6R complex associates with a second protein, gp130 (5, 6). Signaling via membrane-bound IL-6R is termed classic signaling. Though gp130 is present in all cells, IL-6R is only expressed by a select few, most notably hepatocytes and macrophages. Therefore, only certain cells are IL-6 responsive under usual circumstances. However, during acute inflammatory states, IL-6R is cleaved by ADAM-17, creating a soluble receptor, sIL-6R, which is capable of binding IL-6. The IL-6/sIL-6R complexes that subsequently form are capable of binding gp130. This process, known as trans-signaling, thereby enables cells that do not express IL-6R to become IL-6 responsive.

Critically, the antiinflammatory and antibacterial activities of IL-6 are mediated via classical signaling, whereas the proinflammatory activities of IL-6 are mediated by trans-signaling (5, 6). This is important, as monoclonal antibodies against IL-6R do not discriminate between classical or trans but instead block both types of IL-6R signaling. This is the rationale for increased bacterial infection in patients treated with tocilizumab. IL-6 is also necessary for resolution of H1N1 influenza infection by protecting neutrophils from virus-induced death in the lung and by promoting neutrophil-mediated viral clearance (7).

In addition to pathogen clearance, the acute phase proteins such as α-1 antitrypsin (AAT) are also induced via classical IL-6 signaling. A treatment that ablates the AAT response altogether would seem risky. Tocilizumab cannot be reversed once administered and has a terminal half-life of approximately 21.5 days. Furthermore, the safest way to wean patients with COVID-19 from this therapy has yet to be agreed upon. We believe that treatment aimed at changing the level or activity of a specific cytokine such as IL-6 may represent a double-edged sword and that therapeutic approaches that address the underlying cause of changes in IL-6 and other mediators are more likely to be successful. In the event that inhibition of the inflammation driven by IL-6 alone is required, specific blockade of IL-6 trans-signaling would preserve cytokine balance and bacterial clearance and might therefore be a superior strategy. ■

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Respiratory Drive Measurements Do Not Signify Conjectural Patient Self-inflicted Lung Injury

To the Editor:

We read with interest the editorial by Gattinoni and colleagues on the role of respiratory drive in the application of mechanical ventilation in patients with coronavirus disease (COVID-19) (1).

Gattinoni and colleagues conclude that measurements of airway occlusion pressure ($P_{0.1}$) and maximal deflection in airway pressure during end-expiratory airway occlusion (ΔPocc) "displayed good prognostic performance in predicting respiratory deterioration at 24 hours" and can forewarn against patient self-inflicted lung injury (P-SILI).

Apart from the arbitrary definition of respiratory deterioration, the scatter plot in Figure 1 of the article by Esnault and colleagues (2) shows that the vast majority of data overlap between the two groups: 66% of $P_{0.1}$ values in nine "Relapse" patients overlap with 74% of $P_{0.1}$ values in 19 "Non-Relapse" patients. Only one value of ΔPocc in the "Relapse" group does not overlap with values in the "Non-Relapse" group. Gattinoni and colleagues fail to point out that the "break-points" were

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selected in a *post hoc* manner—a step known to markedly overestimate the accuracy of predictive indexes (3). No conclusions about reliability of a predictive index can be reached without the threshold being prospectively tested with a validation data set.

In addition to methodological problems, there is no justification for judging $P_{0.1}$ 4 cm H_2O as a worrisome high value. Such values are seen in patients with stable chronic obstructive pulmonary disease and in patients successfully weaned from mechanical ventilation (4). There is no biological rationale for proposing that this level of respiratory motor output likely causes structural injury of the lung or respiratory muscles. The claim by Gattinoni and colleagues that $P_{0.1} \geqslant 4$ cm H_2O "portends subsequent worsening of respiratory function" constitutes major overinterpretation of the data.

Gattinoni and colleagues convey that $P_{0.1}$ provides a reliable measure of respiratory motor output in individual patients. For decades, it has been known that numerous difficult-to-control factors alter the relationship between $P_{0.1}$ and inspiratory muscle pressure output (4). Moreover, $P_{0.1}$ exhibits a coefficient of variation as high as 38% in critically ill patients.

Gattinoni and colleagues claim that $P_{0.1}$ and ΔPocc "correlate well with relatively more precise methods for effort estimation." On the contrary, $P_{0.1}$ ~4 cm H_2O is associated with a wide range of pressure–time product: ~110 to ~420 cm $H_2O \cdot s \cdot min^{-1}$ (Figure 3H of Reference 5). $P_{0.1}$ ~1 cm H_2O is associated with a wide range of peak electrical activity of the diaphragm: ~5 to ~20 $\mu V \cdot s^{-1}$ (Figure 3B of Reference 5). ΔPocc of approximately −9 cm H_2O is associated with a wide range of pressure–time product: ~2.5 to ~10 cm $H_2O \cdot s \cdot breath^{-1}$ (Figure E1 in the online supplement of Reference 6). Investigators excluded 30 of 82 recordings because the ratio of ΔPocc to change in esophageal pressure fell outside the range of 0.7–1.3. Basing decisions on $P_{0.1}$ and ΔPocc regarding mechanical ventilation in individual patients is perilous.

Gattinoni and colleagues draw conclusions based on observed rapid shallow breathing index of 49 breaths/min/L. It has been known for decades that measurements of rapid shallow breathing index in the presence of un-estimated levels of respiratory work—inevitable with pressure support ranging between <4 and >11 cm H_2O and positive end-expiratory pressure <10 to >14 cm H_2O—are uninterpretable (3).

Gattinoni and colleagues continue to claim that the study by Tonelli and colleagues supports the existence of P-SILI (7). If inspiratory efforts were causing P-SILI, one would expect a decrease in V_T-to-transpulmonary pressure swing ratio—a surrogate of lung compliance; yet, V_T-to-transpulmonary pressure swing ratio remained constant across 24 hours of noninvasive ventilation. Chest radiography cannot be linked mechanistically to P-SILI because radiologists were not blinded.

Mechanical ventilation plays a crucial role in the management of patients with COVID-19. Conducting rigorous research is vital to enlighten clinicians at the bedside. A pandemic is no time to engage in speculation and broad generalizations based on dubious interpretations of small data sets. On the contrary, ventilator research in COVID-19 needs to aspire to the highest internal validity. ■

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Reply to Tobin *et al.*

From the Authors:

We read with some perplexity the comments by Tobin and colleagues to our editorial (1). Indeed, many of their questions or concerns should be more properly addressed to Esnault and colleagues, the authors of the original paper (2).

We believe that an important role of an editorial is first to bring fresh ideas to the fore and place them against an engaging conceptual background. Regarding the specific concerns of Tobin and colleagues, we find it fruitless to argue whether 4 cm H_2O of occlusion pressure at 100 milliseconds is tolerable or not in

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