Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
COVID-19-related complications and decompression illness share main features.
Could the SARS-CoV2-related complications rely on blood foaming?

Pierre A. Denis

Occupational Medicine, Mutualité Sociale Agricole (M.S.A.), 12 rue de Paimpont 22025 Saint-Brieuc Cedex, France

ARTICLE INFO

Keywords:
COVID-19
Decompression illness
Angiotensin II
SARS-CoV
Oxygen
Red blood cells

ABSTRACT

A study by Saraiva et al. (2011) demonstrated the presence of Angiotensin II receptors on the erythrocyte membrane. This little-known information should be deemed as crucial as the SARS-CoV-2 relationships with oxygen saturation and the Renine Angiotensin System but it currently remains unexploited.

The pulmonary and cardiovascular systems are involved in any typical complications of COVID-19 but numerous other unrelated symptoms may occur. To fill the gap, we shall first emphasize some similarities between the complications of this infectious disease and Decompression Illness (DCI), which involves bubble formation.

We theorized that the Angiotensin II clearance by the red blood cells could trigger the release of its oxygen content in the bloodstream. The resulting foam would worsen the widespread endotheliitis, worsen the gas exchange, trigger the coagulation process, the inflammation process and the complement pathway as typically occurs in DCI. At the end, we propose a plausible mechanism.

Introduction

According to Kuba et al. in 2006, one mystery of SARS-CoV is why, in contrast to the other coronaviruses infecting humans, infections with the SARS-CoV trigger severe lung disease with such high mortality [1]. Eighteen years after the SARS outbreak, this assumption unfortunately remains true for SARS-CoV-2. We shall therefore propose a novel hypothesis to better understand the COVID-19 pathophysiology. As a matter of fact, an astounding amount of similarities between Decompression Illness (DCI) and COVID-19-related complications have attracted our attention.

In occupational medicine, we deal with specific work conditions such as caisson workers. DCI (or caisson disease) covers both arterial gas embolism, in which alveolar gas or venous gas emboli are introduced into the arterial circulation, and decompression sickness, which is caused by in-situ bubble formation from dissolved inert gas. Both syndromes can occur in divers, compressed air workers, aviators, and astronauts, but arterial gas embolism also arises from iatrogenic causes unrelated to decompression [2].

Symptoms of pulmonary DCI are similar to those of a thrombotic pulmonary embolism; specifically, subterminal pain, cough, and dyspnea, which may progress quickly to pulmonary edema, respiratory failure, right ventricular dysfunction, and cardiovascular collapse [3].

Results

Pulmonary and cardiovascular systems

The patients with Covid-19 pneumonia, fulfilling the Berlin criteria of ARDS, present an atypical form of the syndrome [4]. The cardiovascular system is also affected, with complications including myocardial injury, myocarditis, acute myocardial infarction, heart failure, dysrhythmias, venous thromboembolic events [5] and stroke [6]. Both large and small vessels are affected with manifestations ranging from pulmonary embolism to purpuric lesions on extremities [7].

There are several hypotheses as to the mechanism of cardiovascular symptoms. SARS-CoV-2 infection facilitates the induction of a widespread endothelium dysfunction such as endotheliitis in several organs as a direct consequence of viral involvement [8].

Interestingly, there is evidence of endothelial dysfunction in diving [9] as in decompression bubbles in animals. In addition to mechanically obstructing blood flow through the pulmonary vasculature, vascular bubbles may directly contact and damage the vascular endothelium [10]. After hyperbaric decompression, bubbles in the body may be located within tissues or carried along with the bloodstream [11]. The interface between the blood and the bubbles produces red cell sludging in the microcirculation, causes protein denaturation, increases platelet
adhesiveness, and promotes the formation of lipid emboli [12]. Vascular bubbles may cause direct blockage, aggregate platelets and red blood cells, and trigger the coagulation process, causing local and downstream clotting [13].

