The prognostic significance of $V_D$phys/V_T has been established in patients with acute respiratory distress syndrome, and the best available index of $V_D$phys/V_T is the Enghoff equation: $(Pa_{CO_2} - PE_{CO_2})/Pa_{CO_2}$, in which mean expired partial pressure of CO_2 (PE_{CO_2}) corresponds to the ratio between $\dot{V}CO_2$ and $\dot{V}E$ (3). With the increase of $V_D$phys/V_T, ventilation in nonperfused alveoli impairs CO_2 clearance (4).

Surrogate indices of $V_D$phys/V_T have commonly been used for patients on mechanical ventilation (MV) at first but not in ECMO. Concerning patients only supported on MV, surrogate indexes include $\dot{V}E$ and arterial samples of PCO_2; nevertheless, they always exclude the uncontrolled $\dot{V}CO_2$ variable (2). From another point of view, $\dot{V}E/\dot{V}CO_2$ specifically means ventilatory efficiency to clear CO_2 and depends on $V_D$phys/V_T. The $\dot{V}E/\dot{V}CO_2$ ratio corresponds to the $\dot{V}E$ used to achieve a certain Pa_{CO_2} level for a given $\dot{V}CO_2$ and is strongly related with $V_D$phys/V_T.

Under this rationale, in a previous study of our group, in 43 patients on MV without ECMO, we evaluated the performance of common surrogate parameters in relation to $V_D$phys/V_T, also including VR. Patients were sedated and in stable condition. We tested the correlation between $V_D$phys/V_T and the following variables: VR, $(Pa_{CO_2} - Et_{CO_2})/Pa_{CO_2}$, $Pa_{CO_2} - Et_{CO_2}$, and $\dot{V}E/\dot{V}CO_2$, where Et_{CO_2} represents end-tidal CO_2.

Results demonstrated significant correlations between $V_D$phys/V_T and VR ($r = 0.45$), $(Pa_{CO_2} - Et_{CO_2})/Pa_{CO_2}$ ($r = 0.60$), $Pa_{CO_2} - Et_{CO_2}$ ($r = 0.63$), and $\dot{V}E/\dot{V}CO_2$ ($r = 0.88$), respectively, highlighting that the best correlated of these indexes was $\dot{V}E/\dot{V}CO_2$. Even more, $\dot{V}E/\dot{V}CO_2$ was even better for patients with $Pa_{O_2}/FI_{O_2} < 200$ ($r = 0.91$) and for patients with a $Pa_{CO_2} > 45$ mm Hg ($r = 0.96$) (5).

Under controlled MV, Pa_{CO_2} tightly depends on the mechanical ventilator adjustments; thus, the $\dot{V}E/\dot{V}CO_2$ ratio excludes the controlled variable Pa_{CO_2}. By the other side, VR ignores the noncontrolled variable $\dot{V}CO_2$ but depends on it. From an operational point of view, on MV $V_D$phys/V_T is obtained by volumetric capnography and an arterial sample of blood gases, while VR is obtained by assumptions of $\dot{V}E$ (based on predicted body weight) and Pa_{CO_2} and only an arterial sample of blood gases. In the measurement of $\dot{V}E/\dot{V}CO_2$, a volumetric capnography is needed (nowadays present in most mechanical ventilators), with online response and without the lag and intermittency of arterial samples (5). So, in consequence with the high correlation between $\dot{V}E/\dot{V}CO_2$ and $V_D$phys/V_T, this ratio could improve the support of their conclusions only on patients with MV. ■

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Pulmonary Vascular Changes in Acute Respiratory Distress Syndrome due to COVID-19

To the Editor:

This letter is in response to an article published in a recent issue of the *Journal* by Patel and colleagues (1). The authors' observation is consistent with a previous report, suggesting varying grades of pulmonary thromboembolism, pulmonary vascular microthrombosis, and pulmonary vascular dilatation in an advanced stage of acute hypoxemic failure owing to coronavirus disease (COVID-19) (1, 2). In the current study, radiologic findings were obtained when nearly 50% of patients were on extracorporeal membrane oxygenation (ECMO). Therefore, interpretation and generalization of the findings becomes somewhat more intriguing because of complexities arising from hemodynamic, oxygenation, and hematologic alterations induced by ECMO (3). Venoarterial ECMO is known to increase afterload, left ventricular (LV) end diastolic pressure, left atrial pressure, and postcapillary venous dilatation. Furthermore, femoral arterial oxygenated flow may not reach the coronary circulation because of the watershed effect (north–south syndrome) and may induce LV ischemia and aggravate LV dysfunction (4). In addition, the venous return diversion to the ECMO circuit may induce stagnation in the pulmonary circulation, which may get further aggravated by an increase in pulmonary vascular resistance because of positive end-expiratory pressure. However, total lung–blood volume may get reduced and there is a lesser hydrostatic pressure gradient for pulmonary edema formation. Therefore, a reduction in dynamic compliance may be expected during venoarterial ECMO because of a fall in total pulmonary fluid volume. Undoubtedly, venovenous

