have been severe enough to cause dependent atelectasis, making "solid-like behavior" unlikely. *2*) Inspiratory effort in the P-SILI group may not have been strong enough, precluding local injury to focus on dependent regions (5). Apart from oxygenation, did the authors measure any other parameter to ensure that severe ALI was effectively achieved? It would be valuable to provide tomographic lung images after ALI and respiratory effort indexes to account for these possible confounders.

The authors propose that morphological characteristics of damage may depend on whether mechanical stress is applied by mechanical ventilation (positive pressure) or by SB (negative pressure). Nonetheless, it is worth noting that V_T in the VILI group (12 ml/kg) was double that in the P-SILI group (~5–6 ml/kg) and certainly was driving pressure (DP). More than 30 years ago, Dreyfuss and colleagues showed that negative pressure ventilation may be even more damaging than positive pressure ventilation when DP is comparable (6). Even though the respiratory rate (RR) was higher in the P-SILI group, possibly balancing the injury risks of both strategies, it is debatable to compare a "higher V_T /DP–lower RR" with a "lower V_T/DP–higher RR" strategy, considering that DP seems to be the main determinant of lung injury (7, 8). Also, the VILI group was subjected to 5 cm H_2O of positive end-expiratory pressure, which unfaithfully increased the chances of lung overdistension and augmented the risk of lung injury compared with zero positive end-expiratory pressure in the P-SILI group. Why did the authors select these apparently unequally harmful strategies?

Finally, CO_2 concentrations were not controlled. In this sense, the P-SILI group may have been subjected to higher hypercapnia than the VILI group, given that, at comparable respiratory minute volume, the weight of the dead space ventilation (dead space ventilation/V_T relationship) is increased with lower V_T and higher RR (9). This fact possibly modulated the inflammatory response in the P-SILI group (10).

In summary, Cruces and colleagues' study adds to the growing evidence supporting unassisted SB as possibly injurious. However, further investigations are necessary to conclude that VILI causes a lung injury different from and more severe than P-SILI. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Acknowledgment: The author thanks Dr. Tommaso Mauri and Dr. Elena Spinelli (Ospedale Maggiore Policlinico, Milano, Italy) for their critical appraisal and valuable contribution to the content.

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Reply to Pérez

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From the Authors:

We thank the editors for giving us the opportunity to reply to the issues raised in the letter by Dr. Pérez (1) in response to our recent study published in the *Journal* (2). Strong respiratory effort is

Supported by Consejo Nacional de Desarrollo Científico y Tecnológico CONICYT Chile through grant Fondecyt Regular 1220322 and Proyectos en Ciencias Biomédicas y Clínicas 2021, Universidad Andrés Bello (DI-07-20/CB).

Originally Published in Press as DOI: 10.1164/rccm.202303-0364LE on March 23, 2023

recognized as a potential "second hit" in acute lung injury (ALI) and acute respiratory distress syndrome, introducing the concept of "patient self-inflicted lung injury" (P-SILI) (3). It is pertinent to note that, even though P-SILI differs conceptually from the lung injury induced by hyperventilation in healthy lungs, unfortunately, it is often misconstrued. Our findings were consistent with the "solid-like behavior" of injured lungs. Figure 1A in our paper (2) clearly shows that the lung injury in the P-SILI group was predominant in regions adjacent to the diaphragm. Also, the vascular damage in P-SILI was greater than in the protective mechanical ventilation (MV) group, specifically hyperemia and edema (figure 1C in our paper [2]). In the regional analysis, both parameters were higher in P-SILI in the basal region, in striking contrast to the other groups (data not shown). In a previous report (4), using the same P-SILI model, mapping the lung regional volumetric strain with a tomographic-based biomechanical analysis, we found a progression of regional strain, mainly in basal regions. Also, the nonaerated tissue compartment increased in dependent areas, although the tidal volume was close to 6 mL/kg. Controlled MV prevented these alterations (4).

The injury mechanisms proposed in P-SILI may bear similarities to those classically described in ventilator-induced lung injury (VILI) (5). Still, topographic distribution and specific damaged structures may differ between them. Our study aimed to describe the histological lung damage superimposed by unmodulated respiratory effort on injured lungs (2). The thought process of the MV setting was to maintain an equivalent minute ventilation between groups, avoiding hyperventilation as a confounding factor, with a positive end-expiratory pressure that is unlikely to cause overdistention in a model of alveolar instability. Contrary to Pérez's interpretation, the most relevant comparison is between the P-SILI and protective MV groups. Through this analysis, we assessed the extent of additional damage (i.e., second hit) caused by the respiratory effort in comparison with a conservative ventilatory approach. The VILI group was established only as a positive control of mechanical damage. Thus, the magnitude of injury in this group is not the most meaningful finding.

Although interesting, it is difficult to study the contribution of the blood CO_2 concentration to inflammation or other parameters in our model because small-animal models have intrinsic limitations that preclude serial blood sampling for common analytic techniques. However, we did not find differences in the inflammatory response between the P-SILI and protective MV groups in our experiment (figure 1C [2]). Additionally, it is essential to clarify that the "dead space" follows a U-shaped function, with increases at the low and high ends of tidal volume.

Another concept to have in mind is that the consequences of respiratory effort will depend on factors such as the magnitude and timeline of respiratory effort (6), the alveolar–capillary barrier indemnity, and the distribution of regional deformation.

In summary, our data suggest that respiratory effort adds a characteristic pattern of damage in acutely injured lungs despite the absence of hyperventilation. However, just like VILI, P-SILI has more than two aspects. To understand in depth the expansion of knowledge of this fascinating topic in recent years, a thorough review of previous research, particularly the methodology and analysis, is crucial. Numerous faces and dimensions have emerged to form a complex polyhedron that requires a multifaceted approach to comprehend fully. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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How Can Allergen Immunotherapy Protect against COVID-19?

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To the Editor:

Respiratory viral infections with rhinoviruses, respiratory syncytial viruses, and influenza are the primary agents responsible for asthma exacerbations, acute hospitalizations, and intensive care admissions. Frequent and recurrent infections lead to the worsening of lung function, remodeling, and increased severity of disease. Moreover, epidemiologic studies have shown that allergic patients exposed to

Supported by Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung grant 310030_189334/1 (M.S.).

Originally Published in Press as DOI: 10.1164/rccm.202302-0317LE on March 29, 2023