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Positive Bubble Study in Severe COVID-19 Indicates the Development of Anatomical Intrapulmonary Shunts in Response to Microvascular Occlusion

To the Editor:

We read with interest the recent article by Reynolds and colleagues (1) describing the transcranial Doppler bubble study findings in patients with coronavirus disease (COVID-19) with acute respiratory distress syndrome. The authors conclude that pulmonary vascular dilatation may be present in COVID-19, analogous to the microvascular changes that occur in hepatopulmonary syndrome (HPS), as a contributory mechanism of hypoxemia in COVID-19 acute respiratory distress syndrome. Although the findings on bubble study are indisputable, we share several concerns with the conclusions in the article.

First, in HPS (2), even though both $\dot{V}/\dot{Q}$ mismatch from overperfusion (capillary and precapillary dilatation) and anatomical shunt (abnormal arteriovenous communications) contribute to hypoxemia, positive bubble study is solely due to abnormal arteriovenous connections. As the diameter of the saline microbubbles is typically more than 24 μm and the diameter of pulmonary capillaries rarely exceeds 15 μm even after capillary distension (1, 3), the microbubbles are unlikely to pass through the capillaries. Thus, a positive bubble study in patients with severe COVID-19 does not automatically imply capillary dilatation or loss of hypoxic vasoconstriction but rather only the presence of abnormal pulmonary arteriovenous connections or an intracardiac shunt.

Second, although peripheral vessel dilatation is observed in COVID-19 on imaging studies (4), and frequently interpreted as abnormal vasoregulation, this cannot be equated to vasodilatation at the microcirculatory level. The converse may be true, as several imaging studies indicate that the subsegmental vascular dilation is a result of distal microvascular occlusion. Quantitative computed tomographic analysis by Lins and colleagues (5) revealed a marked loss of blood volumes in small vessels in patients with COVID-19 with increased blood volumes in medium and large vessels. This suggests increased pulmonary vascular resistance at the small-vessel level due to either microthrombi or arteriolar vasoconstriction. Furthermore, perfusion imaging studies using dual-energy computed tomographic imaging by Patel and colleagues (4) have shown a universal presence of perfusion defects in severe COVID-19, attributed mostly to microvascular thrombosis, involving a median extent of 46% of the entire lung.

Third, anatomical intrapulmonary shunts are present physiologically and may open up in response to increases in flow and pulmonary vascular resistance, akin to "pop-off" valves. For instance, exercise has been found to open up these shunts, contributing to increased alveolar–arterial oxygen gradient (3).

Fourth, diffuse pulmonary microvascular thrombosis and associated chemokine-mediated pulmonary vasoconstriction is sufficient to explain the atypical clinical features in COVID-19 such as silent hypoxemia and abrupt clinical deterioration (6). The mechanism of hypoxemia, similar to other pulmonary vaso-occlusive disorders, is flow redirection, resulting in overperfusion of the nonoccluded segments of the lung with reduced $\dot{V}/\dot{Q}$ ratios. Additionally, pulmonary vasoconstriction, if present, decreases red blood cell transit time (T_{RBC} = microcirculatory volume/microcirculatory flow) in the alveolar capillaries, especially when exposed to higher flows, resulting in diffusion limitation, further exacerbating hypoxemia (Figure 1). As pulmonary infarction is not immediate after pulmonary vascular occlusion, lung compliance may be normal during the initial stages of pulmonary vascular occlusion, with preserved work of breathing. Dyspnea may, therefore, be absent despite profound hypoxemia in the initial stages of respiratory failure. However, minor changes in mixed venous saturation due to increased effort or deterioration in right ventricular function may cause a quick downward spiral resulting in rapid clinical deterioration. Progression of early COVID-19 respiratory failure thus mimics large pulmonary embolism, with similar lung mechanics and hemodynamics.

