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

Robin Cherian, M.B. B.S.*
National University Heart Centre Singapore
Singapore, Singapore

Bharatendu Chandra, M.B. B.S.
National University Hospital
Singapore, Singapore

Moon Ley Tung, M.B. B.S.
National University Cancer Institute
Singapore, Singapore

Alain Vuylsteke, M.D.
Royal Papworth Hospital NHS Trust
Cambridge, United Kingdom

ORCID ID: 0000-0003-1563-4340 (R.C.).

*Corresponding author (e-mail: robin_cherian@nuhs.edu.sg).

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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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hemodynamic effects of diffuse pulmonary microthrombi in some patients with COVID-19 respiratory failure. Pulmonary microthrombi and associated chemokine-mediated vasoconstriction increase PVR, whereas pulmonary vasodilation decreases PVR; when both processes occur simultaneously, each can "cancel out" the hemodynamic effect of the other. The coexistence of both obliterative and vasodilatory processes in the pulmonary vasculature is reminiscent of what can occur in chronic liver disease, specifically portopulmonary hypertension (obliterative) and HPS (vasodilatory) (11). At the end-stage of COVID-19 respiratory failure, the balance between vasodilatory and obliterative processes may tip heavily toward obliterative, ultimately leading to severe RV failure and cardiogenic shock (12).

Although vasodilatory and obliterative processes may mutually offset each other hemodynamically, their coexistence may synergistically amplify the gas exchange abnormalities that occur in COVID-19 respiratory failure. Vasodilated regions experience increased blood flow, creating low ventilation–perfusion ratios. Microthrombi and vasoconstriction in other areas of the lung reroute additional blood flow to the vasodilated regions and further drive down the ventilation–perfusion ratio, culminating in significant hypoxemia. The simultaneous presence of both vasodilatory and obliterative processes creates the ultimate in ventilation–perfusion mismatch and may explain the marked disconnect between gas exchange and compliance noted in COVID-19 respiratory failure (13). ■

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Alexandra S. Reynolds, M.D.
Alison G. Lee, M.D., M.S.
Icahn School of Medicine at Mount Sinai
New York, New York

Joshua Renz, R.V.T.
Katherine DeSantis, M.S.
NovaSignal Corp
Los Angeles, California

John Liang, M.D.
Charles A. Powell, M.D.
Icahn School of Medicine at Mount Sinai
New York, New York

Corey E. Ventetuolo, M.D., M.S.
Brown University
Providence, Rhode Island

Hooman D. Poor, M.D.*
Icahn School of Medicine at Mount Sinai
New York, New York

*Corresponding author (e-mail: hooman.poor@mountsinai.org).

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Opioids for Dyspnea in Chronic Obstructive Pulmonary Disease: Short on the Details

To the Editor:

In a recently published guideline on pharmacologic management of chronic obstructive pulmonary disease (COPD), Nici and colleagues (1) make a "conditional recommendation" for using opioids among individuals experiencing refractory dyspnea. The recommendation rests on a meta-analysis conducted by the authors that demonstrated that in "patients with advanced refractory dyspnea, there was a statistically and clinically meaningful improvement in dyspnea with opioid treatment" (standardized mean difference [SMD] in dyspnea scores for opioids vs. placebo = −0.60; 95% confidence interval [CI],

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