INVITED EDITORIAL

Exploring new heights with pulmonary functional imaging: insights into high-altitude pulmonary edema

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THE UNIQUE ENVIRONMENTAL CHALLENGE to the pulmonary physiology from exposure to high altitudes may hold unique insights into regulation of pulmonary function under stress. For example, high-altitude pulmonary edema (HAPE) is a mysterious disease characterized by individual differences in response to high-altitude challenge. Patz et al. (11) measured regional ventilation using specific ventilation imaging (SVI) (12) and multiple breath inert gas washout (MBW) in HAPE-susceptible (HAPE-S) and HAPE-resistant (HAPE-R) individuals. They hypothesized that HAPE-S individuals would have a more heterogeneous pattern of ventilatory distribution that could explain their heterogeneous hypoxic pulmonary vasoconstriction (5). Interestingly, they found the opposite, that is ventilatory distribution was more homogeneous in HAPE-S individuals.

Imaging of lung function with MRI has advanced significantly in the past decade in response to the limitations of conventional pulmonary function tests (2). These emerging pulmonary MRI methods exploit the general strengths of this modality, including three-dimensional (3D) chest coverage and multiple types of image contrast related to ventilation (7) and perfusion (10) without ionizing radiation. Although this has opened the door to investigate both dynamic and regional features of ventilation and perfusion in interventional and longitudinal studies, in most cases these techniques have not fully matured in their ability to capture interpretable physiologic measurements.

Important exceptions have been the pioneering work on high-altitude pulmonary edema (3, 5, 6, 11). By using an oxygen-enhanced MRI method previously validated to map regional specific ventilation, the authors demonstrate that an increase in ventilation heterogeneity is not apparent in HAPE-S individuals under normoxic breathing when compared with HAPE-R subjects. These investigators compared the MRI findings with multiple-breath inert gas washout under both normoxia and hypoxia. Importantly, neither conductive (S_{cond}) nor acinar (S_{acin}) measures of gas washout suggest ventilation heterogeneity differences between HAPE-S or HAPE-R subjects with a trend toward lower S_{acin} in HAPES subjects at baseline but no changes in either group with hypoxia.

Although this work represents a powerful combination of a novel functional imaging with an established physiologic measure of ventilation heterogeneity, the results stand in contrast to lung perfusion findings in HAPE. Two different perfusion MRI studies have independently demonstrated markedly increased perfusion heterogeneity after hypoxic challenge in HAPE (3, 5). These perfusion data were interpreted to reflect accentuated heterogeneous hypoxic pulmonary vasoconstriction (HPV). Because blood flow is more tightly regulated than ventilation under circumstances of hypoxia, it is possible ventilation is not initially affected, but it would still be surprising not to observe some level ventilation heterogeneity arising as a result of heterogeneous regional HPV, because we know that changes in regional pulmonary blood flow evoke changes in the accompanying ventilation (13).

Therefore, these compelling results remain inconclusive. Clearly, a follow-up study to compare both SVI and perfusion MRI in the same subjects, i.e., regional V/Q, is the natural next step. The same investigators have demonstrated such an approach in other studies (4). However, an important limitation of the specific ventilation MRI method is its dependence on breathing oxygen gas as a source of contrast, precluding measures under hypoxic challenge and its limited lung coverage (i.e., a single 2D sagittal slice). Previous results from perfusion MRI studies suggest hypoxic challenge may be necessary to stress the mechanosensory regulation of gas exchange leading to HPV. It, therefore, remains possible that ventilation heterogeneity only emerges under prolonged hypoxia and is exacerbated with exercise in response to HPV, mimicking the onset of HAPE in high-altitude alpine environments. Moreover, a fully 3D method with full lung coverage will inevitably be better suited to investigating regional heterogeneity of both ventilation and perfusion.

Alternative functional MRI approaches offer advantages for further testing the mechanisms of HAPE. Several studies, for example, have explored ventilation heterogeneity using hyperpolarized gas MRI after exercise in asthma (8), and methods combining dynamic contrast-enhanced imaging (1) with hyperpolarized gas MRI (9) can also measure regional V/Q in 3D and on time scales short enough to observe dynamic response to interventions such as hypoxia and exercise. Nonetheless this work is a major advance and demonstrates that emerging pulmonary MRI techniques can open a unique window on the etiology of HAPE and other poorly understood lung diseases.

DISCLOSURES

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AUTHOR CONTRIBUTIONS

S.B.F. and M.W.E. edited and revised manuscript; S.B.F. and M.W.E. approved final version of manuscript.
REFERENCES


