

the hypercoagulability state was mainly attributed to platelets and fibrin. Similarly, a recent study suggests that heparin treatment does not change mortality in severe COVID-19 cases (4). In contrast, a case series study suggests that tissue plasminogen activator treatment improved COVID-19-associated acute respiratory distress syndrome (5). Based on these findings, antiplatelet or fibrinolytic drugs could be studied for thrombosis prevention and treatment for patients with COVID-19 in the future.

However, this study raised several concerns. First, this study only included patients who underwent CTPA. The contrast medium used in CTPA may cause renal damage, which is also a common complication of COVID-19, and thus CTPA may not be routinely performed in patients with severe COVID-19 but only in those with suspected pulmonary embolism in the clinical practice. This may lead to a selection bias of patients and overestimate the rate of pulmonary embolism in patients with COVID-19 on mechanical ventilation, especially in such a retrospective study. Second, the average platelet counts were $(272 \pm 77) \times 10^9/L$ in the patients who received mechanical ventilation in this study, which were different from the previous cohort study in which thrombocytopenia has been reported to be common in patients who were critically ill with COVID-19 (6). Third, the therapy from pulmonary embolism was not discussed in this study; it would be interesting to discuss whether the treatment for pulmonary embolism in patients with COVID-19 should be different from pulmonary embolism treatment in patients without COVID-19.

Overall, Patel and colleagues' study (2) is interesting in demonstrating a high rate of peripheral pulmonary vessel dilation and pulmonary embolism in patients with COVID-19, which may suggest that pulmonary vasculature is a common target of COVID-19. How these vascular changes affect COVID-19 development may need further study. ■

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Reply to Sanfilippo *et al.* and to Caviedes *et al.*



From the Authors:

We thank Sanfilippo and colleagues for their letter regarding the potential for convalescent plasma (CP) to promote macro- and microvascular thromboses in patients with coronavirus disease (COVID-19). CP is obtained through apheresis, at least 14 days following full recovery, from COVID-19 survivors who mount a satisfactory response with a high level of IgG antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). Implicit in this is that, at the time of collection, 1) the inflammatory response has subsided in potential donors and 2) levels of procoagulant (e.g., factor VIII, fibrinogen, von Willebrand factor, and inflammatory cytokines) and anticoagulant (including protein C, protein S, and antithrombin) proteins have normalized. In this way, the composition of CP simulates that of standard fresh frozen plasma (FFP), except for the presence of neutralizing antibodies against SARS-CoV-2. Both standard FFP and CP contain procoagulant and anticoagulant proteins, together with fibrinolytic activators such as plasminogen. One unit of CP

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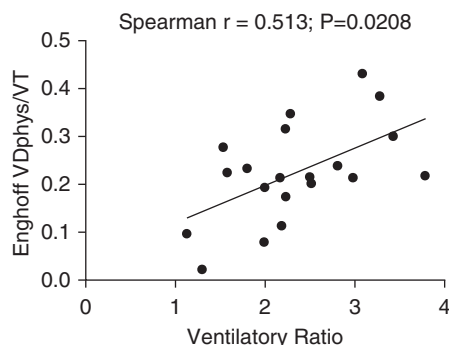


Figure 1. Ventilatory ratio and dead space as calculated with the Enghoff equation shows a good correlation in 20 patients with severe coronavirus disease (COVID-19) (Spearman $r = 0.513$, $P = 0.0208$). Enghoff V_{Dphys}/V_T = physiologic dead space, which is the sum of the anatomic and alveolar dead space/ V_T .

comprises a volume of 200–250 ml with a standard dose being a total of 2 units given 12 hours apart. A standard adult dose of FFP (namely, 10–15 ml/kg and equivalent to 4 U of FFP) should increase coagulation factor levels by around 20–30% (2). Therefore, by infusing 1 unit of CP, we expect coagulation factors to rise only by 5.0–7.5% from baseline levels, and as most of the coagulation factors have a shorter half-life—approximately 8–12 hours for factor VIII and around 16 hours for Von Willebrand factor—hypercoagulability induced by increasing the levels of these coagulation factors is unlikely to be significant. That said, clearly, this needs to be evaluated systematically through longer follow-up. At present, studies in the UK are assessing the thrombotic events up to 90 days following the infusion of CP (3). Hypothetically, CP contains neutralizing antibodies to SARS-CoV-2, which would be expected to reduce the inflammatory and prothrombotic effect of the virus on endothelium and, in so doing, might potentially downregulate any endothelial injury, thereby minimizing immunothrombosis. Although inflammation undoubtedly promotes both micro- and macrothrombosis, patients with COVID-19 seem to develop more microangiopathy as opposed to thrombotic embolism *per se* as described in our original work (4). Any potential impact of CP should be considered in the context of the postulated mechanisms that lead to the immune-mediated thrombosis of COVID-19 and acknowledge that the mechanisms for thrombosis in the microcirculation may differ from those seen in systemic macrothrombosis and, notably, pulmonary embolism.

