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Physiology for the pulmonary functional imager[☆]

David L. Levin, MD, PhD^{a,*}, Mark L. Schiebler, MD^b, and Susan R. Hopkins, MD, PhD^c
[Professor of Medicine and Radiology]

^aDepartment of Radiology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States

^bDepartment of Radiology, UW-Madison School of Medicine and Public Health, 600 Highland Avenue, Madison, WI 53792-3252, United States

^cDivision of Physiology 0623A, University of California, San Diego, 9500 Gilman Dr., La Jolla, CA 92093, United States

Abstract

As pulmonary functional imaging moves beyond the realm of the radiologist and physicist, it is important that imagers have a common language and understanding of the relevant physiology of the lung. This review will focus on key physiological concepts and pitfalls relevant to functional lung imaging.

Keywords

Pulmonary functional imaging; Lung physiology; Quantitative pulmonary perfusion; Quantitative pulmonary ventilation

1. Introduction

The lung presents many unique challenges to imagers and physiologists alike. From an imaging standpoint, many of these stem from properties inherent in the functioning lung, including a structure that consists primarily of air, interspersed with a complex diaphanous network of soft tissue, and limited ability to suspend respiratory and cardiac motion. From a physiology standpoint, difficulties arise in large measure from the readily deformable nature of the lung, which changes relative to position (gravity) and throughout the cardiac and respiratory cycles.

As pulmonary functional imaging moves beyond the realm of the radiologist and physicist, it is important that imagers have a common language and understanding of the relevant physiology of the lung. This review will focus on key physiological concepts and pitfalls relevant to functional lung imaging. We have purposefully excluded a detailed examination of specific methods, as these can change rapidly, limiting the usefulness of such a

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*Corresponding author. levin.david@mayo.edu (D.L. Levin), shopkins@ucsd.edu (S.R. Hopkins).

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discussion. Instead, we focus on the physiology of the lung and how that influences imaging and the interpretation of image data. These concepts are universal and apply equally to current and future imaging methods. We begin with a discussion of the spatial resolution needed for physiological imaging and then discuss factors that influence the imaging evaluation of pulmonary perfusion and ventilation.

2. What spatial resolution is needed for physiological imaging of the lung?

With anatomic pulmonary imaging, radiologists traditionally have pushed for greater spatial resolution to find the earliest structural features of pulmonary parenchymal disease. While this may be required for the diagnosis of some diseases, such as idiopathic pulmonary fibrosis (IPF), physiological and functional imaging of the lung may be accurately performed with much larger voxel sizes. From a physiological standpoint, the highest level of resolution required is only as small as a functional lung unit. To achieve resolution below this level does not necessarily add to the physiological information but may offer disadvantages. For one, increasing levels of resolution can be associated with a substantial decrease in image signal to noise, which is often already limited in many functional imaging studies. Also, for CT, the amount of radiation needed increases significantly with smaller voxel sizes. With this in mind, there are several ways to estimate the level of spatial resolution needed for physiological imaging.

A key determinant of the required resolution is the functional size of the gas exchange unit, i.e. the size of an acinus. The acinus can be described from a functional standpoint as the largest airway unit in which all airways contained therein participate in gas exchange [1]. Anatomically, these are all of the airways served by a respiratory bronchiole. Proximal to this, the airways serve to conduct gas and no meaningful gas exchange occurs. Parenthetically, the exception to this statement is found for those gases that are highly soluble in water, such as ethyl alcohol. This property contributes to the inaccuracy of the alcohol breath test (“breathalyzer”) and is the scientific basis for legal challenges its use to establish the presence of driving while under the influence (DUI) [2].

Haefeli-Bleuer [1] found a mean acinar volume of 187 mm^3 in the human lung using histological methods, which was nearly identical to the estimate of 183 mm^3 made earlier by Hansen and Ampaya [3]. This corresponds to a mean acinar diameter of roughly 7 mm. Using bronchography, Gamsu et al. [4] found a similar mean acinar diameter of 7.4 mm in human lung. Using a canine model, Young et al. [5] used graded embolization of pulmonary arterioles to estimate the size of a pulmonary gas exchange unit. Embolization using beads of $150 \mu\text{m}$ consistently led to regions of increased VA/Q ratio, whereas embolization with beads $<150 \mu\text{m}$ did not. This suggested that the regions of lung supplied by vessels of $150 \mu\text{m}$ represented the functional unit for gas exchange. In the dog, vessels of this size supply a volume equal to roughly six acini. If a similar relationship were present in humans, this would represent a volume slightly greater than 1000 mm^3 ($10 \times 10 \times 10 \text{ mm}$).

