compared with tracking a specific lung ROI from one lung volume to another. This has been validated in healthy animals (2) as well as in humans undergoing radiotherapy treatment planning (3–5). Based on this approach (2), we calculated a correction factor for the parameter (VT_{CT}/EELV) calculated by Bellani and coauthors (1) to the actual volume strain sVol. As is evident from Figure 1, the data of Bellani and colleagues may underestimate the actual volume strain by 2- to 10-fold, depending on the end-inspiratory density of the ROI. It is possible that correcting these data will result in a greater correlation between K_i and sVol and strengthen the conclusions of their study.

Our method has some limitations (2). If the lung is heterogeneously inflated within this ROI, our approach using mean density will underestimate the maximum strains experienced by the lung. Evolving methods in which continuous image registration tracks regional deformation on a voxel level will eventually permit high-resolution measurement of regional lung expansion and mechanical properties (6–10) and further innovative investigations such as this one.

The measurement of regional lung function in human subjects, whether regional metabolic activity or lung deformation, is a challenging frontier for investigators that we believe will provide unique insight into how the interactions between mechanical and biological mechanisms result in the emergence of lung diseases and pathological syndromes. The application of complementary CT and PET imaging modalities (1) is an intriguing example of how the assessment of regional lung function may permit delineation of important pathophysiologic relationships, even in the presence of heterogeneous lung injury.

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From the Authors:

We welcome the interest of Kaczka and colleagues in our work (1). We are certain that there are many other, possibly more elegant and sophisticated ways to analyze our data. Regarding the issues raised in their letter, however, we want to clarify some fundamental points.

First, we did not portray or even suggest VT_{CT}/EELV as a measurement of lung strain. Whether and how computed tomography (CT) can measure regional lung strain in acutely injured lungs is highly controversial (2), and we carefully avoided any allusion in this respect. In fact, the word "strain" does not even appear anywhere in the manuscript or in the online supplement. Consequently, their statement that VT_{CT}/EELV represents "volume strain as reported by the authors" and its corollary that this measurement is "flawed" are, in our opinion, completely unjustified based on what is written in the article.

Second, we need to clarify the interpretation of the VT_{CT} measurement. In a carefully worded sentence of the Methods, we explicitly stated that "VT_{CT} [of normally aerated lung] reflects the tidal change in gas volume of those voxels whose mean density falls within the normally aerated compartment boundaries on CT_{FUSION}" (page 1195, first column, second sentence). Relating to the example of Kaczka and colleagues, if a 1-ml voxel with CT attenuation of −500 HU at mean airway pressure increases its gas content by 0.1 ml at end inspiration, its attenuation will decrease to −600 HU, and the difference in CT attenuation between the two inflation pressures corresponds to the change in gas volume of that voxel, exactly as we wrote in the Methods. Because the gas content in the voxel increases by 0.1 ml, the "tissue" in the voxel must decrease by 0.1 ml, meaning that some normally aerated lung tissue expands beyond the voxel boundary during inflation. The problem with this approach is that VT_{CT} does not account for the volume of gas that inflates normally aerated tissue that leaves the region of interest (ROI) during inflation. In fact, it is worth noting that, in the example of Kaczka and colleagues, they keep the volume of tissue constant at 0.5 ml while that of gas increases from 0.5 to 0.8 ml. It is this conservation of mass that confers the nonlinearity between changes in regional attenuation and regional volume. The translation of their example to the clinical reality would require that we track normally aerated lung tissue identified from CT_{FUSION} onto both the end-inspiratory and end-expiratory CT scans and that we measure its volume or density changes between end inspiration and end expiration. Indeed, it is important to note that in the elegant paper in which they proposed and validated sVol (3), the ROIs on which such validation was based were identified anatomically, based on clearly identifiable anatomical landmarks, such as airway or vessel branch points, that were used to match the same lung region between end-expiratory and end-inspiratory CT scans. Accurate image registration (i.e., the ability to map the same part of lung on CT images obtained at different lung volumes) is an important component of accurate sVol determination. Even when density instead of volume changes are used, proper sVol determination requires that distinct ROIs be identified on the end-inspiratory

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and end-expiratory scans to delineate approximately the same region of lung tissue at, respectively, end inspiration and end expiration (3, 4).

