Ventilation heterogeneity: small length scales, big challenges

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The distribution of regional ventilation is heterogeneous in normal lung and increases dramatically under pathological conditions. This has been demonstrated both in humans and in animal models using a number of different imaging techniques. General anesthesia and mechanical ventilation can significantly alter the distribution of specific ventilation ($sV$), both through changes in the diaphragmatic and chest wall motion, and due to the development of atelectasis and airway closures, particularly when high inspired oxygen concentrations are used (6). The uneven distribution of ventilation has major fundamental and clinical implications. Ventilation heterogeneity affects the matching of regional ventilation and perfusion, leading to less efficient gas exchange, and can significantly affect the apparent degree of mechanical obstruction.

In the current issue of the Journal of Applied Physiology, Wellman et al. (12) used positron emission tomography to assess the heterogeneity of $sV$ at length scales ranging from 60 mm down to an effective resolution of 12 mm, but also, using ingenious methodology, below this resolution. They applied a multiple-compartment mathematical model to describe the kinetics of intravenously administered [13N]nitrogen washout from the alveoli of supine anesthetized and mechanically ventilated sheep. An important finding of their study is that ventilation heterogeneity increased proportionally to poor aeration in initially normal sheep lung at all length scales, including at those below the effective resolution (<12 mm), in animals ventilated with a high tidal volume ($V_t$) and zero end-expiratory pressure (ZEEP) vs. low $V_t$ and a relatively high level of positive end-expiratory pressure (PEEP) of 19 cmH2O. There was a significant relation between ventilation heterogeneity and the fraction of regions with decreased $sV$, particularly at small length scales. First, as discussed by the authors, this finding highlights the role of small-airway (likely <1 mm) narrowing in increased ventilation heterogeneity, with the loss of parenchymal tethering in poorly aerated regions. Second, the presence of regions with complete gas trapping suggests the occurrence of complete airway closures. Third, local differences in alveolar inflation and alveolar collapse may have contributed to the observed ventilation heterogeneity, as suggested by an increased shunt fraction within the poorly aerated regions. Some of the observed decreased $sV$ with ZEEP and a high $V_t$ may have been due to either small airway narrowing, or intermittent airway opening and closure, a proposed mechanism (2) of low-volume ventilator-associated lung injury (VALI).

Large-scale topographical ventilation heterogeneity, i.e., differences in regional ventilation between lung units ranging approximately from lobes down to subsegments or regions larger than acini, is considered to be convection dependent and mainly determined by differences in the regional mechanical time constant between lung units, which are not evenly distributed, even among isogravimetric lung regions. These differences, in turn, arise from inequalities, both in regional compliance, or pressure-volume relationship, and in the resistances of parallel airways leading to each unit, which are only partially explained by the effect of gravity on the lung (7) and determined in part by the branching structure of the airway tree.

Ventilation remains heterogeneous, even at smaller length scales. Early evidence for small-scale ventilation heterogeneity was provided by Engel et al. (4), who, by studying the pattern of $N_2$ washout from small subsegments distal to 3-mm airways in dogs, found that a substantial portion of total heterogeneity was occurring at the level of these small lung units. Subsequently, Rodarte et al. (9), studying the changes in computed tomography density during lung inflation in isolated dog lung lobes, found that not only is lung expansion heterogeneous within an isogravimetric image plane, but this heterogeneity increases as the size of the sampled region becomes smaller. Similarly, invasive measurements of regional ventilation by quantifying the deposition of fluorescent microspheres have shown that ventilation is heterogeneous down to lung samples of ~1 cm3 in sheep (8).