Vascular bubbles activate the inflammatory cascade, which can result in or contribute to pulmonary edema and pulmonary hypertension [14]. Mesenteric injury and organ infarction such as stroke are typical sequelae of severe DCI [3,15].

We suggest that previous infectious endotheliitis might be amplified by bubbles. Finally, in COVID-19, stroke, acute myocardial infarction, findings of thrombi in small pulmonary arterioles of lung parenchyma and exudative/proliferative diffuse alveolar damage are consistent with the above findings in DCI.

**Radiological findings**

The radiological findings in COVID-19 are ground-glass opacity [16] and bilateral patchy shadows. In severe form of DCI of chest involvement, radiological results are similar [17].

**Biological findings**

Numerous biological anomalies affect COVID-19 patients. Complete blood counts revealed lymphocytopenia in most hospitalized cases. According to researchers, multiple mechanisms work together to cause lymphopenia [18]. Less common are elevated levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK), and d-dimer [19]. Acute decompression stress (in rats) has also been shown to cause a transient lymphocytic leucopenia [20] and to result in significantly increased ALT values [21]. There is also evidence of rhabdomyolysis (high CK levels) secondary to arterial gas embolism in skeletal muscles [22].

Finally, COVID-19 and DCI biological features share a number of anomalies.

**Immune system and inflammatory features**

The pathogenesis in the later stages of SARS-CoV and SARS-CoV-2 infections results not only from direct viral toxicity but also from immune dysregulation and hyperactivity (IL-6, TNF-α) [23]. Furthermore, the complement system plays a vital role in the host immune response to SARS-CoV infection [24].

Interestingly, the lung tissue mRNA levels of TNF-α, IL-1β and IL-6 were significantly increased at 0.5 h after simulated fast buoyancy ascent escape in an animal experiment [25]. In vitro, plasma samples incubated with air bubbles activated complement pathway (C3a and C5a) [26].

Eventually, there is an argument that the COVID-19-related “cytokine storm” [23] might be related to a nucleation of bubbles in the blood (foaming process). Moreover, there is evidence that bubbles activate the inflammatory cascade [25], which could explain COVID-19 hyper-inflammation.

Vascular and vasculitic skin changes including petechiae, purpura, ecchymosis, livedoid lesions, have been described in mostly pediatric COVID-19 patients. COVID-19 may show signs of small blood vessel occlusion such as petechiae or tiny bruises [27]. It is noteworthy that livedoid eruptions and rashes are typical skin manifestations seen in divers [3]. Hence, nucleation of bubbles in the skin microvasculature could be involved in COVID skin manifestations.

**Discussion**

The COVID-19-related complications and decompression illness strikingly bear shared features. We have revealed an astounding amount of similarities regarding the clinical but also radiological, biological, immunological and finally humoral features. We believe that the vascular abnormalities and the hyper-inflammatory parameters measured in various COVID-19 organs may be related to the systemic toxic effects of bubbles in the bloodstream elicited by SARS-CoV2 infection. Hereafter, we shall provide a possible mechanism in order to explain how bubbling could occur in COVID-19 as it is obvious that no decompression arises.

Methemoglobinemia occurs when the redox balance of the iron in the hem group is disturbed. In this condition, the patient might experience a “refractory hypoxemia” and COVID-19 critical cases also experience refractory hypoxemia [28]. The analogy with methemoglobinemia suggests that the complication stage of COVID-19 would be secondary to a disturbance in hemoglobin. We shall consequently put forward the hypothesis of a deregulation in the affinity of COVID-19 patient hemoglobin.

Firstly, there is evidence that red cells express Angiotensin II receptors (AT1 and AT2) [29]. This little-known information should be deemed as crucial as the SARS-CoV-2 relationships with oxygen saturation and the Renine Angiotensin System [23] but it currently remains unexploited. Thus and according to Nobre et al. in 2019, there are no studies deciphering the effect of Angiotensin II and its receptors on the red blood cell membrane [30].