In summary, the positive shunt study in severe COVID-19 indicates that abnormal arteriovenous communications open

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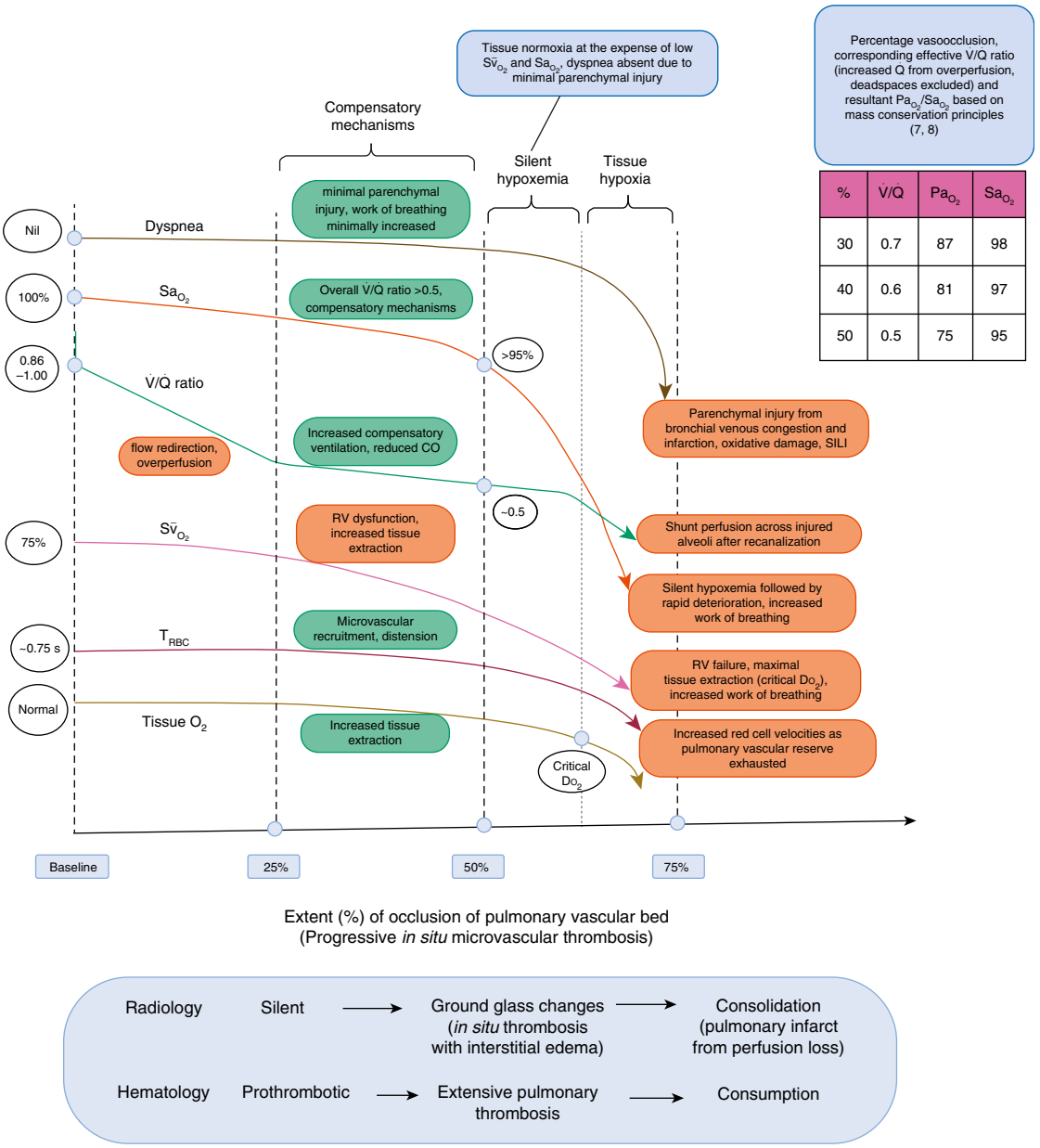

Figure 1. Schematic representation of the mechanisms of hypoxemia in coronavirus disease (COVID-19) lung injury and clinical implications. Pulmonary *in situ* thrombosis results in hypoxemia owing to flow diversion and overperfusion of other areas with intact perfusion, leading to reduced V/Q ratio in these segments. The dead spaces that occur because of loss of perfusion do not participate in gas exchange and are not relevant for oxygenation. Extensive perfusion loss is required before becoming clinically apparent owing to its moderate effect on effective V/Q ratio, nonlinear relationship between V/Q ratio and Pa_{O_2} (7, 8), and the presence of early compensatory mechanisms. However, when these mechanisms are exhausted, clinical deterioration is quick, aggravated by right heart compromise owing to acute pressure overload and reduced mixed venous saturations. Silent hypoxemia can be explained by a state of increased tissue extraction maintaining tissue oxygenation, at the expense of low arterial and venous oxygen saturations. This is facilitated by the subacute nature of the disease process and the lack of significant parenchymal injury at this stage; the work of breathing is not significantly increased, and dyspnea is minimal. CO = cardiac output; critical Do_2 = critical oxygen delivery; O_2 = oxygen; RV = right ventricular; SILI = self-induced lung injury; $S\bar{v}_{O_2}$ = mixed venous oxygen saturation; T_{RBC} = red blood cell transit time in the alveoli.

