dynamic lung stress, resulting in less systemic inflammation. Therefore, prone position may reduce the risk of effort-dependent lung injury in moderate-to-severe ARDS.

The intensity of spontaneous inspiratory effort was lower in prone position (vs. supine position) despite matching levels of sedation. Several plausible explanations for this finding may be offered. First, prone position improved oxygenation (i.e., \( \text{PaO}_2 \)), which might work as a modifier of respiratory drive. Second, prone position is known to increase end-expiratory lung volume (2). The force generated by diaphragmatic contraction (i.e., \( \Delta P_{\text{di}} \)) is linearly decreased as lung volume is increased, a phenomenon that has been shown in animals, healthy volunteers, and patients with acute respiratory failure (6–9). However, careful monitoring is necessary because individual data shows that in some patients, prone position was not effective to decrease spontaneous inspiratory effort (Figure 1B); in such patients, the potential risks of proning might outweigh the benefits.

Our clinical study consisted of a small number of patients and was still exploratory and descriptive. Thus, caution is necessary in extrapolating the current data to the large clinical context. IL-6 is known as an early, proinflammatory mediator, which is released into circulation within 1 hour after commencing injurious mechanical ventilation (10). But prone position always followed supine position because of the nature of study design, and thus we cannot exclude natural trends in serum IL-6 in recovering patients.

Despite limitations, the current study suggests that prone position is a promising technique to render spontaneous effort less injurious. It may synergize the benefits of spontaneous breathing (less muscle atrophy) with the benefits of prone position per se (lung recruitment). Thus, as a next step, the current data may support a larger clinical study to confirm the benefits of prone position to render spontaneous effort less injurious.

Conclusions
Prone position may reduce the risk of effort-dependent lung injury in ARDS. In comparison with supine position, prone position during spontaneous breathing improves gas exchange, reduces the intensity of spontaneous inspiratory effort and dynamic lung stress, and attenuates systemic inflammation.

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Is Fibrosis Really Fibrosis?

To the Editor:

We read with great interest van Gassel and colleagues’ report of pulmonary sequelae in mechanically ventilated survivors of coronavirus disease (COVID-19) (1) and commend the authors on
their systematic assessment of these patients. We hope the authors could help clarify some of our queries.

van Gassel and colleagues report a remarkably high prevalence of fibrosis in their cohort (91.3%), but it is possible that the definition of fibrosis used requires further consideration. The etiology and trajectory of fibrous bands remains uncertain, but they could represent areas of consolidation seen in organizing pneumonia, which regress with time (2). It would be interesting to learn what proportion of patients with fibrous bands had other signs of fibrosis (volume loss and/or architectural distortion and/or traction bronchiectasis) and whether using an altered definition including the aforementioned features of fibrosis would significantly change the prevalence rates.

We appreciate that not all patients were screened for pulmonary embolism as per the authors’ comments, but regardless, it would be interesting to know what proportion of patients underwent a computed tomography (CT) pulmonary angiogram during their acute admission and the incidence of pulmonary embolism, as this could have accounted for the hypoperfusion seen on CT imaging. Even in the absence of detectable pulmonary embolism, microthrombosis, only detectable using dual-energy CT imaging, could add further challenges to high-resolution CT interpretation.

Twenty-five percent of patients showing new emphysematous destruction or cavitation is a very interesting finding. Cystic changes have been noted in mechanically ventilated patients (3), and as a complication of acute respiratory distress syndrome (ARDS) even in the absence of mechanical ventilation (4). The etiology of these cysts includes infarction or fibrosis (5), so what is reported as emphysema could in fact be ARDS-related cystic change. CT imaging performed between admission and follow-up may provide insights into the timing and rate of development of these changes. The authors suggest this is a new finding compared with severe acute respiratory syndrome or Middle East respiratory syndrome, but this may simply reflect the severity of ARDS caused by COVID-19.

As the authors state, the etiology of ground-glass changes in the post–COVID-19 cohort remains speculative, but it is possible that these changes are steroid responsive (6), consistent with the authors’ description of a nonspecific interstitial pneumonitis–like distribution of changes. Furthermore, an overlap syndrome of organizing pneumonia/nonspecific interstitial pneumonitis has been described (7), but longitudinal data are required to better understand the radiological trajectory of these changes.

The median 6-minute-walk time of 81.5% predicted is likely to be multifactorial, including limitations posed by deconditioning after acute illness. Over 4% desaturation in the 8.3% of the cohort (n = 4) at 3 months is more concerning, and the corresponding radiological findings would have been informative.

