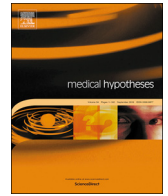




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## Hypoxemia in COVID-19 patients: An hypothesis

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### ABSTRACT

The current SARS-Cov-2 virus pandemic challenges critical care physicians and other caregivers to find effective treatment for desperately ill patients — especially those with sudden and extreme hypoxemia. Unlike patients with other forms of Acute Respiratory Distress Syndrome, these patients do not exhibit increased lung stiffness or dramatic dyspnea, even in the presence of arterial blood oxygen levels lower than that seen normally in mixed venous blood. Urgent intubation and mechanical ventilation with high inflation pressures and raised inhaled oxygen concentration have proved unhelpful or worse, but why? Our Hypothesis is that sudden opening of a previously undetected probe-patent foramen ovale (PPFO) may explain this mystery. As hypoxemia without acidosis is a rather weak stimulus of dyspnea or increased ventilation, and opening of such an intracardiac shunt would not worsen lung mechanical properties, the absence of dramatic symptom changes would not be surprising. We point out the high frequency of PFO both in life and at autopsy, and the physiological evidence of large shunt fractions found in Covid-19 patients. Published evidence of hypercoagulability and abundant evidence of pulmonary emboli found at autopsy are in accord with our hypothesis, as they would contribute to raised pressure in the pulmonary arteries and right heart chambers, potentially causing a shunt to open. We review the interaction between viral corona spike protein and ACE-2 receptors present on the surface of alveolar lining cells, and contribution to hypercoagulability caused by the spike protein. Search for an open PFO after a large drop in arterial oxygen saturation can be performed at the bedside with a variety of well-established techniques including bedside echocardiography, nitrogen washout test, and imaging studies. Potential treatments might include balloon or patch closure of the shunt, and various drug treatments to lower pulmonary vascular resistance.

### Introduction

During the past 7 months the disastrous world wide pandemic of infection with SARS-Cov-2 virus has sickened more than 6.8million people and caused death in more than 362,000 as of June 6, 2020. In the United States the numbers are 1.9 million known cases and 110,000 deaths [1]. Multiple organ systems are involved [2], but nearly all autopsy reports mention extensive lung injury, as seen with other causes of ARDS. Several recent autopsy reports stress hypercoagulability, with large and small pulmonary emboli.

For bedside clinicians a big challenge has been the abrupt and unanticipated appearance of severe hypoxemia without obvious cause. Saturation levels are described as “plummeting”, to levels as low as 50% saturation [3]. Dyspnea is not prominent, and lung stiffness has not increased, as would be expected with the hypoxemia of typical ARDS [4]. The profound hypoxemia may not respond to non-invasive oxygen therapy [3]. In half of Gattinoni’s first sixteen patients, the hypoxemia was attributable to large “shunt fractions”, even exceeding 50% of cardiac output. One patient breathing room air had an arterial oxygen tension of 55 mmHg, corresponding to an O<sub>2</sub> saturation of approximately 80% and a shunt fraction of 50%. Since oxygen extraction from coronary blood flow at rest is normally about 3/4 of the available oxygen content, blood entering the coronary circulation with only 80% saturation might bring disastrously low blood pO<sub>2</sub> to

myocardial tissue dependent on end-of-the-line vessels. Reports of young patients suffering myocardial infarction without coronary artery plaques found at subsequent autopsy may reflect the severity of this hypoxemia [5].

This severe and abrupt hypoxemia has often led to urgent intubation and mechanical ventilation, but without survival benefit in a disturbingly large fraction of cases, even with additional use of extra-corporeal membrane oxygenation ECMO [6–8]. Calls for re-evaluation of the indications for mechanical ventilation in these patients are increasing, as evidence mounts of futility and even iatrogenic injury [4]. There is widespread recognition that without greater chances of recovery patients are not likely to welcome invasive ventilation, because of inability to communicate with caregivers or loved ones in their final days of life [3]. Optimum alternative treatment has not yet been identified.