We also thank Caviedes and colleagues for their letter discussing the calculations of dead space ventilation. We agree that ventilatory ratio (VR) does not consider CO_2 production and that the Enghoff equation $[(Pa_{CO_2} - P_{E_{CO_2}})/Pa_{CO_2}]$ (where $P_{E_{CO_2}}$ represents partial pressure of expired carbon dioxide) probably reflects the dynamics more accurately. Indeed, although all these formulae have been validated in a number of settings to relate to dead space, it is important to note that shunting increases not only the alveolar–arterial O_2 gradient but also the arterial–alveolar CO_2 difference and, because the Enghoff dead space assumes Pa_{CO_2} as a surrogate for $P_{a_{CO_2}}$, this may increase calculated physiological dead space. Needless to say, calculation of dead space cannot be performed if an artificial membrane lung is used during extracorporeal support. For clarity, we performed computed tomography (CT) scans during the pandemic for patients transferred on extracorporeal membrane oxygenation (ECMO) on admission, and calculations of VR were taken using the last ventilation settings and

matched blood gases prior to the patient being placed on ECMO. In non-ECMO patients, ventilator settings used were immediately before CT scanning. However, it is important to note that our study was not a prospective physiological study and, accordingly, we did not capture $P_{E_{CO_2}}$. Instead, we retrospectively obtained temporally matched end-tidal capnography from 20 patients within our cohort in whom there was a significant correlation between VR and Enghoff V_{Dphys} (physiologic dead space, which is the sum of the anatomic and alveolar dead space)/ V_T (Figure 1: $P = 0.0208$; Spearman $r = 0.513$). Of note, these $P_{E_{CO_2}}$ readings were captured without analysis of capnograph waveforms and, so, the actual reading may not accurately reflect the proportion of dead space. Nonetheless, a correlation between Enghoff and VR suggests a relationship between these dead space measurements between individuals. We also note the authors' own data indicating the strong correlation with \dot{V}_E/\dot{V}_{CO_2} in moderate and severe acute respiratory distress syndrome. We did not have the opportunity to test this index, as we did not measure \dot{V}_{CO_2} . However, if it were possible to accurately measure volumetric capnography, we would have advocated that Enghoff V_{Dphys}/V_T be calculated using Pa_{CO_2} and $P_{E_{CO_2}}$ rather than any of its surrogate indices. Indeed, in our center, arterial blood gases are frequently measured and are not an operational overreach. Our reporting of physiology was a pragmatic approach to benchmark our observations to other reports for COVID-19 (5) and to facilitate discussion of the vascular abnormalities seen on imaging in patients with severe COVID-19.

In summary, COVID-19 has a significant vascular inflammatory component, which, in addition to the dynamic immune response (6), activates the coagulation cascade. The early onset of angiogenesis in COVID-19 pathogenesis has yet to be confirmed. However, our observations from dual-energy CT (DECT) imaging and those of others have revealed perfusion defects even in patients with mild (non-ICU) COVID-19 (7). Hence, CT findings (such as vascular tree-in-bud or DECT perfusion abnormalities) might provide a vital noninvasive “window” to better highlight disease progression and/or ascertain the beneficial or deleterious treatment responses to therapeutic strategies such as CP. In this regard, we have recently shown that perfusion defects on DECT imaging tend to resolve over time in COVID-19 (8), an observation that might influence the nature and direction of ongoing research efforts. Finally, careful monitoring (including radiological evaluation) of patients for both short- and long-term complications of CP in well-controlled randomized clinical studies is of utmost importance. The understanding of disease pathogenesis is key to the personalized application of therapies, and prospective validation of accurate bedside measures of dead space ventilation could present opportunities to target angiopathy through physiological enrichment in clinical trials. ■

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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 V/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 V/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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