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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Martin J. Tobin, M.D.*
Amal Jubran, M.D.
Franco Laghi, M.D.
Hines Veterans Affairs Hospital
Hines, Illinois
and
Loyola University of Chicago
Maywood, Illinois
*Corresponding author (e-mail: mtobin2@lumc.edu).

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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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coronavirus disease (COVID-19) pneumonia. The real concern is that, at the time of our writing, the pandemic has caused about 1 million deaths initiated by pneumonia and respiratory failure. Because intensive care mortality has been reported to range from 10–20% to 80–90% of patients needing respiratory assistance, it is appropriate to ask ourselves to what extent different treatment choices may have contributed to such high differences in mortality. Indeed, it is conceivable that ill-timed decisions or inappropriate ventilatory settings may worsen the natural course of the disease. In this framework, the well-documented observations of heightened drive and sudden deterioration in patients with COVID-19 imply the genuine possibility of patient self-inflicted lung injury (P-SILI). It is also to be remembered that there exists a body of literature produced by other experts that expresses similar concerns and documents the reproducible nature of P-SILI (3–9). No one is entitled to pontificate on issues to which neither we nor Tobin and colleagues have found the answers. (We certainly are not "claiming" to know specifics, contrary to what the repeated mantra "Gattinoni and colleagues claim…" suggests.) However, in the context of the pressing clinical need to formulate a logical approach, an informed editorial hypothesis should be welcomed. Our intent was to underline that the assessment of abnormal drive is a step forward toward better understanding (and treatment) of COVID-19 pneumonia. Indeed, although the interplay between respiratory drive, muscular work, and applied energy is complex and far from completely understood, the possibility of excessive self-induced stress, strain, and edema (P-SILI) in these inflamed lungs must be taken into account. The work from Esnault and colleagues calls attention to this potential problem and is a first step toward its better understanding. Every measurement has its own biases and limitations, but measuring the strength of the respiratory drive and monitoring its changes must be better than not doing so and basing key decisions regarding respiratory support on mere guesswork. ■

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Luciano Gattinoni, M.D., F.R.C.P.*
University of Göttingen
Göttingen, Germany

John J. Marini, M.D.
Regions Hospital and University of Minnesota
St. Paul, Minnesota

Luigi Camporota, M.D., Ph.D.
King's College London
London, United Kingdom

ORCID ID: 0000-0001-5380-2494 (L.G.).

*Corresponding author (e-mail: gattinoniluciano@gmail.com).

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The Role of Eosinophils during the Withdrawal of Inhaled Corticosteroids in Chronic Obstructive Pulmonary Disease

To the Editor:

We read with great interest a *post hoc* analysis of the IMPACT trial that investigated the effect of inhaled corticosteroid (ICS) withdrawal in patients with chronic obstructive pulmonary disease (1). Han and colleagues (1) demonstrated that the benefit of fluticasone furoate/umeclidinium/vilanterol combination therapy on exacerbation reduction, lung function, and quality of life was not associated with the abrupt withdrawal of ICSs in the IMPACT trial (1, 2). However, we wonder whether the baseline eosinophil count would play another important role that could impact the effect of ICS withdrawal.

In the European Respiratory Society guideline (3), which is based on the analysis of four studies, COSMIC (4), WISDOM (5), INSTEAD (6), and SUNSET (7), they strongly recommend that ICSs should be continued in patients who have blood eosinophil counts $\geqslant$300 cells/μl, with or without a history of frequent exacerbations. In this meta-analysis (3), they found that no effect of ICS withdrawal was observed on exacerbation rate (rate ratio [RR], 1.03; 95% confidence interval [95% CI], 0.90–1.18; $P = 0.71$;

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