Specialists in pulmonary and intensive care medicine are too few to satisfy the urgent need for their services in various hot spots around the globe—and the supply may need to be supplemented in many places by caregivers less practiced in these disciplines [9]. We believe it is timely to review what is presently known about the pulmonary aspects of this illness and emphasize the possibility that severe and sudden hypoxemia in Covid-19 patients might be due to abrupt opening of a right-to-left inter-atrial shunt through a probe-patent foramen ovale. Establishing such a diagnosis may not yet always lead to life-saving treatment, but if futile treatment can be avoided while better options are developed,

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patients may still benefit.

## Clinical background

Roughly 80% of patients infected with SARS-Cov-2 do not require hospital care, and still fewer require intensive care. Among those who do, the odds of recovery from intubation, sedation, paralysis and mechanical ventilation are grim [6–8]. The disease severity and chances of recovery are dramatically worse with increasing age [10]. Patients may gradually develop pneumonia detected by imaging with little dyspnea or phlegm, or may be desperately ill from early in their hospital course.

Mason [11] has provided an analysis of the clinical stages and cell biology that evolve in lungs infected by SARS-Cov-2 and other coronaviruses. Initially the virus attacks cells of the nose and upper airway [12] then invades the lower airways, and finally reaches the peripheral parts of the lungs [13]. This third stage can be recognized in CT scans of the chest. Like previous coronavirus outbreaks, this one involves viral attack on cell surface ACE2 enzyme receptors, which then permit viral invasion of the cell [14,15]. ACE2 receptors are prominent on the surface of alveolar lining cells, and Coronavirus particles have been seen in alveolar spaces and in Type 2 alveolar lining cells in patients studied during the present pandemic, as have alveolar flooding and hyaline membranes [16]. Pulmonary surfactant is secreted by Type 2 alveolar lining cells, and extensive viral destruction of those cells could lead to ARDS, a condition similar to that seen in babies born too immature to secrete surfactant.

Hypoxemia in the large majority of patients can be treated successfully with prone positioning and non-invasive supplemental oxygen administered by nasal prongs, face masks, non-rebreathing masks, and continuous positive airway pressure systems including those converted from sleep therapy equipment (CPAP). Success with this form of therapy implies that a major contributor to the hypoxemia in such patients was regional mismatch of ventilation to perfusion. Impaired reflex hypoxic vasoconstriction could increase that mismatch. It is not yet clear what fraction of patients have hypoxemia that is not responsive to such treatments, but the average shunt fraction was 50% in the first sixteen patients reported by Gattinoni [4]. In half of their patients, the calculated shunt fraction was three times as large as the estimated fraction of lung that appeared airless based on CT scans, while in ARDS patients the shunt fraction is typically only 1.25 as great as the airless lung volume would predict. Hypoxic vasoconstriction would be expected to reduce this shunt fraction, not increase it above the normal mean  $V/Q$  ratio of one.

## Our hypothesis

The main objective of this paper is to draw attention to the possibility that severe atypical hypoxemia can result from opening a probable patent foramen ovale. Estimates of frequency of patent foramen ovale in the population vary, but even if it were as low as one percent, there will already have been more than 19,000 such patients ill with proven COVID-19 in the United States alone. However, an autopsy study of 965 hearts at the Mayo Clinic found an incidence twenty-five times higher [17]. With normal physiology, the higher pressure in the left atrium keeps the PPFO closed, but in the presence of pulmonary hypertension, right atrial pressure can exceed left atrial pressure. The PPFO may then open, sometimes leading to a large shunt of venous blood directly into the left atrium and peripheral circulation [18]. Failure of supplemental oxygen therapy to correct hypoxemia should thus raise the likelihood of an intra-thoracic shunt [19], including PPFO). Treatment of such a patient with mechanical ventilation will not close the shunt or correct the hypoxemia: it may make things worse due to the increased pulmonary vascular resistance and the barotrauma of high inflation pressures, and could produce still more leaky and wet lungs by excessive alveolar stretching [4]. Even if Type 2 alveolar lining cells have not yet been extensively damaged by the virus, the presence of leaked lung

fluid and protein into alveolar spaces will affect surfactant biophysics and contribute to greater work of breathing and to development of areas of atelectasis. These can function as intrapulmonary shunts.

