Published in final edited form as:

Crit Care Med. 2018 June ; 46(6): 1033–1035. doi:10.1097/CCM.0000000000003109.

Follow the Voxel – A New Method for the Analysis of Regional Strain in Lung Injury

Aranya Bagchi, M.B., B.S. and Marcos F. Vidal Melo, MD, PhD

Dept. of Anesthesia, Critical Care and Pain Medicine Massachusetts General Hospital, Boston, MA

Keywords

Lung Functional Imaging; Acute Lung Injury; Mechanical Ventilation; Lung Strain; ARDS; Positron Emission Tomography; Computed Tomography

It has long been recognized that *how* we ventilate a patient can be as important in optimizing outcomes as the fact that a patient needs to be ventilated. In 1974 Webb and Tierney demonstrated that it was possible to cause serious lung injury by mechanical ventilation, and that the application of positive end expiratory pressure (PEEP) had an important protective effect against ventilator induced lung injury (VILI)(1). In a major advance in the care of the critically ill patient, the ARDS network showed that lung protective ventilation (defined as the use of lower tidal volumes and appropriate PEEP) had a mortality benefit over conventional ventilation in patients with ARDS(2), in the process establishing the standard of care in the field.

The work of Gattinoni and colleagues(3) provided a further conceptual advance in our understanding of VILI when they established that ARDS affects the lung in an extremely heterogeneous fashion and that areas of comparatively normal lung density may exist adjacent to areas of high density, presumably containing severely damaged alveoli. Thus, not only is the lung in ARDS a ‘baby lung’, it is also a ‘scattered lung’. This has profound implications for clinicians – not only may low tidal volumes not be sufficient to prevent VILI, but predicting which patients with similar global characteristics (lung compliance, driving pressures, etc.) are at greater risk for VILI is essentially impossible with current available clinical methods. In an age of precision medicine, the intensivist is forced to apply a ‘one size fits all’ approach to an incredibly heterogeneous group of disorders we collectively describe as ARDS. Indeed, the recently emphasized relevance of driving pressures to outcomes of ARDS(4) and surgical patients(5) indicates how important individualization is even at the global level.

An approach that has become increasingly popular in providing a framework for understanding regional lung injury caused by mechanical ventilation is to think in terms of stress and strain. These are physical quantities drawn from the field of solid mechanics and key determinants of material failure. Stress can be defined as the force per cross-sectional

area of lung tissue – in practical terms estimated from the transpulmonary pressure. Strain is the ratio of the change in dimension (length, area or volume) divided by the resting dimension during respiration. It measures the degree of relative stretch applied to the whole lung and lung regions during breathing. The key insight here is that because of the ‘scattered lung’ in ARDS with widely varying mechanical properties both at the macroscopic and microscopic levels(6), stress and strain in some parts of the lung may significantly exceed the stress and strain averaged over the entire lung. Thus, the regions of the lung that experience the greatest degrees of stress and strain would be expected to contribute the most to the pathogenesis of VILI. Testing this hypothesis *in vivo* requires an imaging technique that can identify heterogeneous distribution of stress and strain in lungs with sufficient granularity, and a surrogate for inflammatory injury.

Positron Emission Tomography (PET) combined with Computed Tomography (CT) or respiratory-gated PET techniques have been used to tackle this problem. Lung CT allows detailed visualization of the lung parenchyma at sequential phases of respiration. Sophisticated image analysis platforms can analyze volumetric units of the lung (called voxel, a pixel in three-dimensional space) and track their displacement during inspiration and expiration, allowing the calculation of strain across the lungs and producing maps that can identify regions that undergo highest strain. To determine whether the areas that experience the highest strain also experience more inflammation, and hence drive VILI, lung computed tomography is combined with positron emission tomography using [^{18}F] fluoro-2 deoxy glucose (FDG-PET). Inflamed white cells (predominantly neutrophils) undergo a metabolic ‘switch’ becoming primarily glycolytic, i.e. using glucose as their primary energy source(7). FDG is taken up by cells in proportion to their glycolytic activity and is, thus, avidly taken up by inflamed neutrophils(8). PET-CT imaging allows the estimation of FDG activity across lung regions, providing an elegant *in vivo* method that permits the superimposition of ‘strain maps’ and ‘inflammation maps’ in the lung.

