american physiological society

JOURNAL OF APPLIED PHYSIOLOGY

J Appl Physiol 133: 1295–1299, 2022.
First published October 21, 2022; doi:10.1152/japplphysiol.00458.2022

RAPID REPORT

Long-Term Recovery from SARS-CoV-2 (COVID-19)

CT-derived measurements of pulmonary blood volume in small vessels and the need for supplemental oxygen in COVID-19 patients

Wendel Dierckx,[1,3,10] Wilfried De Backer,[1,10] Muriel Lins,[2] Yinka De Meyer,[3,10] Kris Ides,[1,8,10] Jan Vandevenne,[4,5] Jan De Backer,[3] Erik Franck,[9] Ben R. Lavon,[3] Maarten Lanclus,[3] and Muhunthan Thillai[6,7]

[1]*Faculty of Medicine, University of Antwerp, Antwerp, Belgium;* [2]*General Hospital Sint-Maarten, Mechelen, Belgium;* [3]*Fluidda NV, Kontich, Belgium;* [4]*Department of Radiology, Ziekenhuis Oost-Limburg, Genk, Belgium;* [5]*Faculty of Medicine, University of Hasselt, Diepenbeek, Belgium;* [6]*Interstitial Lung Disease Unit, Royal Papworth Hospital NHS Foundation Trust, Cambridge, United Kingdom;* [7]*Department of Medicine, University of Cambridge, Cambridge, United Kingdom;* [8]*Department of Engineering, Cosys Labs, University of Antwerp, Antwerp, Belgium;* [9]*Centre for Research and Innovation in Care, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium; and* [10]*Multidisciplinary praxis Medimprove, Kontich, Belgium*

Abstract

Throughout the COVID-19 pandemic, a portion of those affected have evolved toward acute hypoxic respiratory failure. Initially, this was hypothesized to result from acute lung injury leading to acute respiratory distress syndrome (ARDS). In previous research, a novel quantitative CT post-processing technique was described to quantify the volume of blood contained within pulmonary blood vessels of a given size. We hypothesized that patients with lower BV5 blood flow would have higher supplemental oxygen needs and less favorable arterial blood gas profiles. From the initial data analysis, 111 hospitalized COVID-19 patients were retrospectively selected based on the availability of CT scans of the lungs with a slice thickness of 1.5 mm or less, as well as PCR-confirmed SARS-CoV2 infection. Three-dimensional (3-D) reconstructions of the lungs and pulmonary vasculature were created. Further analysis was performed on 50 patients. Patients were divided into groups based on their need for oxygen at the time of CT scan acquisition. Eighteen out of 50 patients needed >2 L/min supplemental oxygen and this group demonstrated a significantly lower median percentage of total blood flow in the BV5 vessels compared with the 32 patients who needed <2 L/min supplemental oxygen (41.61% vs. 46.89%, P = 0.023). Both groups had significantly less blood as a proportion in BV5 vessels compared with healthy volunteers. These data are consistent with the hypothesis that reduced blood volume within small (BV5) pulmonary vessels is associated with higher needs for supplemental oxygen and more severe gas exchange anomalies in COVID-19 infections.

NEW & NOTEWORTHY This research provides, by using new imaging analysis on CT imaging, an insight into the pathophysiology of patients with COVID-19 infection. By visualizing and quantifying the blood in small vessels in the lung, we can link these results to the clinical need for oxygen in patients with COVID-19 infection.

BV5; COVID-19; functional imaging; pulmonary blood vessels

INTRODUCTION

Throughout the COVID-19 pandemic, a portion of those affected have evolved toward acute hypoxic respiratory failure (1). Initially, this was hypothesized to result from acute lung injury leading to acute respiratory distress syndrome (ARDS), with many patients meeting the imaging requirements of the Berlin criteria for ARDS (2, 3). Treatment protocols for these patients were therefore designed based on the current guidelines for ARDS management, including mechanical ventilation with high levels of positive end-expiratory pressure (PEEP) (3). A growing number of reports suggest that some patients with COVID-19 present with relatively normal lung compliance but severe and refractory hypoxemia, which is inconsistent with the conventional understanding of ARDS, indicating that an alternate pathophysiology may be involved (4–6).