SARS-CoV and SARS-CoV-2 bind to ACE2, a metalloenzyme normally responsible for the degradation of Angiotensin II, which down-regulates ACE2 expression and therefore disturbs Angiotensin II clearance. In an animal study, spike protein of former SARS-CoV in mice led to a significant increase in Angiotensin II levels in the lung tissue [1] and recent findings indicate that it is also true in SARS-CoV-2 human infection. Red cells might therefore carry out the clearance of Angiotensin II during the course of the illness.

Body temperature, 2,3-BPG level, and PCO₂ are well-known parameters that modulate hemoglobin affinity. We propose that a high level of Angiotensin II suddenly shifts the dissociation curve of hemoglobin to the right during the red cell transit in the lungs, through an unknown molecular mechanism. In lungs, the oxygen load would be normal but the Angiotensin-II-mediated shift would lead to an early (and pathological) oxygen release. For a limited fraction of blood volume, the release would therefore occur in the arterial tree (lungs, heart, brain, liver, kidneys) and not in the capillary beds. The blood would be locally supersaturated and would eventually bubble.

The median time from first symptom to hospital admission (7·0 days) and to ARDS (8·0 days) [31] is consistent with a time-dependent accumulation of foam in the vasculature and onto the endothelial areas.

In other tissues that exhibit ACE2 receptors, the sudden shift in the dissociation curve would produce a surge in free O₂, giving rise to DCI-like symptoms. The same effect could result in a foaming process in any ACE2-containing tissue (see picture) Fig. 1.

Last, COVID-19 patients with hypertension comorbidity who are taking Angiotensin II Receptor Blockers (ARBs) as anti-hypertension drugs may be less likely to develop severe lung disease compared to patients who take no anti-hypertension drugs [32]. This observation is consistent with the suggested mechanism.

A case study [33] recently reported successful applications of hyperbaric oxygen treatments (HBOTs) in COVID-19, HBOT being the standard treatment in DCI. We suggest that future controlled-clinical trials explore the potential usefulness of HBOT among COVID-19 patients with respiratory conditions.

**Conclusion**

This paper deals with the theoretical potential possibility of a critical biophysical event during COVID-19, namely bubble nucleation or foaming.

Doppler ultrasonography and echocardiography are valuable tools for researching into venous gas emboli and are urgently needed to assess the previous assumptions. At the end, spectrophotometry assays of
Angiotensin II-binding red cells are needed to assert the above assumptions.

We would like to thank the editor for putting this hypothesis forward in publishing this paper. It is the authors' sincere hope and intent that this novel and original theoretical point of view be largely shared.

Credit author statement

I am the sole author of the manuscript.

Role of funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics committee approval

Irrelevant.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

I am grateful to Cécile Jones for her technical support concerning the English language.

