Conclusions on Ventilator-induced Mechanical Injuries Associated with Ventilation Using Abnormally Large Tidal Volume

To the Editor:

I have read with interest the study of lung inhomogeneities and time course of ventilator-induced mechanical injuries, recently published in Anesthesiology by Cressoni *et al.*[1]

This study aimed at investigating the genesis of ventilator-induced lung injury in healthy piglets, with particular attention to the interface between inhomogeneous lung structures, and at determining whether the induced lung injury was associated with collapse or consolidation.

In 6 of the 12 animals considered, approximately 7.5% of the total lung volume had abnormal density on computed tomography scan, indicating consolidated tissue, and affecting respiratory system elastance. It is interesting that, if computed tomography scanning had not been performed, this potentially important abnormality could have been neglected. This is an important factor in the study of animals that are presumed healthy, but where health status is often overlooked, possibly affecting the results and conclusions of the studies.

One of the most important experimental details in this study is that the piglets were ventilated with strain greater than 2.5 (tidal volume/end-expiratory lung volume), corresponding to a tidal volume of about 40 ml/kg. This value is more than three times greater than the 12 ml/kg found harmful for the ventilation of patients with the acute respiratory distress syndrome[2] and was chosen to apply very high stress and strain to the lung parenchyma. As stated, it is known that "excessive stress and strain induce lung injury." In this sense, the observation that abnormally large tidal volumes were associated with changes in lung density at the interface between structures with different extensibility becomes difficult to interpret in relation to a critical care scenario. Here, much smaller stress and strain would be applied to the lung, and the role of stress raisers may not be as important as other factors such as, for example, overdistension. As the authors state, the results from the experiments as they were performed are not transferrable to human patients. It is possible that similar experiments performed at stress and strain values resembling those used in clinical settings (and scaled to the pulmonary mechanics of the animal species used) may generate more clinically important evidence in support of the stress raisers hypothesis.

A minor but potentially confounding element of the experimental design is the large F_{IO_2} (50%) used throughout the study and the associated high P_{aO_2}/F_{IO_2}. It is possible that absorption atelectasis may have occurred, especially during the long duration of the experiments, and contributed to the recruitable nature of alveolar collapse.

Competing Interests

The authors declare no competing interests.

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In Reply:

We thank Dr. Formenti for his careful reading of our work and for his comments. Dr. Formenti is right when he questions the translatability of these healthy animal data in the clinical scenario of acute respiratory distress syndrome. Our study was designed to corroborate the hypothesis that "stress raisers"[1,2] are possible facilitators of ventilation-induced lung injury. Our results[3] did not contradict the hypothesis. In fact, we found that the lesions first appeared where the stress raisers are physiologically present, primarily at the interface between visceral pleura and subpleural alveoli and, in piglets with consolidation, at the interface between consolidations and the healthy parenchyma. Dr. Formenti suggests that the stress raisers may be less important than overdistension. We believe that stress raisers and overdistension are two aspects of the same reality: in fact, the stress raisers, being pressure multipliers, first induce local overdistension with overstretching and microfractures of the extracellular matrix, which appear as higher density regions due to edema and hemorrhage in the extracellular matrix. Dr. Formenti correctly states that the tidal volume we used (40 ml/kg) is far from what has been shown as harmful in clinical practice (12 ml/kg). However, we believe that it is nearly impossible to produce in a reasonable time (3 days) macroscopic lesions in the healthy parenchyma using 12 ml/kg. In these piglets, it would correspond to a strain of 0.8, which is at least three times lower than the one we found lethal.[4] Inferring from our data,[3] we could speculate that to obtain lethal stress/strain with 12 ml/kg in these experimental animals, the functional residual capacity should be reduced to two-thirds or the stress

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raisers should be highly diffused in the parenchyma and be able to multiply three times the applied transpulmonary pressure. These conditions (or their combination) may occur only if the lung is diseased. Unfortunately, we still lack an animal model that could realistically mimic the human acute respiratory distress syndrome as a whole and not only some of its aspects. Finally, with the high tidal volumes we used, we believe unrealistically that 0.5 F_{IO_2} may induce reabsorption atelectasis.[5]

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Competing Interests

Drs. Cressoni and Gattinoni have an Italian patent for lung inhomogeneities determination (0001409041) and applied for European and U.S. patents. The other author declares no competing interests.

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