Medical Hypotheses 144 (2020) 109918

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

COVID-19-related complications and decompression illness share main features.
Could the SARS-CoV2-related complications rely on blood foaming?

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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 embolus; specifically, substernal 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

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https://doi.org/10.1016/j.mehy.2020.109918
Received 8 May 2020; Accepted 28 May 2020

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 heme 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-kown 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 downregulates 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 PCO_2 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 endothelium areas.

In other tissues that exhibit ACE2 receptors, the sudden shift in the dissociation curve would produce a surge in free O_2, 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

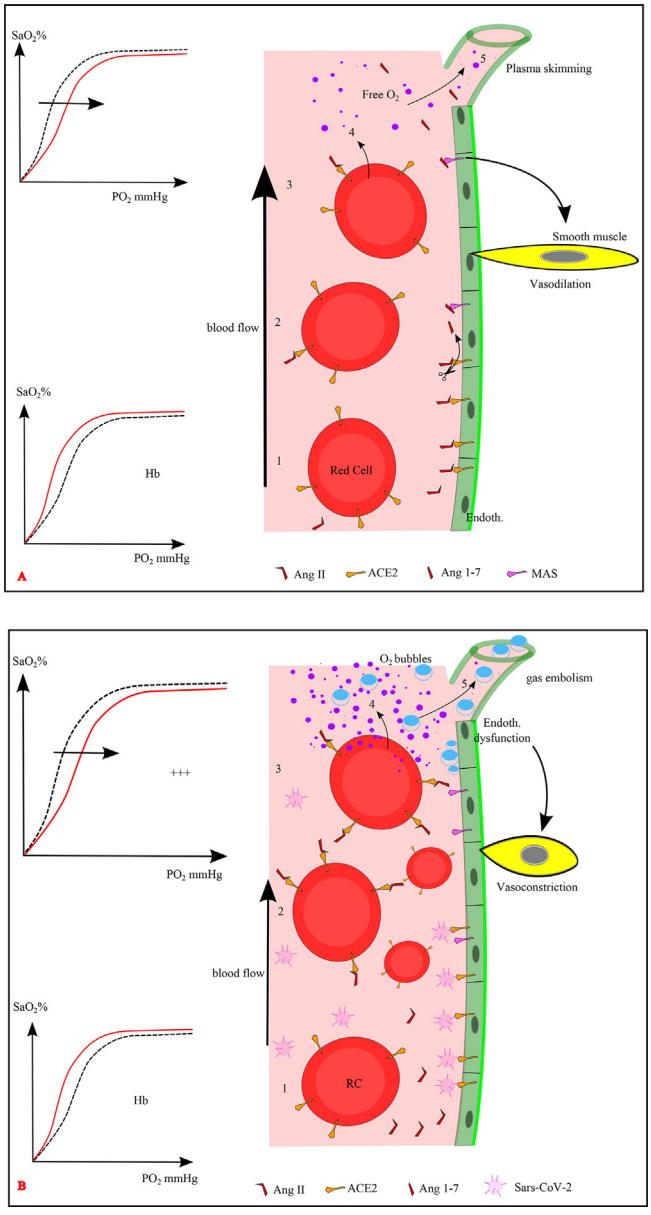

Fig. 1. A. Physiological condition (hypothesis).
In a tissue experiencing a sustained oxygen demand (contractile bowels, active skeletal muscles, myocardic muscle, metabolically active brain and renal tissues), we depicted a blood vessel during an Ang 1–7 – mediated endothelium vasorelaxation (MAS receptor). Ang 1–7 is produced as a result of endothelial ACE2 peptidase activity on Ang II.
Ang II binds to the red blood cell ACE2. We propose that it triggers a shift on the dissociation curve of hemoglobin to the right. This speculative mechanism would provide a supply in free O_2 in the cell free capillaries, a process called "plasma skimming", which results in a reduced hematocrit on the downstream vessels from the first bifurcation.
B. COVID-19 condition (hypothesis).
In a tissue infected by SARS-CoV-2, virus particles are attached to endothelial ACE2 and downregulate ACE2 expression, reducing Ang II clearance.
When the tissue is at rest, capillary beds are more or less shut and the remaining vessels carry a high load of red cells (high hematocrit). As Ang II is not cleared, it could bind to the red cell Ang II receptors. As explained above, we propose that it triggers a shift on the dissociation curve of hemoglobin to the right. This speculative mechanism would provide an overload in free O_2 but would occur in a blood flow overwhelmed with fully oxygenated red cells, moreover in a tissue at rest (vasoconstriction). This would involve oxygen supersaturation hence the bubble nucleation. Foaming would worsen the widespread (infectious) endotheliitis (depicted as endothelial dysfunction), worsen the gas exchange, trigger the coagulation process, the inflammation process and the complement pathway, as occurs in decompression illness.

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.

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