The causes and mechanisms of ventilation heterogeneity at small length scales are complex and remain incompletely understood. The very abrupt increase in the total cross-sectional area of the conducting airways leads to a sharp transition between convective or bulk flow and diffusive transport along the axial path leading to the alveoli. Previous modeling studies by Verbanck and Paiva (11) have shown that, within this critical transitional zone, interaction between convective and diffusive gas transport during inspiration can establish parallel differences in gas concentration in subtending lung acini, when some degree of asymmetry in their structural geometry is present. It is usually considered that gas concentrations become relatively homogenous within the acini due to forces that contribute to gas mixing, such as diffusion and cardiac oscillations. However, since the gas exchange units are arranged serially along the pathway from the entrance of the acinus to the terminal sacs, it has been proposed that $O_2$ uptake by the most proximal alveoli can establish a $P_{O_2}$ gradient toward the periphery of the acinus, a phenomenon referred to as “stratification” or “diffusional screening” in more recent computational studies by Sapoval et al. (10). Actually, the present understanding of the heterogeneity of ventilation and gas distribution at small length scales is mainly inferred from overall measurements of inert gas washout and computational modeling studies. Direct in vivo measurements of the extent and pathophysiological significance of the gas distribution...
heterogeneity at small length scales, within the spatial bound-
aries of the acinus, are lacking. Such measurements remain
extremely challenging because imaging methods allowing
quantitative measurements of the distribution of regional ven-
tilation lack enough spatial resolution.

The study by Wellman et al. (12) brings a number of ques-
tions and challenges to light. Down to what length scales
does ventilation and gas distribution within the air spaces
remain heterogeneous? The best spatial resolution for in vivo
ventilation studies so far is provided by K-edge subtraction
synchrotron imaging (1). Using this technique, ventilation was
found to be heterogeneous down to units as small as 1.5 mm$^3$
in rabbit, where the average acinar volume is 3.4 mm$^3$ (5). Yet
imaging techniques with even higher spatial and temporal
resolution are needed to depict within-acinar ventilation heter-
ogeneity directly, and such techniques are not yet available.

Another question is that, although nonuniform small air-
way diameters and dispersion in tissue elastance both contrib-
ute to the heterogeneity of the local mechanical time constants
and that of $s V$ at small length scales, these cannot be separately
measured. The respective roles, therefore, of airway narrowing,
cyclic reopening of airways, and that of alveoli with each
breath cannot be directly determined. The independent assess-
ment of these factors is crucial, however, since increased local
stress and strain of lung tissue by excessive regional inflation
and by tidal reopening of airways or alveoli at low lung
aeration have both been implicated in the development of
VALI (3). In their study, Wellman et al. (12) found that
relatively high levels of PEEP improved lung aeration and
reduced ventilation heterogeneity, particularly at small length
scales. However, PEEP levels higher than 10 cmH$2$O can
impede venous return, decrease cardiac output, and redistribute
blood flow toward more dependent regions of the lung, where
atelectasis is more likely to occur, thereby increasing physio-
logical dead space without eliminating shunt (6). In the end,
what optimal level of PEEP would be beneficial to ventilated
patients during routine anesthesia? This question deserves a
cautious answer and is a topic still under investigation.

Without a clear understanding of the contribution of mech-
anisms acting at microscopic scales, such as mechanical stresses
due to tidal recruitment of airways and alveoli, devising
mechanical ventilation strategies to prevent VALI will
remain highly challenging. The study by Wellman et al. (12)
gives an elegant example of how combining quantitative im-
aging and mathematical modeling can be used to bring new
insight into the mechanisms and significance of ventilation heterogeneity at length scales even smaller than the resolution
of their imaging technique. Given the important role of the
lung structural heterogeneity in establishing differences in
ventilation and gas concentrations between parallel pathways
at small length scales, ideally, the morphometry of the airways
should be quantified and confronted with the dynamic mea-
surements of regional ventilation. This is a highly challenging
goal, since both technical improvements in the spatial and
temporal resolution of imaging techniques and multiscale com-
putational models will be crucial in putting together the large
quantities of structural and functional data that state-of-the-art
imaging techniques can produce and in furthering our under-
standing of the complex behaviour of the lung at small length
scales.

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AUTHOR CONTRIBUTIONS

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