up in response to extensive small-vessel occlusion as the disease progresses. The findings fail to explain the initial severe hypoxemia in COVID-19 with preserved lung mechanics, as the degree of transpulmonary microbubble transit directly correlates with worsening lung compliance. The comparison with HPS is not appropriate owing to the evidence against microcirculatory dilatation in COVID-19. To conclude, anatomical pulmonary shunts do not contribute significantly to hypoxemia in early atypical COVID-19 respiratory failure and the distinct clinical features are best explained by progressive pulmonary vascular occlusion and subsequent diffuse lung injury due to various natural (infarction and oxidative damage) and iatrogenic sequelae. ■

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Reply to Cherian *et al.*

From the Authors:

We appreciate Cherian and colleagues' interest in our research letter (1). The medical community's knowledge of coronavirus disease (COVID-19) and its impact on the pulmonary system is evolving rapidly; we believe this kind of open, iterative dialogue is critical to informing our approach to patient care. In their letter, Cherian and colleagues suggest that transpulmonary bubble transit in hepatopulmonary syndrome (HPS) is solely due to abnormal pulmonary arteriovenous connections. They note that because the diameter of saline microbubbles is larger than the diameter of the normal pulmonary capillary, microbubbles would not be able to pass through the pulmonary capillary. However, capillaries in HPS are notably abnormal. Pathologic studies in HPS have demonstrated pulmonary capillary dilation up to 100 μm in diameter, creating passageways large enough for saline microbubbles to traverse (2, 3). Similarly, autopsy studies in COVID-19 have demonstrated pulmonary capillary deformation (4); thus, we propose that the positive bubble studies in our cohort represent transit through dilated pulmonary capillaries. Because the degree of microbubble transit in our study correlates with worse Pa_{O_2}:$F_{I_{O_2}}$ ratios, and because prior work has failed to demonstrate a relationship between transpulmonary bubble transit and Pa_{O_2}:$F_{I_{O_2}}$ ratios in traditional acute respiratory distress syndrome (5), we believe that pulmonary capillary dilation is a significant cause of hypoxemia that is specific to COVID-19 respiratory failure. We do, however, acknowledge that we cannot rule out arteriovenous connections or intracardiac shunt.

We also acknowledge that pulmonary microthrombosis plays a role in the gas exchange abnormalities in at least a subset of patients with COVID-19 respiratory failure. In fact, we previously reported rapid physiologic improvement with the administration of thrombolytics in a small group of patients with COVID-19 respiratory failure who had evidence of increased dead-space ventilation (6). We do not, however, believe that microthrombi or associated chemokine-mediated pulmonary vasoconstriction explain the presence of microbubbles. Cherian and colleagues posit that diffuse microthrombi and associated pulmonary vasoconstriction lead to increased pulmonary vascular resistance (PVR) with compensatory opening of anatomical intrapulmonary shunts. Although certainly possible, there is currently no evidence that either PVR or pulmonary artery pressure (PAP) are routinely elevated in COVID-19 respiratory failure. Using echocardiography, Pagnesi and colleagues noted pulmonary hypertension in only 12% of hospitalized patients with COVID-19 (7). Unpublished observations of invasive hemodynamics in patients with COVID-19 respiratory failure note low PVR, low PAP, and high $\dot{Q}$ (8). If the presence of microbubbles in COVID-19 respiratory failure were a result of increased PVR and PAP, one would expect to observe echocardiographic evidence of increased right ventricular (RV) afterload, specifically RV dilation. In our study, 8 of the 18 patients had transthoracic echocardiograms performed within a week of the transcranial Doppler study. Seven of these eight patients demonstrated normal RV size. Although hemodynamics were not available in our cohort, this finding argues against significantly elevated RV afterload. Interestingly, this hemodynamic profile is in contrast to that observed in classical acute respiratory distress syndrome, which is often characterized by increased PVR and PAP, thus again highlighting the unique pathophysiology in COVID-19 respiratory failure (9, 10).

We speculate that the presence of a primary pulmonary vasodilatory process mitigates and clinically masks the

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