As shown, the results of multiple studies suggest that the spatial resolution needed at a functional level is significantly less than that typically used for assessment of lung structure.

A resolution of $10 \times 10 \times 10 \text{ mm}^3$ (1 cm^3) is likely an appropriate spatial scale for physiological imaging. In some situations, even lower spatial resolution may be perfectly adequate. This is because ventilation and perfusion have been shown to be spatially clustered, such that high perfusion regions tend to be adjacent to other high perfusion regions with low perfusion regions also adjacent to one another [6]. A similar statement can be made about the spatial distribution of ventilation. By comparison, a resolution of approximately 2 cm^3 has been used in numerous microsphere experiments to evaluate pulmonary physiology [7–9].

3. Quantification of pulmonary perfusion

The lung presents several challenges for the measurement of perfusion. In a tissue such as the brain, where the density is close to 1 g/cm^3 , the quantification of perfusion as measured per unit weight (ml/min/g tissue) is not substantially different than per-fusion measured per unit volume (ml/min/cm^3). In addition, the relative contribution of blood within the tissue to the overall density of the brain is relatively small, comprising about 4% of the total [10]. However, in the lung, the measurement of perfusion per unit volume gives a very different value than the measurement of perfusion per unit weight. This is because the lung density at functional residual capacity is approximately one-third of that of the brain and the blood volume itself contributes to more than one half of the weight of the lung [11]. For this reason, it is important that comparisons of quantitative perfusion between studies use the same units of comparison.

3.1. The Slinky® effect

The normal lung is a highly compliant organ and deforms regionally under the influence of gravity. As a simple conceptual model, the lung behaves like a Slinky®: a deformable spring that distorts under its own weight [12]. This has the net result that the density of the lung is significantly greater in the gravitationally dependent lung compared to the nondependent lung. West and Matthews [13] described this more than 40 years ago and pointed out that the regional differences in density would be accentuated by increased blood volume in the dependent portions of the lung. Brudin [11] further showed that the vascular component was the major contributor to vertical density gradients in the lung. This has been investigated using both magnetic resonance imaging (MRI) [12] and nuclear medicine single photon emission computed tomography (SPECT) [14]. These techniques have shown that a major determinant of measured regional blood flow is the relative distribution of lung tissue, which is heavily influenced by gravity.

In the normal lung, the effect of gravity on regional tissue density is critical, as compression of dependent lung regions will be reflected in measures of regional perfusion. This is because a given volume of lung in the dependent regions will contain more tissue (capillaries) and less air, and will thus have a greater density than in non-dependent regions. This does not explain all of the gravitation distribution of blood flow, which is also subject to effects related to hydrostatic forces [15] and vascular branching structure [6]. The reader is referred to a recent comprehensive review [16].

In addition to the deformation of the tissue itself, blood contained within the pulmonary circulation will provide additional deformation forces within the lung under gravity according to its distribution in the lung. This deformational property also means that the lung changes its shape and size markedly between maximal inspiration (total lung capacity, TLC) and full expiration (functional residual, FRC capacity). During that transition, mean lung proton density, as measured by MRI, changes nearly three-fold from ~0.10 g/ml to 0.27 g/ml [17].

In contrast to other organs, the measurement of total pulmonary blood flow is straightforward, as it receives essentially all of the cardiac output. However, the evaluation of regional pulmonary blood flow is critical in both the evaluation of normal physiology and clinically relevant pathophysiology. Thus, regional lung deformation and its effects on measured blood flow must be understood and accounted for. In general, measures of regional blood flow corrected for lung density are more useful than blood flow measured per unit volume, but this will depend on the research question under consideration.