We did not attempt image registration for several reasons: because it is much harder to register images in acutely injured than in normal lungs like those of Fuld and coworkers (3), because our research question led us to define aeration-based ROIs rather than anatomically defined ROIs, and because, in this context, we did not have the analytical capability to do it. Given that we did not attempt image registration and that we wanted to maximize the matching between CT and PET (the latter being acquired continuously during breathing without respiratory gating), we deemed it reasonable to define an ROI of normally aerated lung on the CT obtained at mean airway pressure (CT_{FUSION}) and then compute the gas volume change within this ROI between end inspiration and end expiration ($V_{T_{CT}}$). Obviously, $V_{T_{CT}}$ is not equal to the tidal change in gas content of the lung tissue that is normally aerated at mean airway pressure (i.e., the lung tissue encompassed by the normally aerated ROI on CT_{FUSION}). This tissue will have a higher gas content than that of the ROI at end inspiration, as it expands beyond the boundary of the ROI, and a lower gas content at end expiration, as it compresses inside the boundary. Consequently, EELV, as we measured it, is expected to overestimate the end-expiratory gas volume of lung tissue that is normally aerated at mean airway pressure. Because of these considerations, we carefully avoided stating that our $V_{T_{CT}}$/EELV measurement was a measurement of volumetric lung strain.

From their letter, it would appear that Kaczka and colleagues suggest that we should have applied the sVol formula of Fuld and colleagues (3) to derive a measurement of regional lung volume strain from our data. We emphasize that, in the absence of registration of the ROI defined from CT_{FUSION} onto both the end-inspiratory and end-expiratory CT scans, this approach can introduce an error because the assumption that density is a smooth function of position in the lung parenchyma might not hold in the acutely injured heterogeneous lung, especially at the boundary of density-based ROIs. Furthermore, it was our impression from the article of Fuld and colleagues (3) that sVol was introduced mainly as a surrogate for measuring regional ventilation without inhaled tracers rather than as a measurement of lung strain. Nonetheless, we were happy to heed their suggestion. We computed sVol of the normally aerated tissue as $V_{T_{CT,\ normally\ aerated}}/EELV_{CT,\ normally\ aerated}$ multiplied by $1{,}000/(H_{i,\ normally\ aerated}+1000)$, where $H_{i,\ normally\ aerated}$ represents the average density (in Hounsfield Units) of the normally aerated ROI at end inspiration. We found a significant correlation between sVol and both $Ki_{normally\ aerated}$ and $Ki_{normally\ aerated}/Ki_{not\ aerated}$ ($r^2 = 0.35$ and $r^2 = 0.33$, respectively, $P < 0.05$ for both).

Finally, we would like to recall that the ratio $V_T/EELV_{CT,\ whole\text{-}lung}$ was significantly correlated with lung metabolic activity ($Ki_{whole\text{-}lung}$). In this case, tidal volume was that measured by the mechanical ventilator. Consequently, V_T was free of any potential bias affecting CT measurements of gas volume changes.

In closing, we welcome the opportunity that Kaczka and colleagues provided for us to clarify the interpretation of our measurements, and their interest in our work.

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ICU-Acquired Weakness: An Extension of the Effects of Bed Rest

We read with interest the essay by Dr. Misak on ICU-acquired weakness (1). While her comments are limited to the effects of her stay in the ICU, we believe that there are other health care issues—for example, the effects of bed rest on functional capacity and the long undirected process to regain normal or higher cardiorespiratory fitness.

The effect of bed rest on cardiovascular fitness first gained national attention in patients with acute myocardial infarction (MI), and led to the implementation of phase I–III cardiac rehabilitation (2). The many deleterious effects of hypokinesia have been a concern of NASA in connection with space flight and living in microgravity. These effects include significant loss of bone, heart muscle, and skeletal muscle and exercise capacity (3). Indeed, just as skeletal muscle loses mass that is prominent visually in the muscle wasting of chronically ill patients, cardiac muscle also atrophies at a rate of approximately 1% per week of bed rest (4). The multisystem effects of bed rest alone were clearly defined in the classic study by Saltin and coworkers on five healthy, active young men after 3 weeks of simple bed rest (5). Thirty years later these same five men were studied again, and it was observed that the decline in functional capacity over 30 years of aging was equal to the decline seen after only 3 weeks of bed rest (6). This shows that the decline in functional capacity with bed rest needs to be regained, or may forever be lost with further aging. It is also remarkable that a substantial amount of "deconditioning" is observed within as little as 24 hours of forced bed rest (7).

Now we broaden this related issue to the concerns of not only bed rest but the consequences of ICU care such as being intubated, sedated, restrained, sleep deprived, and rehabilitated to sit, stand, and walk, and the process by which to gain cardiorespiratory fitness. Hopefully, Dr. Misak's enlightening essay and the informative editorial by Drs. Griffiths and Jones (8) will