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ECMO maintains better cardiorespiratory interaction than venoarterial ECMO, and it does not increase LV end-diastolic pressure, left atrial pressure, and pulmonary venous pressure. A rise in mixed venous oxygen saturation diminishes hypoxic pulmonary vasoconstriction response to increase pulmonary vascular dilatation in diseased lobes. Furthermore, a higher minute ventilation because of hypoxic and hypercarbic drive may subside during ECMO, and the ventilatory ratio may also come down substantially. Admittedly, physiological dead space, shunt fraction, and ventilation perfusion matching would be entirely different in patients with acute hypoxemic failure on ECMO compared with patients not on ECMO. Furthermore, clinicians may be tempted to change the ventilator settings during ECMO run. Peripheral pulmonary vascular dilatation gets obscured by opacification of the lung, and the presence of such dilatation in a healthy aerated lung region suggests extraalveolar vessel dilatation as a result of intraalveolar vessel compression owing to positive end-expiratory pressure (5). Demarcation of pulmonary vascular dilatation between precapillary and postcapillary component could have helped in assessing the role of pulmonary vascular resistance and LV dysfunction. Even though the sample size was small, stratification and comparison of oxygenation parameters and the computed tomographic scan findings in patients on ECMO and in patients not on ECMO would have provided an additional pathophysiological insight. In addition, comparisons among patients on different types of ECMO would have been worthwhile. The study did not provide sufficient data to suggest whether the correlation between different ventilatory and oxygenation parameters were assessed before ECMO or after ECMO. Furthermore, the author's interpretation that there was no correlation between the computed tomographic scan findings and $Pa_{O_2}/F_{I_{O_2}}$ ratio or the ventilatory ratio seems to suggest an overwhelming role of ECMO in improving $Pa_{O_2}/F_{I_{O_2}}$ ratio and ventilatory ratio in nearly 50% of patients. An increase or decrease in the incidence of pulmonary vessel dilatation, microthrombosis, and pulmonary thromboembolism during ECMO may indicate the qualitative and quantitative change required in anticoagulation therapy. A persistent increase in the incidence of pulmonary thromboembolism while on ECMO despite adequate activated clotting time could be worrying. In addition, establishing a correlation between change in prevalence of pulmonary vascular dilatation with increasing duration of ECMO run would also have been meaningful. ■

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Pulmonary Vasculature: A Target for COVID-19

To the Editor:

Coronavirus disease (COVID-19) is rapidly emerging and becoming a pandemic worldwide. The pathogen, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), infects the hosts via an ACE2 receptor, which is expressed in vascular endothelial cells. And SARS-CoV-2 has been found in blood vessels and causes a variety of vascular complications, including thrombosis (1). In a recent issue of the *Journal*, Patel and colleagues found a high rate of pulmonary embolism and distal pulmonary vascular dilation using computed tomography (CT) pulmonary angiography (CTPA) scans, and lung perfusion defects via dual-energy CT scans in patients with COVID-19 who were mechanically ventilated (2). It is the first report of peripheral pulmonary vessel dilation presenting as a vascular tree-in-bud pattern that was not reported in acute or chronic pulmonary embolism before. Interestingly, presence of peripheral pulmonary vessel dilation is associated with longer duration of hospitalization and ventilation. As SARS-CoV-2 infects blood vessels (1), the peripheral pulmonary vessel dilation could be caused by the virus infection or COVID-19–induced inflammation, which may be characteristic vascular damage in COVID-19 and associated with the severity of the disease. Lung pathology from patients with COVID-19 shows thrombus in the microvasculature (3), but whether these changes contribute to peripheral pulmonary vessel dilation in CTPA may need further investigation. In addition to lung CT examinations, thromboelastography was also performed on the patients in this study and showed hypercoagulability characterized by higher maximal amplitude and absent fibrinolysis at 30 minutes (lysis index 30 [LY30] = 0%). These thromboelastography findings may explain the reason why 38.5% of the patients had pulmonary embolisms even with anticoagulant prophylaxis, as

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