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

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Positive Bubble Study in Severe COVID-19: Bubbles May Be Unrelated to Gas Exchange Impairment

To the Editor:

Data obtained using the multiple inert gas elimination technique show that hypoxemia in acute respiratory distress syndrome arises from regions with shunt and/or low $\dot{V}/\dot{Q}$ mismatch (1) but, more importantly, show no diffusion limitation of oxygen uptake into the pulmonary capillaries. Hypoxemia in patients with coronavirus disease (COVID-19)–associated lung disease may also be reasonably believed to result from $\dot{V}/\dot{Q}$ mismatch and shunt, but this has not been tested by definitive means. With this as brief background, we read the interesting study by Reynolds and colleagues (2), who used contrast-enhanced transcranial Doppler (TCD) after injection of agitated saline to detect transpulmonary transit of microbubbles as evidence for pulmonary microvascular dilatations in patients with severe COVID-19, a finding noted at autopsy (3). The authors made three key observations: *1*) 83% of patients had detectable microbubbles with a median of 8 detected, *2*) the Pa_{O_2}/FI_{O_2} was inversely correlated with the number of microbubbles, and *3*) the number of microbubbles was inversely correlated to lung compliance. On the basis of their findings, they suggest that these pulmonary microvascular dilatations may explain the disproportionate degree of hypoxemia in some patients with COVID-19–associated lung injury akin to the perfusion–diffusion limitation for oxygen uptake occurring in the greatly enlarged pulmonary microvascular dilations of hepatopulmonary syndrome, as discussed in the accompanying editorial by DuBrock and Krowka (4).

We find several problems with the interpretation of these results. First, patent foramen ovale (PFO) is rather common, and because PFO presence was not examined in this study, we cannot rule out this as a contribution to their TCD microbubble detection. It would have been useful for the investigators to have performed TCD in patients with equally severe acute respiratory distress syndrome as a control group to detect whether the two conditions differ in this regard with their methodology. Second, the issue is not one of TCD sensitivity to detect microbubbles (5) but rather whether the microbubbles represent a cause of meaningful gas exchange derangement. For example, Stickland and colleagues (6) studied animals without PFO with a similar amount of bubble transit on transthoracic echocardiography, which are a result of naturally occurring intrapulmonary arterial–venous anastomoses. Despite a large amount of bubble contrast traversing the pulmonary circulation and appearing in the left ventricle, there was no evidence for a diffusion limitation of oxygen, and the actual shunt quantified by both 25 μm microspheres and the multiple inert gas elimination technique was small ($<$1.5% of $\dot{Q}$). These data also showed that, although contrast echocardiography is extremely sensitive, it is nonspecific and frequently detects very small anatomical shunts that are $<$1% of $\dot{Q}$ and of trivial importance for gas exchange. Consequently, the nonquantitative nature of transthoracic echocardiography and/or TCD does not permit any conclusions as to whether hypoxemia is caused by the putative microvascular dilatations described by Ackermann and colleagues (3) and others. Although the autopsy data show congested capillaries and slightly increased diameters, any comparison with the far greater vessel dilation (up to 100 μm) and the perfusion–diffusion limitation in hepatopulmonary syndrome is tenuous (4). It is more likely that the correlations of the TCD bubble score with compliance and the severity of hypoxemia as assessed by the Pa_{O_2}/FI_{O_2} simply reflect the amount of lung involvement with shunt and low $\dot{V}/\dot{Q}$ ratios, with TCD bubble detection from a PFO and/or recruitment of intrapulmonary arterial–venous anastomoses because of hypoxia, higher $\dot{Q}$, and/or increased pulmonary artery pressure (6). ■

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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)

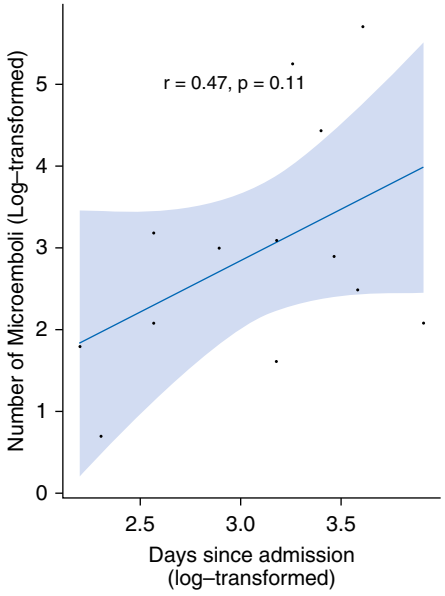

Figure 1. Association between number of microbubbles and hospitalization day at the time of performing the transcranial Doppler. This represents a scatterplot of log-transformed number of microbubbles as detected by transcranial Doppler and log-transformed days since hospital admission in participants 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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