Received: 22 June 2020 | Accepted: 21 July 2020

DOI: 10.1002/jmv.26342

SHORT COMMUNICATION

JOURNAL OF MEDICAL VIROLOGY WILEY

SARS-CoV-2 infection causes pulmonary shunt by vasodilatation

Anderson Brito-Azevedo[1,2,3] | Eduardo Costa Pinto[1,4] | Gabriel Angelo de Cata Preta Corrêa[4] | Eliete Bouskela[3]

[1]Transplant Department, Liver and Pancreas Unit, São Lucas Hospital, Rio de Janeiro, Brazil

[2]Internal Medicine Department, Adventista Silvestre Hospital, Rio de Janeiro, Brazil

[3]Biomedical Department, Laboratory for Clinical and Experimental Research on Vascular Biology (BioVasc), State University of Rio de Janeiro, Rio de Janeiro, Brazil

[4]Intensive Care Department, Intensive Care Unit, Panamericano Hospital, Rio de Janeiro, Brazil

Correspondence
Anderson Brito-Azevedo, Transplant Department, Liver Transplant Unit, Adventista Silvestre Hospital. Ladeira do Ascurra, 274-Cosme Velho, Rio de Janeiro, RJ, 22241-280.
Email: andersonbrito.a@gmail.com

Abstract

Patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may present a significant hypoxemia. The exactly mechanism of such hypoxemia in patients with coronavirus disease 2019 (COVID-19) is not well described. It has been suggested that microthrombosis contributes to this mechanism, increasing pulmonary dead space. However, dead spaces would not be sensible to oxygen supplementation, and also, enlargement of pulmonary vessels it has been evidenced. Shunt mechanism by vasodilatation, instead, could explain decubitus dependence in oxygenation by blood redistribution as observed in these patients, and moreover, would be more sensible to oxygen supplementation than dead spaces. We hypothesized that SARS-CoV-2 causes an intrapulmonary vascular dilatation (IPVD), determining a shunt mechanism by vasodilatation. We performed contrast-enhanced transthoracic echocardiography to search IPVD shunt in patients with confirmed COVID-19, hospitalized in an intensive care unit. Ten patients were recruited; one patient was excluded due to low quality of echocardiographic image, and nine patients were included. IPVD was found in seven (78%) patients, with different grades, including patient with normal compliance and the one without invasive ventilation. We demonstrated that shunt by IPVD is present among patients with COVID-19, and this mechanism is probably implicated in significant hypoxemia observed.

KEYWORDS

ACE-2, angiotensin-converting enzyme, ARDS, bradykinin, coronavirus, COVID-19

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) patients present significant hypoxia since the beginning of the disease, with marked dependence of oxygen supplement along its duration. Heterogeneous pulmonary characteristics were described among patients with respiratory failure by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and different phenotypes of adult respiratory distress syndrome (ARDS) were suggested.[1] Classical ARDS presents a widespread occlusion of the pulmonary microvasculature.[2] An autopsy study including patients with COVID-19 has suggested the presence of microthrombosis, which would lead to an increase in dead spaces, contributing to worsening the hypoxemia.[3] Noteworthy, dead spaces would not be sensible to an increase/reduction in oxygen supplementation; instead, shunt mechanism by vasodilatation could explain decubitus dependence in oxygenation by blood redistribution as observed in these patients. Also, the exactly mechanism of hypoxemic patients without dyspnea and preserved compliance continues to need more explanation as well.

Computed tomography findings show an enlargement of pulmonary vessels[4] possibly caused by vasodilatation, responsible, at least partially, for the important hypoxia, possibly due to vascular shunt mechanism. Considering that vasodilatation prevails, blood flow would not be homogeneously oxygenated, as observed in other pathologies, like hepatopulmonary syndrome in cirrhosis.