Correspondence: K. Ides (kris.ides@uantwerpen.be); W. Dierckx (Wendel.Dierckx@outlook.com).
Submitted 3 August 2022 / Revised 14 October 2022 / Accepted 14 October 2022

In previous research, a novel quantitative CT postprocessing technique was described to quantify the volume of blood contained within pulmonary blood vessels of a given size (7). In comparing scans of 103 patients with PCR-confirmed COVID-19 to 108 healthy volunteers, it was observed that patients with COVID-19 have significantly less blood (as a portion of total pulmonary blood volume) contained in pulmonary vessels below 5 mm^2 in cross-sectional area ("BV5"), and significantly more in vessels greater than 10 mm^2 in cross-sectional area ("BV10") (Fig. 1*A*). These changes are equivalent to a redistribution of pulmonary blood away from the small pulmonary vessels and into larger vessels, consistent with increased pulmonary vascular resistance downstream. This may be due to dysregulated vasoconstriction, thrombotic events in the microvasculature, or both. The endothelial inflammatory pathways may play an important role in this dysregulation (8). Any of these could contribute to the observed refractory hypoxemia by impairing gas exchange across the alveolar-capillary membrane. These data suggest a possible pathophysiological explanation for the impression of severe dead space ventilation reported by intensivists (6).

Considering these previous data, the relationship (or predictive value) between CT-derived measures of small blood vessel loss and the degree of gas exchange anomaly experienced was investigated. Paired clinical data were analyzed from 43 of the 103 patients previously analyzed (7), as well as eight additional patients included after the previous research concluded. We hypothesized that patients with lower BV5 blood flow would have higher supplemental oxygen needs and less favorable arterial blood gas profiles.

METHODS

From the initial data analysis, 111 hospitalized COVID-19 patients were retrospectively selected based on the availability of CT scans of the lungs with slice thickness of 1.5 mm or less, as well as PCR-confirmed SARS-CoV2 infection. Thin-sliced CT scans were provided by the respective hospitals where they were acquired. Institutional review board approval was granted by the respective local committees. Written informed consent was obtained from the patients, volunteers, and/or institutions included in the article. Ninety-one scans came from Belgium [51 from AZ Sint-Maarten (Mechelen), 40 from Ziekenhuis Oost-Limburg (Genk)], 10 from the United Kingdom (Royal Papworth Hospital), and 10 from China (Wenzhou Medical University). It should be noted that the previous work included only 43 patients from AZ Sint-Maarten; the additional eight were provided after that research concluded. One hundred eight inspiratory scans from healthy patients were acquired from the COPDGene cohort (NCT00608764) and were used as reference data. No statistical comparison between these data and COVID-19 data set was performed (9, 10). Because scans