3.2. Large vessels present on perfusion images do not represent local blood flow and need to be excluded for quantitative perfusion imaging

An additional consideration is the presence of the larger vessels in some images of pulmonary blood flow, such as those derived from contrast studies and from arterial spin labeling. These images are often quite appealing to radiologists, as they resemble angiographic images, and the bright signal in these structures tends to dominate the image despite their relatively low fractional volume in the image. Analysis of these larger vessels is often used to describe regional blood flow and estimate function. Indeed, images dominated by these structures are often called perfusion images. However, these large vessels serve to conduct and distribute blood flow throughout the lung. They do not represent pulmonary perfusion, do not participate in gas exchange, and cannot be used to evaluate lung function, per se. Furthermore, the blood within the larger vessels in a particular region will likely contribute to gas exchange in remote downstream regions from the large vessel location. Methods that reduce the contribution of larger vessels to measured pulmonary perfusion aid significantly in the evaluation of lung function [18,19].

One way that imaging of these large vessels has misled imagers is found in the tenacious idea that there are large central to peripheral gradients in perfusion within the normal lung. Central to peripheral gradients in perfusion have been reported in humans using contrast-enhanced MRI [20] and by Hakim et al. using SPECT imaging in both canine [21] and humans [22], where it was reported that perfusion in the hilar regions was up to ten times that of the periphery. At the highest level of scrutiny this seems improbable, as the distribution of ventilation is quite uniform within an isogravitational plane. If a ten-fold variation in perfusion were present, this would result in much greater ventilation-perfusion heterogeneity than is found in the normal lung [23,24]. The use of single-photon-emission-computed tomography in these studies was criticized because of attenuation and reconstruction artifacts in the lung periphery [25]. Multiple subsequent studies using a variety of techniques have failed to find significant gradients [26]. Consequently, this idea has been largely abandoned by physiologists, particularly in humans [27]. A significantly

smaller central to a peripheral perfusion gradient has been demonstrated using microspheres in sheep [28]. However, this species has substantial differences in vascular structure when compared to humans.

4. Quantification of pulmonary ventilation

Gas moves from the external world to the acinus by two processes: convection and diffusion [29]. Convective or bulk transportation of gas occurs within the conducting airways from the trachea to the terminal bronchioles. This represents approximately 15 generations of airway branching. Beyond this, gas moves primarily by diffusion and the bulk of alveolar ventilation occurs by this process [1]. However, not all of the inspired gas reaches the alveolus. A portion of each breath does not contribute to gas exchange and remains within anatomic or physiologic dead space. This has significant implications for the evaluation of ventilation by imaging methods.

Many of the current functional imaging techniques are able to rapidly image the spatial distribution of a gas (such as ^3He or ^{129}Xe) during a single inhalation. As the bolus of gas is inhaled, the first 150 ml of the inspiration or so is re-inspiration of gas from the previous breath (dead space). Then transport of the inhaled gas goes to regions of convective delivery. As the inspired gas travels down the airway tree the cross-sectional area becomes larger and the bolus travels more slowly until eventually it reaches zero. At this point conductive gas transport ceases and gas transport is diffusive in nature. The location of this transition, called the diffusive front, occurs at the level of the acinus for nitrogen (air) but is one generation in the airway tree more proximal for Helium and one generation more distal for sulfur hexafluoride gas (SF_6).

The lung deformation discussed above also has significant effects on the distribution of ventilation. In general, lung regions within gravitationally non-dependent lung are stretched compared to the dependent lung. As such, these regions of lung are on different parts of the pressure volume curve and have different overall compliance. This results in non-dependent lung being relatively poorly ventilated when compared to dependent lung during tidal ventilation [30,31]. However, this is neither a simple nor a fixed relationship, as differential regional lung expansion and changes in airway geometry have an effect on gas distribution [32,33]. For example, at functional residual capacity (FRC), inspired gas is distributed preferentially to the dependent portions of lung. At residual volume (RV), though, inspired gas distributes preferentially to non-dependent portions of the lung. Furthermore, the distribution of gas within the lungs is influenced by flow rates, with faster inspiratory flows associated with a more even distribution of gas [34]. While local ventilatory volumes and flows are primarily a function of the distribution of local compliance at rest, this is not necessarily true with exercise or in patients with pulmonary disease, where airway resistance plays a greater role in the distribution of ventilation.