## Supportive evidence

There are good reasons to suspect pulmonary hypertension in COVID-19 patients, starting with hypoxic constriction of pulmonary arteries. Abundant evidence from clinical hematology and pathology shows that severe coagulation disorders occur [20] with both large and small pulmonary clots [21–25]. Evidence from the SARS epidemic showed markedly increased activation of the Urokinase clotting pathway [26] and DIC is often present in COVID-19 patients, with thromboses in peripheral veins and multiple organs. Survival is inversely related to the intensity of the DIC and recovery from the illness is associated with recovery of coagulation indicators. Further, Poissy et al report increased pulmonary emboli in lungs of COVID-19 patients, seemingly out of proportion to peripheral clotting [23]. There is anecdotal evidence that use of tissue plasminogen activator brings immediate relief to some patients, but it's not yet clear if mortality is affected [27].

Reports of severe and even fatal strokes have appeared in COVID-19, including cases of young and middle-aged adults [28]. Some of these strokes in the young have been due to multiple emboli. This surprising finding may be a direct result of DIC, but could also reflect opening of patent foramen ovale with paradoxical cerebral embolization.

Several human coronaviruses use the ACE-2 metallo-protease enzyme as their receptor for cell entry, including the viruses causing SARS and COVID-19 [29,30]. ACE2 is a carboxypeptidase that regulates the balance between opposing effects of Angiotensin II and Angiotensin [1–7] by removing a single amino acid from the carboxyl end of Angiotensin II [31]. X-ray crystallography has shown images of the interaction between ACE2 and the viral receptor binding domains of both the SARS virus and SARS-CoV-2 virus [15,32]. The two binding domains are nearly identical in overall shape and binding site but differ antigenically [15,29,32]. Neutralizing antibodies against SARS would not likely be effective against SARS-CoV-2.

The active site of ACE2 lies within a cleft formed by the hinged region, and is thought to be critical for the homeostatic role of ACE-2 [33]. Exposure to nothing more than the binding domain of the SARS coronavirus Spike protein was sufficient to worsen lung injury in a mouse model of ARDS [30,34]. This effect was not seen in ACE-2 Knockout mice, nor in the presence of the Angiotensin II receptor blocking agent losartan [30,34]. A mutation of Spike protein (I507L) in another coronavirus strain (CoV-NL63) enhanced its ability to utilize the ACE2 receptor for infection, and converted it from being mildly pathogenic to one causing severe lower respiratory tract injury [35]. The Spike protein of SARS-CoV-2 has greater affinity for ACE2 than that of the SARS virus [15,29], and this might be responsible for its greater pathogenicity [35].

## Summary of evidence

We review evidence that previously unexplained features of the abrupt, atypical and severe hypoxemia seen with Covid-19 could be due to an increase in right atrial pressure and subsequent opening of a previously closed foramen ovale (PPFO). We also review evidence of coagulation cascade activation by the spike protein of several coronavirus pathogens.

## Intrathoracic shunt in COVID-19 patients

Is there a right to left shunt within the lungs or within the heart itself? Patent foramen ovale is surprisingly common both at autopsy [17] and in vivo [35]. Routine electrocardiogram is an unreliable guide

to right atrial pressure [37], and bedside echocardiography might not reveal a PPFO while it is still completely or almost completely closed. Imaging will usually reveal intrapulmonary shunt structures, and stethoscope or echocardiogram usually identifies open cardiac shunts. However, patients with a “probe-patent” foramen ovale may have no murmur or shunt flow so long as left atrial pressure exceeds right atrial pressure, as it normally does. Among patients with advanced lung diseases, 13 of 126 had a physiologically demonstrated right to left shunt. Among those with mean pulmonary artery pressure above 50 mm Hg, 40% had such a shunt [36]. Treating hypoxemia due to such a shunt with invasive mechanical ventilation would accomplish nothing positive.