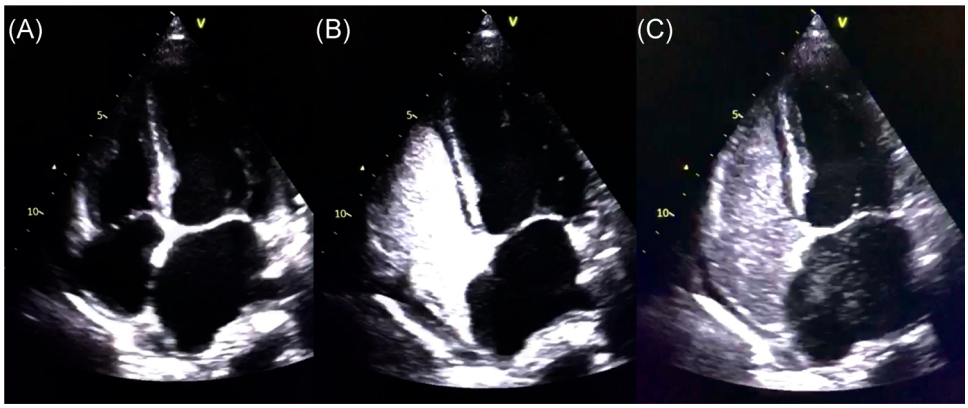

FIGURE 1 Intrapulmonary vascular dilatation (IPVD) grade IV diagnosis by contrast-enhanced transthoracic echocardiography. A, transthoracic echocardiography before contrast injection; B, microbubbles contrasting the right side of heart immediately after contrast injection; C, large number of bubbles in left atrium modifying echogenicity, after three heartbeats, determining a grade IV IPVD

We have hypothesized that SARS-CoV-2 causes an important intrapulmonary vascular dilatation (IPVD), with a shunt mechanism.

2 | METHODS

2.1 | Patients

We have performed an observational study in serially enrolled patients with confirmed COVID-19 hospitalized in an intensive care unit (ICU) of Rio de Janeiro hospital, from 24 to 27 April 2020. Liver cirrhosis was excluded by clinical exam, laboratory/image. Clinical, laboratory and mechanical ventilation parameters were collected. Duration of disease was obtained from clinical history, by the first symptom presented. Static pulmonary compliance was calculated using the following formula: tidal volume/plateau pressure−positive end-expiratory pressure.

2.2 | IPVD evaluation by contrast-enhanced transthoracic echocardiography

IPVD was searched by contrast-enhanced transthoracic echocardiography performed by injecting agitated physiological saline intravenously, producing microbubbles that contrast during echocardiography. In absence of right-to-left shunt, the microbubbles are absorbed in alveoli. Immediate visualization of contrast in the left atrium (LA) (within three heartbeats) indicates intracardiac shunting. Delayed appearance (three to six heartbeats) is a positive test for IPVD (Figure 1). Shunt was graduated as previously described[5]: Grade I, no microbubbles in the LA; grade II, few isolated bubbles in LA without changes in echogenicity; grade III, sizeable number of isolated bubbles in LA without changes in echogenicity; grade IV, large number of bubbles in LA with modified echogenicity; grade V, extensive number of bubbles changing echogenicity, with signal less dense

TABLE 1 Clinical characteristics and intrapulmonary shunt grade of patients

Patient	Gender	Age	BMI	Duration of disease, d	Vaso-pressor	Comorbidities	Invasive ventilation	Pulmonary compliance (mL/cm H_2O)	IPVD Grade
#1	M	43	29	10	YES	None	YES	27	V
#2	M	41	30	11	NO	Hypertension Diabetes	NO	NA	III
#3	M	47	32	7	YES	Hypertension Diabetes	YES	48	III
#4	F	71	23	13	NO	Hypertension Diabetes	YES	35	IV
#5	F	51	29	4	YES	Hypertension Diabetes	YES	23	I
#6	M	49	30	2	YES	None	YES	45	V
#7	M	33	24	7	NO	None	YES	32	II
#8	M	56	26	5	YES	None	YES	76	II
#9	F	58	25	Unknown	YES	Hypertension Cancer	YES	30	I

Abbreviations: BMI, body mass index; FiO_2, fraction of inspired oxygen; IPVD, intrapulmonary vascular dilatation; NA, not applicable; PEEP, positive end expiratory pressure; P/F, ratio of partial pressure arterial oxygen and fraction of inspired oxygen.

than in the right atrium and grade VI, the same amount of microbubbles on both atria, with similar echogenicity.

3 | RESULTS

Ten patients were recruited. One patient was excluded due to low quality of echocardiographic image. Eight patients were in invasive ventilation and the one without it was in oxygen supplementation, with 15 L/minute. Among the patients included, seven (78%) presented IPVD, including the one without invasive ventilation. Basal characteristics and IPVD grade are displayed on Table 1.