Given the above discussion, the question becomes what does the distribution of gas following a single breath mean? Regions of low signal are commonly referred to as defects but this terminology is in error. A defect implies absent ventilation, but many such regions are regions of “slow space”. This terminology is derived from multiple breath inert gas

washout studies which monitor the change in (typically) expired nitrogen following a switch to 100% oxygen breathing [35,36]. Such studies in patients with lung disease such as asthma or COPD typically show a two phase washout indicate that there are substantial populations of lung until that exchange gas slowly. These are not defects, and in the presence of slow space gas distribution will reflect a region of lung that reaches equilibrium only following multiple breaths. This distinction is important clinically because inhaled therapeutic agents can be delivered to regions of slow space but cannot be delivered to regions of absent ventilation. In a single inhalation setting, these two possibilities cannot be distinguished. This is not a function of the imaging technique, but rather a function of the underlying physiology. Most importantly, regions of reduced ventilation may or may not have a significant impact on overall gas exchange (see ventilation/perfusion ratios).

4.1. All imaging measures of ventilation are not equal, or specific ventilation is not alveolar ventilation

The ratio of the delivery of fresh inspired gas in a region of lung to the resident gas contained in the region is called the specific ventilation (SV):

$$SV = \text{volume of gas delivered} / \text{volume of resident gas}$$

Many imaging techniques measure either the local signal intensity or the change in local intensity when a contrast agent, such as oxygen or hyperpolarized gas, is inhaled in order to infer information about the distribution of ventilation. All other imaging considerations aside, after inspiration of an imaging agent, the resultant signal is a function of the ratio of the signal from the contrast agent newly delivered to the region and the local gas content resident within the region. Unless further steps are taken, what is measured is specific ventilation and NOT alveolar ventilation. Alveolar ventilation is the delivery of fresh gas, and is what is important for gas exchange.

As discussed earlier, the deformation of the lung under gravity results in large regional differences in the distribution of lung tissue. Alveoli in the gravitationally non-dependent lung are stretched and are therefore larger and contain more air than those in the gravitationally dependent regions, which are less stretched and may even be compressed. This stretching also means that these regions of lung are on different portions of the pressure-volume curve and, for a given inspiring pressure, stretched nondependent lung will receive less of the inspired agent than the dependent lung. Furthermore, an inhaled contrast agent in the non-dependent (stretched) region will be diluted by a greater volume of resident gas and thus will have a lower signal than in the dependent lung. As a result, there are large regional gravitational differences in both alveolar ventilation and specific ventilation, but these are not identical. Two voxels may have identical specific ventilation but vastly different alveolar ventilation because the amount of resident gas in the voxel differs. One approach to calculating regional alveolar ventilation from specific ventilation is to estimate the local volume of resident gas from density measurements to estimate the concentration of resident gas and to use this information to correct specific ventilation images [24,37].

5. Putting it together: ventilation/perfusion (V_A/Q) ratios

Alterations in the distribution of V/Q ratio can have significant impact of lung function, and may be important markers of disease. Virtually all lung disease is characterized by disruption of V_A/Q matching and reduced gas exchange efficiency. For example, decreased V_A/Q matching is a hallmark of COPD and areas of both abnormally high and low V_A/Q ratio are present [38]. Similarly, pulmonary arterial hypertension [39], asthma [40], pulmonary edema [41], pulmonary fibrosis [42], acute respiratory distress syndrome [43], and high-altitude pulmonary edema [44] also result in increased V_A/Q mismatch. While it might be tempting to focus on the mean V_A/Q ratio of the lung, this is altered by a great many common activities, including exercise, talking, and hyperventilation. The normal mean V_A/Q ratio is ~ 1.3 (i.e., remarkably close to 1).

In the normal lung, there is a range of V_A/Q ratios that typically span values from 0.5–3.0 or so [23,45]. In the normal lung, there are no regions of high V_A/Q ratio other than dead space, and there are no regions of low V_A/Q ratio other than shunt, which is less than 1% of cardiac output (Fig. 1A). This heterogeneity is normal and expected. Functionally, dead space can be thought of as a V_A/Q ratio >100 and shunt a V_A/Q ratio less than 0.005. In patients with lung disease, the V_A/Q distribution may be markedly broadened and there may be increased shunt, increased regions of low and or high V_A/Q ratio, as well as increased dead space (Fig. 1B).

