For instance, plasma is administered in the setting of hemorrhagic shock for its ability to improve hemostasis; thus, the idea of administering plasma to any patient with underlying hypercoagulability should be undertaken very watchfully. Depending on the methods for aiming at inactivating residual virus during the preparation of CP, the content of coagulation factors also may decrease, which would eventually blunt its procoagulant effects (4). However, in the presence of an already stimulated coagulation pathway as demonstrated by Patel and colleagues (1), even small amounts of residual coagulation factors in CP may potentiate the coagulation cascade in patients with COVID-19, representing a source of potential harm.

In our opinion, the progression of thrombosis should not be evaluated only as evidence of new pulmonary embolism, but it may result in worsening oxygenations and gas exchanges. This could be the result of thrombosis and progression of perfusion defects with further dilatation of peripheral lung vessels. Moreover, considering the systemic impact of the underlying hypercoagulability, administration of CP may worsen perfusion in other vital organs, potentially increasing, among others, risks of myocardial and cerebral ischemia. Thus, great caution is warranted in looking for specific adverse events related to CP in patients with COVID-19.

To add more uncertainty on the use of CP, its efficacy for the treatment of COVID-19 has been questioned by a Cochrane systematic review (5). Moreover, according to another recent meta-analysis of randomized controlled trials at low risk of bias, administration of CP to patients with severe influenza has not been shown to reduce mortality, number of days in the ICU, or number of days on mechanical ventilation (6).

In summary, we think the results of the study of Patel and colleagues greatly contribute to the definition of pathogenesis and clinical characteristics of COVID-19, but they are also of great value when considering potential therapeutic strategies and the right approach to control for their safety. New studies on CP in patients with COVID-19 should be encouraged to report the methods of preparation for CP. ■

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References

1. Patel BV, Arachchillage DJ, Ridge CA, Bianchi P, Doyle JF, Garfield B, *et al*. Pulmonary angiopathy in severe COVID-19: physiologic, imaging, and hematologic observations. *Am J Respir Crit Care Med* 2020;202:690–699.
2. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, *et al*. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med* 2020;46:1099–1102.
3. Joyner M, Wright RS, Fairweather D, Senefeld J, Bruno K, Klassen S, *et al*. Early safety indicators of COVID-19 convalescent plasma in 5,000 patients [preprint]. *medRxiv* [online ahead of print] 14 May 2020; DOI: 10.1101/2020.05.12.20099879.
4. Lozano M, Cid J, Müller TH. Plasma treated with methylene blue and light: clinical efficacy and safety profile. *Transfus Med Rev* 2013;27:235–240.
5. Valk SJ, Piechotta V, Chai KL, Doree C, Monsef I, Wood EM, *et al*. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a rapid review. *Cochrane Database Syst Rev* 2020;5: CD013600.
6. Xu Z, Zhou J, Huang Y, Liu X, Xu Y, Chen S, *et al*. Efficacy of convalescent plasma for the treatment of severe influenza. *Crit Care* 2020;24:469.

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Pulmonary Angiopathy in Severe COVID-19: Physiological Conclusions Derived from Ventilatory Ratio?

To the Editor:

We read with interest the article by Patel and colleagues (1) in which they describe imaging, functional, and hematological aspects in 39 patients with acute respiratory distress syndrome due to coronavirus disease (COVID-19). As the authors describe, ventilatory ratio (VR) was calculated in two opportunities, once at admission and once after computed tomographic scan, and it was increased in both. From that, they draw a conclusion about the presence of increased physiological respiratory dead space ($V_D phys/V_T$) based on a single surrogate parameter, the $VR = (\dot{V}_E \times \text{actual } Pa_{CO_2})/(\text{predicted } \dot{V}_E \times \text{predicted } Pa_{CO_2})$, where $\dot{V}_E$ represents actual minute volume. VR includes assumptions in normalizing data and does not consider CO_2 production ($\dot{V}_{CO_2}$) as a variable (2). Furthermore, VR was introduced as a simple bedside method to estimate efficiency of ventilation but not as a means to measure $V_D phys/V_T$ (2). Moreover, VR has not been validated under extracorporeal membrane oxygenation (ECMO) conditions (44% of patients at admission), so because of these reasons, those assumptions lessen support to their conclusion.

Important adjustments are included in the VR formula, where Pa_{CO_2} is controlled by the physician on the mechanical ventilator, and it excludes $\dot{V}_{CO_2}$. So, if a patient suffers changes in his inflammatory behavior, or in his spontaneous ventilatory efforts, the independent variable $\dot{V}_{CO_2}$ will increase, but Pa_{CO_2} is controlled on the ventilator and will remain constant. In this case, $\dot{V}_E$ and VR increase but do not properly represent $V_D phys/V_T$. Even more, in patients under ECMO, Pa_{CO_2} specifically depends on the airflow in the oxygenating machine, and to the best of our knowledge, VR index has not been validated under this condition.

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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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References

1. Patel BV, Arachchillage DJ, Ridge CA, Bianchi P, Doyle JF, Garfield B, *et al*. Pulmonary angiopathy in severe COVID-19: physiologic, imaging, and hematologic observations. *Am J Respir Crit Care Med* 2020;202: 690–699.
2. Sinha P, Calfee CS, Beitler JR, Soni N, Ho K, Matthay MA, *et al*. Physiologic analysis and clinical performance of the ventilatory ratio in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2019; 199:333–341.
3. Nuckton TJ, Alonso JA, Kallet RH, Daniel BM, Pittet JF, Eisner MD, *et al*. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. *N Engl J Med* 2002;346:1281–1286.
4. Sinha P, Flower O, Soni N. Deadspace ventilation: a waste of breath! *Intensive Care Med* 2011;37:735–746.
5. López R, Caviedes I, Graf J. Minute ventilation to carbon dioxide production ratio is a simple and non-invasive index of ventilatory inefficiency in mechanically ventilated patients: proof of concept. *Intensive Care Med* 2017;43:1542–1543.

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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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