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Reply to Chiang and Gupta and to Swenson *et al.*

From the Authors:

We appreciate the continued interest in our research letter (1) and hope our findings lead to new avenues of investigation to clarify the mechanisms of hypoxemia and respiratory failure in this complex and devastating disease.

Chiang and colleagues suggest that transpulmonary bubble transit (TPBT) in coronavirus disease (COVID-19) respiratory failure could result not only from pulmonary vascular dilatations and pulmonary arteriovenous malformations but also from intussusceptive and sprouting angiogenesis as described by Ackermann and colleagues (2). In this autopsy series of seven patients with COVID-19 respiratory failure, Ackermann and colleagues showed that the extent of intussusceptive angiogenesis correlated with hospitalization duration that ranged from 3 to 9 days. In our study, the hospitalization duration at the time of performing the contrast-enhanced transcranial Doppler (TCD) was significantly longer (median duration, 24 d; interquartile range, 13–35 d), which would provide adequate time for the development of such vascular lesions. Notably, of those participants with detected microbubbles ($n = 15$), we find a trend toward increasing number of microbubbles with increasing duration of hospitalization at the time of performing the TCD ($r = 0.47$, $P = 0.11$; Figure 1). Chiang and colleagues posit that pulmonary vasodilation may not only precede but also serve as a stimulus for intussusceptive angiogenesis. If this progression of vascular derangements holds true in COVID-19 respiratory failure, it will be important to identify patients that exhibit abnormal pulmonary vasodilation earlier in the course of disease to design clinical trials of therapeutics that specifically target the pulmonary vasculature.

Swenson and colleagues suggest that patent foramen ovale (PFO) could contribute to microbubble detection in our study. Given that the reported prevalence of PFO in patients with acute respiratory distress syndrome (ARDS) is between 14 and 19% (3–5)

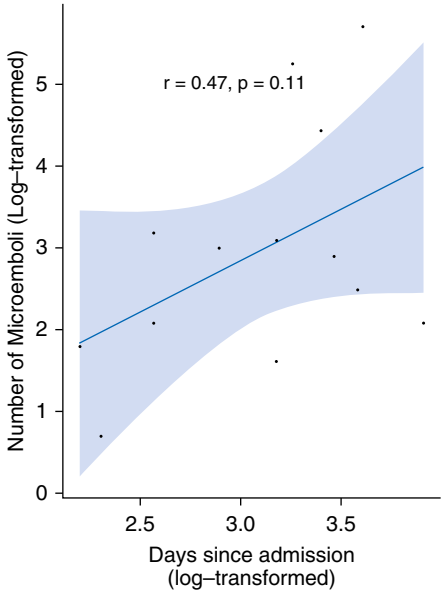

Figure 1. Association between number of microbubbles and hospitalization day at the time of performing the transcranial Doppler. This represents a scatterplot of log-transformed number of microbubbles as detected by transcranial Doppler and log-transformed days since hospital admission in participants with detected microbubbles ($n = 15$). There is a trend toward increasing number of microbubbles with increasing duration of hospitalization at the time of performing the transcranial Doppler ($r = 0.47$, $P = 0.11$).

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and that we detected microbubbles in 83% of the patients in our study, we believe the contribution of PFO to the microbubble detection in our study is minimal. We agree that it would have been useful to perform the contrast-enhanced TCD in patients with equally severe non–COVID-19 ARDS as a control group. However, Boissier and colleagues performed contrast-enhanced transesophageal echocardiography, a technique that is equally sensitive to contrast-enhanced TCD, on 216 patients with classical ARDS who were also ruled out for the presence of PFO (3). The severity of disease in their cohort was similar to ours, with median Pa_{O_2}:FI_{O_2} ratios of 121 mm Hg and 127 mm Hg, respectively. In their study, 96 patients (44%) demonstrated TPBT, but unlike in our study, neither the presence nor the degree of TPBT correlated with Pa_{O_2}:FI_{O_2} or other markers of gas exchange. This suggests that pulmonary vascular dilatations (or intrapulmonary arterial–venous anastomoses) are not a major mechanism of hypoxemia in classical ARDS but may be significant contributors to hypoxemia in COVID-19 respiratory failure. In the future, it will be important to better characterize the gas exchange abnormalities in COVID-19 respiratory failure using more sophisticated techniques, such as the multiple inert gas elimination technique. ■

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Assessment of Airway Closure and Expiratory Airflow Limitation to Set Positive End-Expiratory Pressure in Morbidly Obese Patients with Acute Respiratory Distress Syndrome

To the Editor:

We read the study by De Santis Santiago and colleagues with great interest (1). They demonstrated, in a very elegant crossover study that included morbidly obese patients with acute respiratory distress syndrome (ARDS) (mean body mass index of 57 kg/m^2), physiological respiratory and hemodynamics benefits of a ventilator strategy including a high positive end-expiratory pressure (PEEP) as compared with a strategy with a low PEEP–FI_{O_2} table. The high PEEP strategy was determined with a lung recruitment maneuver with increased stepwise of PEEP until 50 cm H_2O of plateau pressure while keeping constant driving pressure of 10 cm H_2O, followed by a decreasing stepwise of 2 cm H_2O of PEEP until 5 cm H_2O allowing the determination of optimal PEEP (PEEP level for best compliance of the respiratory system + 2 cm H_2O). This strategy was associated with improvement of respiratory mechanics (decrease of driving pressure, increase of respiratory system compliance) and oxygenation through reduction of atelectasis. Interestingly, this was not accompanied by impairment in right and left ventricular functions. Moreover, a very similar swine model confirmed these results.

Besides these findings, we are surprised that some important points of respiratory mechanics in morbidly obese patients are not discussed. First, complete airway closure is a very frequent phenomena in those patients (up to 65% for class III obesity) (2). It can be easily identified as the inflection point on the initial portion of a low-flow inflation pressure–volume when volume started to increase. The lack of consideration of complete airway pressure (by using a PEEP lower than the opening airway pressure) induces an overestimation of driving pressure, respiratory system, and lung elastances (2). Second, the association of low V_T and supine position in obesity may induce consequent expiratory airflow limitation, which can be easily visualized and measured as intrinsic PEEP (3). Therefore, if intrinsic PEEP is not considered, it could mislead correct values of expiratory transpulmonary pressure (total PEEP minus

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