Some clinical studies have reported an entity termed “reversed V_A/Q mismatch, which refers to lung images in which there are regions of absent ventilation with preserved perfusion [45–47]. The term reversed V_A/Q mismatch is not helpful in understanding the underlying pathophysiology and the term should be discontinued. This is because these regions already have a very precise term to describe them: if they are real and reflect underlying pathophysiology, they are regions of abnormally low V_A/Q ratio, if there is a small amount of ventilation, or they are regions of shunt, if ventilation is completely absent.

It is tempting to think that all regions of poorly ventilated lung must result in hypoxemia. However, ventilation alone doesn’t determine local PO_2 . In the absence of impaired diffusion across the alveolar capillary barrier (which is rarely found), it is the ratio of ventilation to perfusion that is the sole determinant of end-capillary PO_2 . This is perhaps best conceptualized by first considering the two extremes of V_A/Q matching, that of shunt (regions that are perfused, but ventilation is zero) and dead space, (regions that are ventilated, but perfusion is zero). In regions of an intrapulmonary shunt, end-capillary PO_2 will be essentially equal to that of mixed venous blood, as no gas exchange has occurred. In regions of dead space, alveolar PO_2 will be equal to that of the inspired gas and again no gas exchange will have occurred (as there was no perfusion). Between these two extremes, the relationship between end-capillary PO_2 and the local V_A/Q ratio for a given lung unit is more complex.

End-capillary PO_2 is relatively insensitive to changes in V/Q at both high and low V_A/Q ratios. As shown in Fig. 2, there is essentially no change in PO_2 of blood leaving a lung unit until the V_A/Q ratio is greater than 0.005 and similarly above a V_A/Q ratio of 100 there is also no change. This severely limits the utility of using measures of regional PO_2 derived

from imaging to infer the underlying distribution of V_A/Q ratios, as large changes in local V_A/Q ratio result in minimal changes in PO_2 in these regions. The relationship between a PO_2 and V/Q has a relatively sharp rise between V_A/Q ratios of 0.1 and 5. Although there is little change in end-capillary PO_2 between V_A/Q ratios of 0.005 and ~0.1, it is important to distinguish these units of very low ventilation from absent ventilation (true shunt), as low ventilation units will respond to interventions, such as supplemental oxygen. These relationships also set the boundary conditions for realistic measures of local blood PO_2 derived from imaging techniques. The PO_2 in the lung cannot be less than that of mixed venous blood (~40 Torr in a normal subject) nor can it be greater than the PO_2 of alveolar gas (~100 Torr). As such, values of end-capillary PO_2 of less than 20 Torr, or greater than 140 Torr, must be erroneous. This is again shown schematically in Fig. 2.

6. Conclusion

Functional pulmonary imaging presents many challenges, both from the difficulties in imaging the lung and the complexities of the underlying pulmonary physiology. While many of the imaging limitations can be overcome with advances in technology and techniques, the physiological limitations can only be mitigated with a thorough understanding of the complexities of lung function. In this context, we have discussed several of the more significant issues that can affect the evaluation of pulmonary perfusion and ventilation from the physiology perspective. While challenging, pulmonary functional imaging holds a great promise to improve our understanding of pulmonary physiology and pathophysiology.

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Fig. 1. Distribution of VA and Q in a healthy subjects and in a patient with COPD.

The overall mean of the VA and Q distributions are similar between a healthy normal subject (a) and a patient with COPD (b) with severe gas exchange impairment being centered close to 1. However, the shape of the distribution differs markedly. In COPD patients with regions of shunt and low V_A/Q ratio the log standard deviation of both ventilation and perfusion distributions is increased. (note dead space ventilation is not to scale)

Fig. 2. Relationship V_A/Q and PAO_2 .

The relationship between V_A/Q ratio and PAO_2 . At low V_A/Q ratios PAO_2 approaches mixed venous, whereas at high V_A/Q ratios it approaches inspired gas. Between a V_A/Q ratio of ~ 0.1 and ~ 5 (gray band), the relationship becomes more linear.