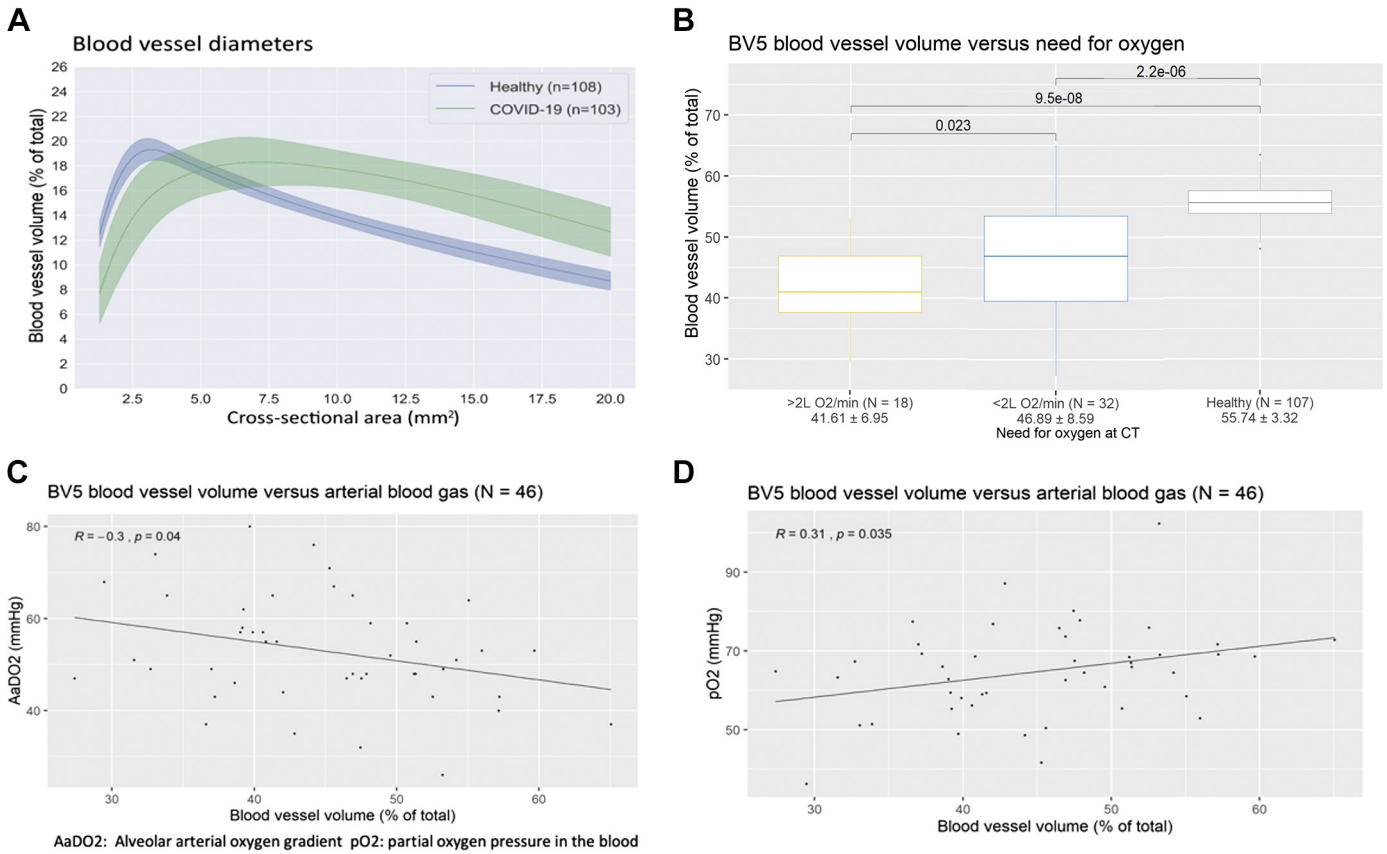


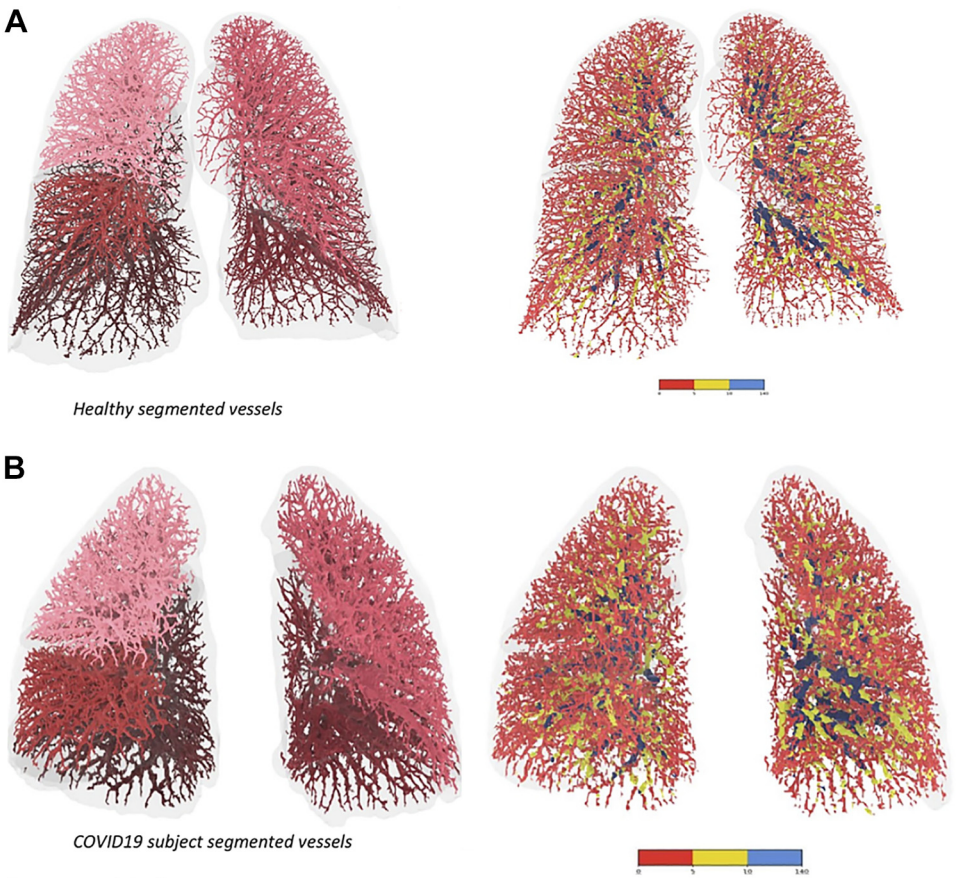
Figure 1. *A*: proportion of pulmonary blood within different caliber levels in COVID-19 vs. healthy volunteers. *B*: proportion of blood within BV5 (blood vessels of <5 mm^2 cross-sectional area) in patients with COVID-19 with different levels of inspired oxygen. *C*: proportion of blood through BV5 levels and correlation with alveolar-arterial oxygen gradient (AaDO2). *D*: proportion of blood through BV5 levels and correlation with Pa_{O_2}.