Using FDG and respiratory-gated PET imaging investigators have shown that local inflammation develops in proportion to regional tidal strain during early lung injury(9). Others have used CT based techniques to suggest thresholds for harmful stress and strain (10), although these remain to be validated prospectively. In this issue of Critical Care Medicine, Retamal et al report that regional strain colocalizes with regional inflammation in a porcine model of ARDS(11). In this carefully performed study, Retamal et al have reanalyzed PET-CT data from a previously published study by the same group, calculating strain in ten demarcated iso-gravitational regions of interest using a porcine model of severe ARDS in which saline lavage was followed by injurious ventilation. Volumetric strain within each one of these iso-gravitational regions was computed in the current work using sophisticated biomechanical analysis that estimates lung deformation with resolution nearing the voxel level. Their previous work had shown that, consistent with other investigators’ results(12), maximum inflammation in their ARDS model occurred in poorly and normally-aerated areas showing larger local tidal ventilation, not in overdistended or collapsed regions(13). Here they show in the same model that the intermediate and dorsal areas along the vertical axis are the lung regions that experience the maximum volumetric strain, and that this volumetric strain is correlated with the magnitude of local lung inflammation.

The work of Retamal et al replicates and expands key findings of their own group and of other investigators, thus increasing the confidence that clinicians and investigators may have in the concept of regional strain as an important determinant of local inflammation. A key aspect of the work published here, however, lies in the methodology of the image analysis – a technique that could potentially allow more precise analysis of strain in experimental and indeed, clinical studies. Most previous methods to compute lung expansion in clinical and translational studies have used large lung regions. Retamal et al. advance a technique that allows for computation of lung deformations at smaller lung regions composed by few voxels. The authors have taken the anisotropic displacement of voxels into account, which would theoretically allow analysis of exactly the same voxels at inspiration and expiration. A computational validation of this concept has been presented elsewhere(14), though more direct experimental validation will be required. Because of the scattered expansion of the ARDS lung, one would expect that regional lung strains would be larger in ARDS than in normal lungs. Using their technique, the authors confirm that presumption reporting in their ARDS model areas of lung with volumetric strains twice as large as those found in normal lungs (30 versus 60%).

A new technique can be particularly valuable when it's application potentially contradicts established conventional wisdom. It is therefore very interesting to note that the current work suggests inflammatory injury to regions of the lung at local strain levels significantly lower than what has been reported to be an injurious global strain threshold by other investigators(15). These findings can be regarded as hypothesis-generating and can potentially lead to a modification in our understanding of the nature of strain induced injury.

Interesting as the work of Retamal et al. is, it is not without flaws. Indeed, the authors are to be commended for providing a detailed accounting of the potential issues with their study. It is important to note, as the authors do, that their analysis of the intensity of the FDG signal (K_i) is not normalized to local lung tissue. Doing so would arguably represent a more accurate picture of FDG activity in the lungs, and in fact, the authors have used this approach previously. It is also possible that FDG activity was influenced by the degree of perfusion of the lung regions as opposed to inflammation alone(16). It would be interesting to carry out such experiments along with an independent means of assessing perfusion, such as by Electrical Impedance Tomography in the same animal to be able to normalize the degree of inflammation to perfusion. Finally, it is worth noting that the use of driving pressures of 40 cm H₂O to produce lung injury is somewhat different from lung injury seen in clinical practice, where ventilation induced strain likely interacts with pre-existing inflammatory pathology to produce VILI.

The use of principles of lung protective ventilation have changed the practice of intensive care and significantly improved outcomes in critically ill patients with ARDS. Retamal et al. call our attention to the fact that lung regions receiving a proportionally larger amount of the tidal volume, radiologically presenting less abnormal densities, are at particular risk for mechanical injury and inflammation. The next major challenge is understanding and defining patterns of regional injury that drive VILI and being able to individualize ventilation to minimize VILI in each patient. We are not close to that goal yet – however, it is work such as presented here by Retamal et al that will help us to move closer to that ideal.

