mortality during seasonal and pandemic influenza outbreaks. In addition, when confronted with other novel pathogenic viruses, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), rhMG53 may offer a treatment option where one does not currently exist. Thus, our findings provide the first proof of concept in support of further clinical development of rhMG53 as a biologic to treat inflammation-driven infectious diseases. ■

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

Acknowledgment: The authors thank Dr. Eugene Oltz and Dr. Sandy Snyder for critical reading of the manuscript.

Adam D. Kenney, B.S.*
The Ohio State University College of Medicine
Columbus, Ohio

Zhongguang Li, B.S.*
The Ohio State University College of Medicine
Columbus, Ohio
and
Shaanxi Normal University College of Life Sciences
X'ian, China

Zehua Bian, Ph.D.*
Xinyu Zhou, Ph.D.
Haichang Li, Ph.D.
Bryan A. Whitson, M.D., Ph.D.
Tao Tan, M.D., Ph.D.
Chuanxi Cai, Ph.D.
Jianjie Ma, Ph.D.
The Ohio State University College of Medicine
Columbus, Ohio

Jacob S. Yount, Ph.D.‡
The Ohio State University College of Medicine
Columbus, Ohio

ORCID ID: 0000-0002-6128-4575 (J.S.Y.).

*These authors contributed equally to this work.
‡Corresponding author (e-mail: jacob.yount@osumc.edu).

References

1. Cai C, Masumiya H, Weisleder N, Matsuda N, Nishi M, Hwang M, *et al*. MG53 nucleates assembly of cell membrane repair machinery. *Nat Cell Biol* 2009;11:56–64.
2. Cao CM, Zhang Y, Weisleder N, Ferrante C, Wang X, Lv F, *et al*. MG53 constitutes a primary determinant of cardiac ischemic preconditioning. *Circulation* 2010;121:2565–2574.
3. Wang X, Xie W, Zhang Y, Lin P, Han L, Han P, *et al*. Cardioprotection of ischemia/reperfusion injury by cholesterol-dependent MG53-mediated membrane repair. *Circ Res* 2010;107:76–83.
4. Sermersheim M, Kenney AD, Lin PH, McMichael TM, Cai C, Gumpper K, *et al*. MG53 suppresses interferon-β and inflammation via regulation of ryanodine receptor-mediated intracellular calcium signaling. *Nat Commun* 2020;11:3624.
5. Bian Z, Wang Q, Zhou X, Tan T, Park KH, Kramer HF, *et al*. Sustained elevation of MG53 in the bloodstream increases tissue regenerative capacity without compromising metabolic function. *Nat Commun* 2019;10:4659.
6. Jia Y, Chen K, Lin P, Lieber G, Nishi M, Yan R, *et al*. Treatment of acute lung injury by targeting MG53-mediated cell membrane repair. *Nat Commun* 2014;5:4387.
7. Weisleder N, Takizawa N, Lin P, Wang X, Cao C, Zhang Y, *et al*. Recombinant MG53 protein modulates therapeutic cell membrane repair in treatment of muscular dystrophy. *Sci Transl Med* 2012;4:139ra85.
8. Matute-Bello G, Downey G, Moore BB, Groshong SD, Matthay MA, Slutsky AS, *et al*.; Acute Lung Injury in Animals Study Group. An official American Thoracic Society workshop report: features and measurements of experimental acute lung injury in animals. *Am J Respir Cell Mol Biol* 2011;44:725–738.
9. Kuriakose T, Man SM, Malireddi RK, Karki R, Kesavardhana S, Place DE, *et al*. ZBP1/DAI is an innate sensor of influenza virus triggering the NLRP3 inflammasome and programmed cell death pathways. *Sci Immunol* 2016;1:aag2045.
10. Ding J, Wang K, Liu W, She Y, Sun Q, Shi J, *et al*. Pore-forming activity and structural autoinhibition of the gasdermin family. *Nature* 2016;535:111–116.

COVID-19, Hypercoagulability, and Cautiousness with Convalescent Plasma

To the Editor:

We read with great interest the elegant study conducted by Patel and colleagues (1) regarding the alterations at pulmonary vessel level in patients with severe coronavirus disease (COVID-19). The authors meticulously presented the combination of physiologic data, the results of high-resolution imaging, and the hematologic observations in a cohort of 39 patients. They showed that the activation of inflammatory and coagulation pathways has a pivotal role in the development of acute respiratory failure induced by COVID-19, demonstrating the great impact of hypercoagulability and reduction of fibrinolysis on the pulmonary vasculature. Such a prothrombotic state finally induces pulmonary (and likely systemic) perfusion abnormalities, heavily contributing to the peculiar phenotype of COVID-19–induced respiratory failure (2).

We believe that the results shown by Patel and colleagues (1), highlighting the presence of dilated peripheral lung vessels (roughly two-thirds of patients) and perfusion defects in all patients, are of great importance in cautiously interpreting the results of a recent study on the use of convalescent plasma (CP) in COVID-19. Indeed, this study evaluated the use of CP in more than 5,000 patients with severe or life-threatening COVID-19 (3) and prompted great (and in our opinion excessive) enthusiasm as the authors reported low incidence of serious adverse effects after CP. However, this safety endpoint was evaluated in a particularly short period of observation (4 h), which is far too limited to entirely account for subtle progression of an underlying hypercoagulability state.

Author Contributions: All the authors read and discussed the content of the article by Patel and colleagues. F.S. and M.A. wrote the draft with the initial idea of discussing the procoagulant effects of convalescent plasma. V.L.R. and F.O. further investigated the issues in preparation of convalescent plasma. All the authors critically revised the final draft and approved.

Originally Published in Press as DOI: 10.1164/rccm.202008-3139LE on October 21, 2020

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. ■

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

Filippo Sanfilippo, M.D., Ph.D.*
Azienda Ospedaliero Universitaria "Policlinico-Vittorio Emanuele" Catania, Italy

Valeria La Rosa, M.D.
University of Catania Catania, Italy

Francesco Oliveri, M.D.
Azienda Ospedaliero Universitaria "Policlinico-Vittorio Emanuele" Catania, Italy

Marinella Astuto, M.D.
Azienda Ospedaliero Universitaria "Policlinico-Vittorio Emanuele" Catania, Italy
and
University of Catania Catania, Italy

*Corresponding author (e-mail: filipposanfi@yahoo.it).

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.

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.

Originally Published in Press as DOI: 10.1164/rccm.202009-3446LE on October 21, 2020