References

[1] Kuba K, Imai Y, Rao S, Jiang C, Penninger JM. Lessons from SARS: control of acute lung failure by the SARS receptor ACE2. J Mol Med 2006;84(10), pp. 814-820.84.
[2] Vann RD, Butler FK, Mitchell AJ, Moon RE. Decompression illness. Lancet 2011;377(9760):153-64.
[3] Hoxdall EJ, Cooper JS. Chokes (Pulmonary Decompression Sickness). NCBI. [Online] 2019. [Cited: 05 4, 2020.] https://www.ncbi.nlm.nih.gov/books/NBK430898/.
[4] Gattinoni L, Coppola S, Cressoni M, Busana M, Chiurimello, D. Covid-19 does not lead to a “typical” acute respiratory distress syndrome; 2020.
[5] Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19; 2020.
[6] Mao L, Wang M, Chen S, et al. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study; 2020.
[7] Klok FA, Krup MHLA, van de Veer NM., et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19; 2020.
[8] Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. 2020;395(10234):1471.
[9] Bruzak AO, Duplancic D, Volic Z, et al. A single air dive reduces arterial endothelial function in man. J Physiol 2005;566(3):901-6.
[10] Nossum V, Hjelde A, Brubakk AO. Small amounts of venous gas embolism cause delayed impairment of endothelial function and increase polymorphonuclear neutrophil infiltration. Eur J Appl Physiol 2002.
[11] Papadopoulos V, Eckerlej SJ, Balestra C, Karapantsios TD, Tang, MX. A critical review of physiological bubble formation in hyperbaric decompression 2013;191:22–30.
[12] Elliot DH, Hallenbeck JM, Bove AA. Acute decompression sickness 1974(3047890):1193-9.
[13] Spira A. Diving and Marine Medicine Review. Part II: Diving Diseases. 1999(3):190-98.
[14] Żurewicz CV, Müller NL, Abboud RT, Lepawsky M. Noncardiogenic pulmonary edema caused by decompression sickness: rapid resolution following hyperbaric therapy. Radiology 1987.
[15] Vann RD (editor). The Physiological basis of decompression: an overview; 1989. p. 1-10.
[16] Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis 2020;20:425–34.
[17] Lee SW, Shim SS, Choi J, Kim Y. Pulmonary involvement in decompression sickness of a self contained underwater breath apparatus diver. Korean J Sports Med 2013;31(1):30-3.
[18] Tan L, Wang Q, Zhang D, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study; 2020;5(1):pp. 1–3.
[19] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult
inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020.

[20] Jacey MJ, Tappan DV, Ritzler KR. Hematologic responses to severe decompression stress. Aerosp Med 1974;45:417–21.

[21] U’Albabe A, Kusmic C, Matteucci M, et al. Gas embolization of the liver in a rat model of rapid decompression. Am J Physiol Regulat, Integrative Comparative Physiol 2010.

[22] Hibi A, Kamiya K, Kasugai T, et al. Acute kidney injury caused by decompression illness successfully treated with hyperbaric oxygen therapy and temporary dialysis. CEN Case Reports 2017.

[23] Ghebawti M, Wang K, Viveiros A, et al. Angiotensin converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system. Circulat Res 2020.

[24] Li G, Fan Y, Lai Y, et al. Coronavirus infections and immune responses 2020;92(4):424–432.

[25] Wang HT, Fang YQ, Ibao XC, et al. Expression changes of TNF-α, IL-1β and IL-6 in the rat lung of decompression sickness induced by fast buoyancy ascent escape. Undersea Hyperb Med 2015;42(1):23–31.

[26] Ward CA, McCullough D, Fraser WD. Relation between complement activation and susceptibility to decompression sickness. J Appl Physiol 1987;62(3):1160–6.

[27] Türsen Ü, Türsen B, Letti T. Coronavirus-days in dermatology. Dermatol Ther 2020.

[28] Matthay MA, Aldrich JM, Gotts JE. Treatment for severe acute respiratory distress syndrome from COVID-19; 2020.

[29] Saraiva VB, de Souza Silva L, Ferreira-DaSilva CT, et al. Impairment of the Plasmodium falciparum erythrocytic cycle induced by Angiotensin peptides. PLoS ONE 2011;6(2).

[30] Nobre GC, Alves LM, Junior BC. Evaluation of the effects of Angiotensin II on normal and sickle cell. PLoS ONE 2011;6(2).

[31] Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. Jama 2020;323(11):1061–7.

[32] Liu Y, Huang F, Xu J, et al. Anti-hypertensive Angiotensin II receptor blockers associated to mitigation of disease severity in elderly COVID-19 patients. medRxi 2020.

[33] Harch PG. Hyperbaric oxygen treatment of novel coronavirus (COVID-19) respiratory failure. Med Gas Res [Epub ahead of print]. [Online] [Cited: 05 03, 2020.] http://www.medgasres.com/preprintarticle.asp?id=282177.