Acknowledgments

Copyright form disclosure: Dr. Bagchi's institution received funding from Department of Defense - Congressionally Directed Medical Research Program Discovery Award (Grant #: W81XWH-17-1-0058), and he received funding from Lungpacer Medical (consultant). Dr. Vidal Melo's institution received funding from National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute and Merck, and he received support for article research from the NIH.

References

1. Webb HH, Tierney DF. Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive endexpiratory pressure. *Am Rev Respir Dis.* 1974; 110(5):556–565. [PubMed: 4611290]
2. Brower RG, Matthay MA, et al. Acute Respiratory Distress Syndrome N. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med.* 2000; 342(18):1301–1308. [PubMed: 10793162]
3. Gattinoni L, Pesenti A. The concept of "baby lung". *Intensive Care Med.* 2005; 31(6):776–784. [PubMed: 15812622]
4. Amato MB, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med.* 2015; 372(8):747–755. [PubMed: 25693014]
5. Ladha K, Vidal Melo MF, McLean DJ, et al. Intraoperative protective mechanical ventilation and risk of postoperative respiratory complications: hospital based registry study. *BMJ.* 2015; 351:h3646. [PubMed: 26174419]
6. Suki B, Hubmayr R. Epithelial and endothelial damage induced by mechanical ventilation modes. *Curr Opin Crit Care.* 2014; 20(1):17–24. [PubMed: 24300621]
7. Sadiku P, Willson JA, Dickinson RS, et al. Prolyl hydroxylase 2 inactivation enhances glycogen storage and promotes excessive neutrophilic responses. *J Clin Invest.* 2017; 127(9):3407–3420. [PubMed: 28805660]
8. Musch G, Venegas JG, Bellani G, et al. Regional gas exchange and cellular metabolic activity in ventilator-induced lung injury. *Anesthesiology.* 2007; 106(4):723–735. [PubMed: 17413910]
9. Wellman TJ, Winkler T, Costa EL, et al. Effect of local tidal lung strain on inflammation in normal and lipopolysaccharide-exposed sheep. *Crit Care Med.* 2014; 42(7):e491–500. [PubMed: 24758890]
10. Chiumello D, Carlesso E, Cadringer P, et al. Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2008; 178(4):346–355. [PubMed: 18451319]
11. Retamal JHD, Villarroel N, Bruhn A, Bugedo G, Amato MBP, Costa ELV, Hedenstierna G, Larsson A, Borges JB. Does regional lung strain correlate with regional inflammation in acute respiratory distress syndrome during non-protective ventilation? An experimental porcine study. *Critical Care Medicine.* 2018 In press.
12. Bellani G, Guerra L, Musch G, et al. Lung regional metabolic activity and gas volume changes induced by tidal ventilation in patients with acute lung injury. *Am J Respir Crit Care Med.* 2011; 183(9):1193–1199. [PubMed: 21257791]
13. Borges JB, Costa EL, Suarez-Sipmann F, et al. Early inflammation mainly affects normally and poorly aerated lung in experimental ventilator-induced lung injury. *Crit Care Med.* 2014; 42(4):e279–287. [PubMed: 24448197]
14. Hurtado DE, Villarroel N, Retamal J, et al. Improving the Accuracy of Registration-Based Biomechanical Analysis: A Finite Element Approach to Lung Regional Strain Quantification. *IEEE Trans Med Imaging.* 2016; 35(2):580–588. [PubMed: 26441413]
15. Protti A, Cressoni M, Santini A, et al. Lung stress and strain during mechanical ventilation: any safe threshold? *Am J Respir Crit Care Med.* 2011; 183(10):1354–1362. [PubMed: 21297069]
16. Costa EL, Musch G, Winkler T, et al. Mild endotoxemia during mechanical ventilation produces spatially heterogeneous pulmonary neutrophilic inflammation in sheep. *Anesthesiology.* 2010; 112(3):658–669. [PubMed: 20179503]