were acquired without a standardized protocol, slice thickness varied between 0.6 mm and 1.5 mm. One patient had highly anomalous arterial blood gas readings (assumed to be a mixed venous sample) and was therefore excluded from the analysis. The measurements were performed on the TLC level without gaiting as this was not possible in this clinical setting. All patients, however, were instructed and encouraged during the scanning procedure to inhale to their maximal inspiration.

3-D reconstructions of the lungs and pulmonary vasculature were created (Fig. 2). An automated blood vessel segmentation algorithm performed an eigenvalue analysis of the Hessian matrix to enhance and identify tubular structures, by returning the probability of each voxel belonging to tubular structure based on shape analysis (11). Hounsfield unit (HU) thresholds, based on the vessels size defined by an automated adaptive iterative threshold method, were used to limit the vessels. During preprocessing, a gradient anisotropic diffusion filter was applied, and a region of interest was defined to remove false positives. Subsequently, the smaller nonconnected parts were removed. To account for the effects of slice thickness on results, sensitivity analysis was performed. Volumes were computed from the cross-sectional area of each vessel. Denoting these measurements "BVX", where "X" indicates a range of vessel sizes in mm^2 (BV5 is the volume of blood contained in vessels between 1.25 and 5 mm^2 cross-sectional area, BV5-10 between 5 and 10 mm^2, and BV10 $>$ 10 mm^2).

To account for variation in lung volume, BVX was normalized to total pulmonary blood volume, allowing for the computation of a "BV spectrum," a curve representing the percent of total pulmonary blood volume contained within vessels of a given caliber as a function of cross-sectional area. This method was previously described and was correlated to the clinical symptoms of patients as validation of the technique.

Further analysis was performed on 50 patients (30 male, 20 female, median age 61.98) included from AZ Sint-Maarten, as these were the patients for whom the most clinical data was available. These patients were divided into groups based on their need for oxygen at the time of CT scan acquisition, with a threshold of 2 L/min chosen a priori ($<$2 L/min O_2 or $>$2 L/min O_2). This threshold was chosen as patients in need of more than 2 L/min are oxygen dependent. Those below 2 L/min have a more intermittent need for oxygen. The oxygen needs of patients with more than 2 L vary over time. We chose to pool patients in this study, rather than analyze the amount of oxygen needed as a continuous variable. BV5 values were compared between cohorts. Nonparametrical spearman correlations were computed between BV5 and Pa_{O_2} AaDO2. Four patients did not have arterial blood gas data available and were therefore excluded from this portion of the analysis. Two-sample *t* tests were used to assess significance ($P < 0.05$). All analyses



Demographic data:

Healthy subject	Female	58 years
COVID19 subject	Female	57 years

Figure 2. Example of blood vessel segmentation in healthy volunteers (*A*) and patients with COVID-19 (*B*).

were performed using the open-source statistical environment R v. 3.2.5 or higher (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Eighteen out of 50 patients needed >2 L/min supplemental oxygen and this group demonstrated a significantly lower median percentage of total blood flow in the BV5 vessels compared with the 32 patients who needed <2 L/min supplemental oxygen (41.61% vs. 46.89%, P = 0.023). Both groups had significantly less blood as a proportion in BV5 vessels compared with healthy volunteers (Fig. 1*B*). The 46 patients for whom arterial blood gas data were available showed that decreased percentage of blood distribution through BV5 vessels correlated with both increased alveolar-arterial oxygen gradient (AaDO2) (Fig. 1*C*) and decreased Pa_{O_2} (Fig. 1*D*).

