Transpulmonary Bubble Transit in Severe COVID-19: Pulmonary Vasodilatation or Angiogenesis?

To the Editor:

We read with great interest the recent publication in the Journal by Reynolds and colleagues describing pulmonary vascular dilatation as the cause of hypoxemia in coronavirus disease (COVID-19)–associated acute respiratory distress syndrome (ARDS) (1). The authors should be commended for this important contribution. The authors correctly point out that in order for transpulmonary bubble transit to occur, pulmonary vascular dilatations or pulmonary arteriovenous malformations must be present. We wish to further contribute by proposing an alternative cause of transpulmonary bubble transit in ARDS due to COVID-19. Ackermann and colleagues have recently described that lungs from patients with severe COVID-19 and ARDS exhibited a combination of 1) a more widespread intussusceptive angiogenesis characterized by intravascular pillar formation spanning the interior lumen of a capillary, resulting in generation of two daughter vessels, and 2) a sprouting angiogenesis by endothelial proliferation (2). The degree of intussusceptive angiogenesis was found to increase significantly with increasing duration of hospitalization (P < 0.001), whereas the lungs from patients with influenza had less intussusceptive angiogenesis and no increase over time (2).

As reviewed by Kolte and colleagues in 2016, intussusceptive angiogenesis is known to be highly dependent on flow alterations and hemodynamic forces, with vasodilation-induced change in shear stress inducing pillar formation (3). Apart from blood flow and hemodynamic forces, intussusceptive angiogenesis is also regulated by molecular factors (3). FGF2 (fibroblast growth factor 2) stimulates intussusceptive angiogenesis by inducing PDGFB (platelet-derived growth factor B)–responsive upregulation of PDGFR receptors (3). Overexpression of VEGF (vascular endothelial growth factor) is associated with sprouting angiogenesis and increased vascular permeability, but the response to VEGF (sprouting vs. intussusceptive) may depend on the amount of VEGF expression, the release modality (slow vs. rapid liberation), and/or the differential expression of VEGF receptors (3). Tie-2 and Ang-1 also play an important role in intussusceptive angiogenesis. Overexpression of Ang-1 or of Ang-1 in combination with VEGF leads to the formation of enlarged vessels with abundant small invaginations in the capillary plexus that are reminiscent of transcapillary pillars encountered during intussusceptive angiogenesis (3).

Among angiogenesis-related genes, FGF2 and VEGFC genes were found to be upregulated in lungs from patients who died of COVID-19 but not in those with influenza A (H1N1) (2). VEGF-induced endothelial proliferation without tip-cell formation caused an initial homogeneous enlargement of preexisting microvessels, which was followed by the formation of intravascular transluminal pillars, hallmarks of intussusception (4). This was associated with increased flow and shear stress, which are potent triggers of intussusception (4). A similar process of enlargement without sprouting followed by intussusception is induced by VEGF overexpression (4).

Therefore, transpulmonary bubble transit, as reported by Reynolds and colleagues, may be caused either by 1) pulmonary vasodilatation, as proposed by the authors, or 2) intussusceptive and sprouting angiogenesis. On the other hand, pulmonary vasodilatation may serve as a stimulus for intussusceptive angiogenesis in severe COVID-19. The endothelial damage may progress through different stages of development in different areas of the lungs as time elapses from the initial injury (2). Therefore, although some areas of the lungs may exhibit pulmonary vascular dilatation, other areas may have progressed to intussusceptive or sprouting angiogenesis. Nitric oxide has been implicated in the pathogenesis of COVID-19, and it is notable that nitric oxide–induced arteriolar vasodilatation precedes development of intussusceptive angiogenesis (5). Understanding the mechanism underlying transpulmonary bubble transit observed by Reynolds and colleagues in severe COVID-19 (that is, pulmonary vascular dilatation, angiogenesis, or both) is of fundamental importance in designing and testing therapeutic strategies for this enigmatic disease.

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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 V/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 V/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 \( \text{Pa}_0_2/\text{Fi}_0_2 \) 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 \( \mu \)m microspheres and the multiple inert gas elimination technique was small (<1.5% of \( \text{Q} \)). 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 \( \text{Q} \) 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 \( \mu \)m) 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 \( \text{Pa}_0_2/\text{Fi}_0_2 \) simply reflect the amount of lung involvement with shunt and low V/Q ratios, with TCD bubble detection from a PFO and/or recruitment of intrapulmonary arterial–venous anastomoses because of hypoxia, higher \( \text{Q} \), and/or increased pulmonary artery pressure (6).