A total of 45.7% of patients had CT changes consistent with new small airway disease. We wonder how the authors made this diagnosis and whether small airways measurements were made during this study. It is possible that patients had a mixed restrictive and obstructive defect, with a more severe restrictive component, hence resulting in a normal FEV1/FVC ratio. Further assessment with bronchodilator reversibility or description of the flow loop would have been interesting. Symptomatology at the follow-up visit with regard to airway-specific symptoms would help further corroborate the CT findings.

We thank the authors again for this well-presented research report, which adds to a rapidly emerging body of evidence highlighting the significant respiratory morbidity in survivors of COVID-19 and emphasizes the need for systematic, long-term follow-up.

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Reply to Vijayakumar and Shah

From the Authors:

We thank Vijayakumar and Shah for their letter regarding our report on the high prevalence of pulmonary sequelae at 3 months in mechanically ventilated survivors of coronavirus disease (COVID-19) assessed by pulmonary function testing and high-resolution computed tomography (HRCT) (1). They raise some important points that are discussed below.

Vijayakumar and Shah rightfully point out that the definition of fibrosis used is relevant for interpretation of our data. Almost all patients had parenchymal bands with a pattern of fibrous residual changes at the 3-month follow-up, and in approximately half, these were accompanied with other signs of fibrosis on chest CT such as parenchymal distortion, volume loss, and/or broncholectasis. The evolution of the fibrous bands over time is interesting but not yet systematically screened for. Currently, around one-fifth of our cohort has had a repeated chest CT after the 3-month follow-up in which the fibrous bands were still unchanged.

Pulmonary embolism was diagnosed in 14 out of 22 participants in whom a CT angiogram was performed during admission. As noted, there was no systematic screening for pulmonary embolism during the initial wave, which limits any judgments about relations. Both macro- and microthrombosis with hypoperfusion are common during COVID-19 admission, but their role in long-term pulmonary dysfunction and responsiveness to anticoagulants is unclear (2). Perfusion defects are difficult to assess on HRCT, which was the standard modality in our follow-up. Follow-up data with dual-energy contrast-enhanced CT would potentially be of added value in this regard.

New low-attenuation areas with pattern of emphysematous destruction or cavitation were present in a quarter of the survivors, which we agree with Vijayakumar and Shah is very interesting. To elucidate its pathophysiology, we aimed to compare the follow-up scan with any available CT scan performed during the admission. Although these data need to be interpreted with caution, they suggest that these lesions evolve either from affected areas showing a vacuole sign or from unaffected areas without infiltration or destruction. Thus, we agree that these new lesions may not be COVID-19 specific but rather a consequence of acute respiratory distress syndrome severity and/or ventilator-induced injury.

The etiology of ground-glass opacifications, either inflammatory or fibrotic, may indeed be of relevance for therapeutic intervention and further recovery. Radiological follow-up to assess their evolution over time will be key to address this issue.

The 6-minute-walk test (6MWT) represents an integrated measure of both cardiopulmonary and skeletal muscle function (3), the latter likely being an equally significant contributor to impaired 6MWT results. The four patients in our cohort with significant (>4%) desaturation during the 6MWT were similarly affected in terms of pulmonary function test, HRCT results, and self-reported shortness of breath.

Small airway disease was indirectly assessed by the presence of air trapping on the expiration HRCT scan (4). Although many patients showed some air trapping, defined as more than 2–3 secondary lobules per lobe, the extent of air trapping was limited. Furthermore, we had no previous expiration CT scans in this study cohort, so we were not able to judge this finding as new. In contrast to its prevalence, the extent of air trapping was limited. This is in agreement with the absence of reversibility in pulmonary function test: no significant effect of bronchodilation on either FEV1 or FVC (median change 1.0 [−1.0 to 4.0] and 0.0 [−2.0 to 2.0] % of predicted, respectively). In addition, none of the patients met the criteria for bronchodilator reversibility (change in FEV1, and/or FVC >12% and >200 ml), demonstrating that restriction, not obstruction, was the dominant spirometry feature seen in the survivors of COVID-19.

We appreciate the remarks of Vijayakumar and Shah, which in our view highlight two key challenges that remain to be addressed in future work: 1) the long-term follow-up of these respiratory sequelae and their evolution/persistence over time and 2) unraveling the role of (micro)thrombosis in the respiratory sequelae as observed in survivors of COVID-19.