Conclusions

These data are consistent with the hypothesis that reduced blood volume within small (BV5) pulmonary vessels is associated with higher needs for supplemental oxygen and more severe gas exchange anomalies in COVID-19 infections. This supports the view that these patients develop acute hypoxemic respiratory failure due, at least in part, to pathologic alterations in the pulmonary microvasculature, which results in elevated pulmonary pressures and attendant impaired alveolar gas exchange. These changes may include occlusion of pulmonary blood vessels by thrombi, unusual vasoconstriction, and direct damage to the membranes across which gas exchange occurs (2, 6, 12). In a previous study, BV5% from patients with COVID-19 was significantly lower than BV5% from a heterogenous cohort of patients without COVID-19. This difference was driven mainly by patients with CT findings, in a multivariate model that did not account for lung opacification. A BV5% threshold below 25% was associated with an odds ratio (OR) of 5.58 for mortality, OR 3.20 for intubation, and OR 2.54 for the composite of mortality or intubation was found. After including the severity of lung opacification in the multivariate analysis, a BV5% threshold of 25% remained significantly associated with mortality, with OR 4.27. The current study shows that smaller changes in BV5% also result in a different need for oxygen, in fact indicating that BV5 changes and related blood redistribution contribute to oxygen need (9). Early signs of treatment efficacy in pilot studies using inhaled nitric oxide and heparin further support this perspective and underscore the potential utility of vasodilators and antithrombotic interventions in preventing dead space ventilation (13, 14). Recruitment of distal airways with mechanical ventilation (with low levels of PEEP and high $F_{I_{O_2}}$) may help to facilitate the transport of the inhaled oxygen toward the alveoli (5). Those conducting clinical trials to assess the efficacy of these interventions should consider the use of small pulmonary blood vessel volumes as an end point.

Further study is needed to understand the role of these CT-derived metrics in monitoring disease progression. It remains to be seen whether longitudinal changes in pulmonary blood volume distribution are related to clinical state, and whether imaging changes can predict clinical outcomes, which could be a useful tool in the context of strained healthcare resources.

ACKNOWLEDGMENTS

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s). The authors declare that they obtained a written informed consent from the patients, volunteers, and/or institutions included in the article. The authors also confirm that the personal details of the patients and/or volunteers have been removed.

DISCLOSURES

W.D., Y.D.M., J.D.B., B.L., and M.Lanclus are employees of FLUIDDA, a company that develops and markets part of the technology described in this article. The other authors have no financial relationships with any organization or company that might have an interest in the submitted work and received no direct funding from FLUIDDA. None of the other authors has any conflicts of interest, financial or otherwise, to disclose.

AUTHOR CONTRIBUTIONS

W.D., W.D.B., M.Lins, J.D.B., E.F., and B.R.L. conceived and designed research; W.D., M.Lins, K.I., J.V., J.D.B., E.F., B.R.L., M.Lanclus, and M.T. performed experiments; W.D., M.Lins, K.I., J.D.B., E.F., B.R.L., M.Lanclus, and M.T. analyzed data; W.D., W.D.B, M.Lins, K.I., J.D.B., E.F., B.R.L., M.Lanclus, and M.T. interpreted results of experiments; W.D., W.D.B., J.D.B., and B.R.L. prepared figures; W.D., W.D.B., J.V., J.D.B., and B.R.L. drafted manuscript; W.D., W.D.B., Y.D.M., K.I., J.V., J.D.B., E.F., B.R.L., M.Lanclus, and M.T. edited and revised manuscript; W.D., W.D.B., M.Lins, Y.D.M, K.I., J.D.B., E.F., B.R.L., M.Lanclus, and M.T. approved final version of manuscript.