4 | DISCUSSION

We have shown that patients with COVID-19 present shunt by IPVD. Although our study was performed only to investigate the presence of a shunt mechanism by IPVD, we could suggest that this mechanism may contribute to hypoxemia along different disease stages. Despite the fact that our study was performed in ICU hospitalized patients, it is possible that this mechanism may be present since the beginning of the disease, contributing to the initial hypoxemia. Noteworthy, cirrhotic patients with hepatopulmonary syndrome, a model of disease with IPVD, also present significant hypoxemia despite the few symptoms. COVID-19 patients have, in addition, the inflammatory component with progression of disease contributing to worsening of hypoxemia and respiratory failure.

Our study has some limitations: first, we performed it in a small number of patients, however, they were consecutively included and we were surprised with the high prevalence of IPVD; second, we did not perform any correlation between IPVD grade and hypoxia, since it was not our aim and also, it should be done in a larger number of patients in different disease phases. Even with oxygen parameters, patients with ICU in mechanical ventilation have many confounding factors that should be adequately controlled in a larger number of patients by a multivariate analysis. Nevertheless, the one patient without mechanical ventilation in our study presented IPVD grade III, suggesting that the mechanism could be present since the beginning of the hypoxemic phase of the disease. Larger studies including different disease stages should be urgently performed. Another question raised with our findings was: why would these patients present this vasodilatation?

According to our hypothesis, since SARS-CoV-2 binds to angiotensin-converting enzyme (ACE-2) localized in pneumocytes, the viral endocytosis reduces ACE-2 availability on cell surface. Since ACE-2 is responsible for metabolization of angiotensin-II (AT-2)[6] one should expect a rise on AT-2 levels that has low vasoconstrictor potential on pulmonary vessels.[7] According to general enzymatic kinetics, high AT-2 levels elicited by ACE-2 reduction would downregulate ACE, an enzyme that converts AT-1 to AT-2 and is also responsible for bradykinin degradation, an inflammatory mediator with strong vasodilatation role that could probably be implicated on observed IPVD in these patients (Figure 1). Interestingly, recent evidence describe pulmonary vascular angiogenesis in patients with COVID-19,[3] and bradykinin is also a recognized mediator in vascular permeability and angiogenesis.[8]

We believe that our study brings to light a novel pathophysiological process about COVID-19 disease and largest studies including bradykinin determination must be performed. Treatment options, as bradykinin inhibition, should be considered as soon as more evidence emerge.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ORCID

Anderson Brito-Azevedo http://orcid.org/0000-0002-3720-4387

REFERENCES

1. Gattinoni L, Coppola S, Cressoni M, Busana M, Chiumello D. COVID-19 does not lead to a "Typical" acute respiratory distress syndrome. *Am J Respir Crit Care Med. Mar*. 2020;201:30-1300. https://doi.org/10.1164/rccm.202003-0817LE
2. Rossaint R, Falke KJ, López F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. *N Engl J Med*. 1993;328(6):399405-399405. https://doi.org/10.1056/NEJM199302113280605
3. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. *N Engl J Med*. 2020;383:120-128. https://doi.org/10.1056/NEJMoa2015432
4. Ye Z, Zhang Y, Wang Y, Huang Z, Song B. Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. *Eur Radiol. Mar*. 2020;30:19-4389. https://doi.org/10.1007/s00330-020-06801-0
5. Aller R, Moya JL, Moreira V, et al. Diagnosis and grading of intrapulmonary vascular dilatation in cirrhotic patients with contrast transesophageal echocardiography. *J Hepatol*. 1999;31(6):1044-1052.
6. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with COVID-19. *N Engl J Med*. 2020;382(17):1653-1659. https://doi.org/10.1056/NEJMsr2005760
7. Mandel MJ, Sapirstein LA. Effect of angiotensin infusion on regional blood flow and regional vascular resistance in the rat. *Circ Res*. 1962; 10:807-816.
8. Ishihara K, Kamata M, Hayashi I, Yamashina S, Majima M. Roles of bradykinin in vascular permeability and angiogenesis in solid tumor. *Int Immunopharmacol*. 2002;2(4):499-509. https://doi.org/10.1016/s1567-5769(01)00193-x

How to cite this article: Brito-Azevedo A, Pinto EC, Corrêa GAdCP, Bouskela E. SARS-CoV-2 infection causes pulmonary shunt by vasodilatation. *J Med Virol*. 2021;93:573–575. https://doi.org/10.1002/jmv.26342