrupeds, particularly in the topography of pulmonary blood flow and in the muscularization of pulmonary vessels, just as the distribution of tuberculous lesions differs (8), which invalidate the comparison. The most important factor potentiating the effect of gravity on blood flow distribution is the level of Ppa in relation to the height of the lung, as Dock (7) pointed out. When PVR is low, most of the central Ppa will be "seen" by the microvasculature and vascular conductance will be dominated by the zone I-III relationships, which are very gravity dependent. In the erect posture, the height of the human lung is large in relation to the low PVR and Ppa. On the other hand, with a high PVR and muscularized pulmonary arteries and arterioles, or when the operating lung volume is low, the effects of gravity may be obscured.

Gravity vs. non-gravity effects. We do not maintain that gravity is the only factor. It is clear that heterogeneity of blood flow increases as the scale of the enquiry narrows (3)—the "what is the length of the coastline?" effect. As the fraction of vascular resistance upstream of the microvasculature increases, so subtle differences in arterial branching ratios may influence flow distribution. As the Seattle group pointed out (11), a daughter:daughter branching ratio of 1.1:1 means a flow variation of $(1.1)^4$, i.e., 1.46:1. With the advent of reasonably accurate reconstructions for small regions of interest (ROIs) using PET or EBCT, sufficient ROIs can be mapped in human lungs for regressions of local blood flow vs. vertical distance to be calculated. On this basis, gravity contributes in the supine lung 24% (18), 34% (16), or 61% (5) to the overall variance of blood flow. Although these are crude estimates, they support our thesis that gravity is the single most important factor in determining blood flow distribution in a large low vascular resistance organ such as the human lung.

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COUNTERPOINT: GRAVITY IS NOT THE MAJOR FACTOR DETERMINING THE DISTRIBUTION OF BLOOD FLOW IN THE HEALTHY HUMAN LUNG

The gravitational hypothesis of blood flow distribution in the lung has been a cornerstone of pulmonary physiology, influencing both the interpretation and direction of studies related to pulmonary function for the past four decades. The model has been taught to generations of students because of its reliance on readily understood physical principles that yield elegant explanations of lung function. Modern studies, however, using high-resolution methods and experiments performed in microgravity provide observations that cannot be explained by the gravitational model alone. A new fractal model explains these anomalies, providing insights and new directions for investigation.

The opponents have constrained the discussion to human physiology by reasoning that there are differences between quadrupeds and bipeds (18). The differences are real, with respect to vascular compliance and muscularity, but of course they do not necessarily mean that observations in animals are not relevant to human physiology. The first study by Banister and Torrance (3) proposing a gravitational model and many other studies validating that model were performed in animals (e.g., Refs. 19, 28). The restriction to human lungs is immaterial as there are a number of modern studies demonstrating that gravity is not the dominant factor determining the distribution of pulmonary blood flow in humans (17, 20, 22–24).

The foundation for this debate must be set on two central issues. First, is the understanding that the spatial resolution of the methods used to measure pulmonary blood flow are central to interpreting the data. Perfusion distribution in the lung is composed of variability along a vertical axis and within horizontal (isogravitational) planes. The methods used to form the basis of the gravitational model used external scintillation counters that measured a mean flow value within horizontal planes (2, 27). None of these studies could therefore detect blood flow heterogeneity within these planes. By mathematically averaging flows within horizontal planes, the spatial resolution of modern studies can be reduced to that available in the first studies reporting a vertical gradient in pulmonary blood flow. When the spatial resolution is reduced in this manner, the distribution of blood flow obtained with modern methods appears virtually identical to the original studies of West and colleagues (19, Fig. 1) However, when blood flow distributions are viewed at a higher resolution, isogravtitational heterogeneity is observed and the relative influence of gravity on regional blood flow becomes secondary (Fig. 2). At even higher spatial resolution, the heterogeneity of perfusion within horizontal planes increases further (16), while the vertical gradient remains unchanged.

Prior to the 1990s, all human studies used data acquisition systems that did not permit the measurement of perfusion heterogeneity within horizontal planes. Hence, only the variability in blood flow over a vertical distance was seen and gravity was reasonably proposed as the sole mechanism accounting for this observation. However, with the realization that isogravitational perfusion heterogeneity exists, these older data can no longer be used as evidence that gravity is the major determinant of pulmonary blood flow distribution.

The second issue is that the lung is an elastic structure and gravity causes lung parenchyma to stretch at the top and compress at the bottom. Consequently, blood flow will appear to be greater toward the lung bases because of the increased density of blood vessels within the parenchyma (17). The pioneering studies that formed the basis of the gravitational model did not account for tissue compression down the lung. Subsequent studies correcting for this tissue redistribution (e.g., Ref. 1), confirmed a vertical gradient of perfusion, but found less difference between the top and bottom of the lung.

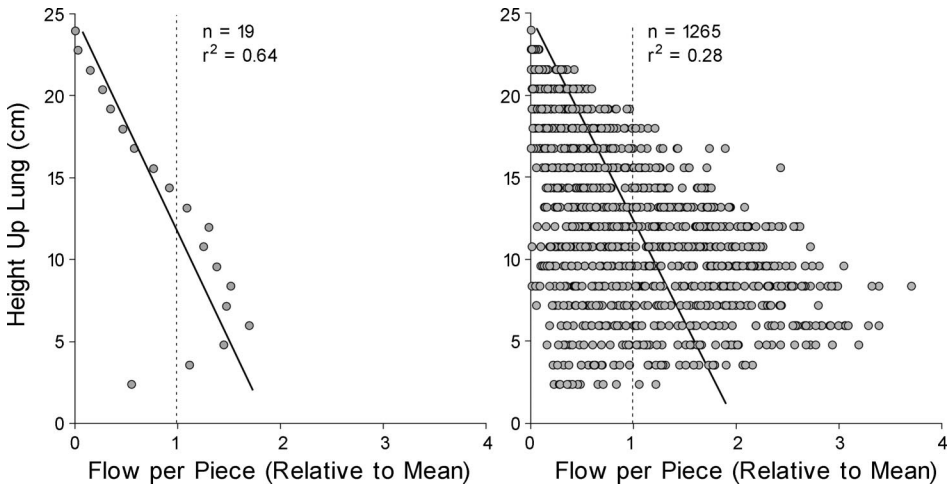

Fig. 2. Blood flow as a function of height up the lung in an upright primate. Data are from 1,265 pieces of lung (2 cm^3 in volume) and were obtained using the microsphere method (9). Left, data averaged within horizontal planes to reproduce the spatial resolution available at the time the gravitational model was conceptualized. Right, same data but at a resolution that permits the heterogeneity of perfusion to be observed. At the lower spatial resolution, the data are remarkably similar to those of Hughes and West (27) and gravity appears to be a major determinant of perfusion (r^2 = 0.640). However, at the higher resolution, gravity can account for at most 28% of the variability in perfusion. Redrawn from Glenny et al. (9).