REFERENCES

1. **Grasselli G**, **Zangrillo A**, **Zanella A**, **Antonelli M**, **Cabrini L**, **Castelli A**, **Cereda D**, **Coluccello A**, **Foti G**, **Fumagalli R**, **Iotti G**, **Latronico N**, **Lorini L**, **Merler S**, **Natalini G**, **Piatti A**, **Ranieri MV**, **Scandroglio AM**, **Storti E**, **Cecconi M**, **Pesenti A**; **COVID-19 Lombardy ICU Network.** Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA* 323: 1574–1581, 2020. doi:10.1001/jama.2020.5394.
2. **Ackermann M**, **Verleden SE**, **Kuehnel M**, **Haverich A**, **Welte T**, **Laenger F**, **Vanstapel A**, **Werlein C**, **Stark H**, **Tzankov A**, **Li WW**, **Li VW**, **Mentzer SJ**, **Jonigk D.** Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med* 383: 120–128, 2020. doi:10.1056/NEJMoa2015432.
3. **Meng L**, **Qiu H**, **Wan L**, **Ai Y**, **Xue Z**, **Guo Q**, **Deshpande R**, **Zhang L**, **Meng J**, **Tong C**, **Liu H**, **Xiong L.** Intubation and ventilation amid the COVID-19 outbreak: Wuhan's experience. *Anesthesiology* 132: 1317–1332, 2020. doi:10.1097/ALN.0000000000003296.
4. **Gattinoni L**, **Coppola S**, **Cressoni M**, **Busana M**, **Rossi S**, **Chiumello D.** Covid-19 does not lead to a "typical" acute respiratory distress syndrome. *Am J Respir Crit Care Med* 201: 1299–1300, 2020. doi:10.1164/rccm.202003-0817LE.
5. **Marini JJ**, **Gattinoni L.** Management of COVID-19 respiratory distress. *JAMA*. 323: 2329–2330, 2020. doi:10.1001/jama.2020.6825.
6. **Archer SL**, **Sharp WW**, **Weir EK.** Differentiating COVID-19 pneumonia from acute respiratory distress syndrome (ARDS) and high altitude pulmonary edema (HAPE): therapeutic implications. *Circulation* 142: 101–104, 2020. doi:10.1161/CIRCULATIONAHA.120.047915.
7. **Lins M**, **Vandevenne J**, **Thillai M**, **Lavon BR**, **Lanclus M**, **Bonte S**, **Godon R**, **Kendall I**, **De Backer J**, **De Backer W.** Assessment of small pulmonary blood vessels in COVID-19 patients using HRCT. *Acad Radiol* 27: 1449–1455, 2020. doi:10.1016/j.acra.2020.07.019.

8. **Robles JP**, **Zamora M**, **Adan-Castro E**, **Siqueiros-Marquez L**, **Martinez de la Escalera G**, **Clapp C.** The spike protein of SARS-CoV-2 induces endothelial inflammation through integrin α5β1 and NF-κB signaling. *J Biol Chem* 298: 101695, 2022. doi:10.1016/j.jbc.2022.101695.
9. **Morris MF**, **Pershad Y**, **Kang P**, **Ridenour L**, **Lavon B**, **Lanclus M**, **Godon R**, **De Backer J**, **Glassberg MK.** Altered pulmonary blood volume distribution as a biomarker for predicting outcomes in COVID-19 disease. *Eur Respir J* 58: 2004133, 2021. doi:10.1183/13993003.04133-2020.
10. **Thillai M**, **Patvardhan C**, **Swietlik EM**, **McLellan T**, **De Backer J**, **Lanclus M**, **De Backer W**, **Ruggiero A.** Functional respiratory imaging identifies redistribution of pulmonary blood flow in patients with COVID-19. *Thorax* 76: 182–184, 2021. doi:10.1136/thoraxjnl-2020-215395.
11. **Yang J**, **Ma S**, **Sun Q**, **Tan W**, **Xu M**, **Chen N**, **Zhao D.** Improved Hessian multiscale enhancement filter. *Biomed Mater Eng* 24: 3267–3275, 2014. doi:10.3233/BME-141149.
12. **Tan CW**, **Low JGH**, **Wong WH**, **Chua YY**, **Goh SL**, **Ng HJ.** Critically ill COVID -19 infected patients exhibit increased clot waveform analysis parameters consistent with hypercoagulability. *Am J Hematol* 95: E156–E158, 2020. doi:10.1002/ajh.25822.
13. **Kobayashi J**, **Murata I.** Nitric oxide inhalation as an interventional rescue therapy for COVID-19-induced acute respiratory distress syndrome. *Ann Intensive Care* 10: 61, 2020. doi:10.1186/s13613-020-00681-9.
14. **Tang N**, **Bai H**, **Chen X**, **Gong J**, **Li D**, **Sun Z.** Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost* 18: 1094–1099, 2020. doi:10.1111/jth.14817.