Although hypoxic vasoconstriction is a normal homeostatic mechanism to limit the degree of V/Q mismatch, its effectiveness varies among individuals. When COVID-19 has reached Mason’s third stage [11], incomplete homeostatic adjustment of regional pulmonary perfusion in severely damaged lung regions may produce a shunt-like effect, and make it impossible to achieve normal oxygen levels by any yet available means. We would expect such badly-damaged lung regions to be detectable by imaging. Early treatment to prevent COVID-19 from progressing to the stage of ARDS is the ultimate goal until the pandemic is tamed. But how?

Losartan protected animals from wet lungs produced by SARS spike protein [30,34]: could it or ACE2 be clinically useful? Using CT pulmonary angiography in place of routine non-contrast chest CT might be appropriate given what we now know about the frequency of pulmonary emboli [38]. Would it be useful to apply trans-venous balloon occlusion or patch closure of any atrial septal defect [39,40] and simultaneously use pulmonary arterial vasodilators? No answer is yet available. Another ray of hope comes from the demonstration that pulmonary hypertension induced by hypoxic ventilation in young calves can be reversed by infusion of supersaturated oxygen-carrying saline solution [41]. Additionally reperfusion microvascular injuries of the heart following 30-minute coronary occlusion were also reversed in similar experiments [42]. Although not yet available for clinical use, such treatment is under development.

We have previously described a condition of severe hypoxemia in which oxygen treatment could easily be given, but was predicted to exacerbate the pathophysiology [43]. COVID-19 challenges clinicians with a different dilemma, in which available oxygen delivery systems have been inadequate for some patients, perhaps because they do not address important (shunt) pathophysiology. In the presence of an abrupt and unexplained decrease in arterial oxygen level, bedside search for a large shunt through a patent foramen ovale can be accomplished using well established techniques such as 2-D echocardiography, pulmonary nitrogen washout, and others.

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NONE.

#### 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.

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#### References

- [1] Covid-19 Dashboard by the Center for Systems Science and Engineering (CSSE) May 16, 2020. <https://coronavirus.jhu.edu/map.html>.
- [2] Wadman M, Courzin-Frankel J, Kaiser J, Metacic C. *Biology*, Coronavirus DOI:10.1126/Science.abc3208.
- [3] Levitan R. The infection that’s silently killing coronavirus patients. *NY Times*. April 20, 2020.
- [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* 2020;201(10):1299–300. <https://doi.org/10.1164/rccm.202003-0817LE>.
- [5] Bangalore S, Sharma A, Slotwiner A, Yatskar L, Harari R, Shah B, Ibrahim H, Friedman GH, Thompson C, Alviar CL, Chadow HL, Fishman GI, Reynolds HR, Keller N, Hochman JS. ST-segment elevation in patients with Covid-19 — a case series. *N Engl J Med* 2020;382(25):2478–80. <https://doi.org/10.1056/NEJMc2009020>.
- [6] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Yi, Zhang Li, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo Li, Xie J, Wang G, Jiang R, Gao Z, Jin Qi, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395(10223):497–506. [https://doi.org/10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5).
- [7] Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajjizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. *JAMA* 2020;323(20):2052. <https://doi.org/10.1001/jama.2020.6775>.
- [8] Bhatraju P, Ghassemieh B, Nichols M, Kim R, Jerome K, Nalla A, et al. Covid-19 in critically ill patients in the Seattle region—case series. *NEJM* DOI:10.1056/NEJMoa2004500.
- [9] Dondorp A, Hayat M, Aryal D, Beane A, Schultz M. Respiratory support in novel coronavirus disease (COVID-19) patients, with a focus on resource-limited settings. *Am J Trop Med Hyg* 2020;1–7. <https://doi.org/10.4269/ajtmh.20-0283>.
- [10] Kim H, Hong H, Yoon S. Diagnostic performance of CT and reverse transcriptase-polymerase chain reaction for coronavirus disease 2019: a meta analysis. *Radiology* 2020. <https://doi.org/10.1148/radiol.2020201343>.
- [11] Mason R. Pathogenesis of COVID-19 from a cell biologic perspective. *Eur Respir J* 2020. <https://doi.org/10.1183/13993003.00607-2020>.
- [12] Sungnak W, Huang N, Becavin C, Berg M, Queen R, Litvinukova M, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. *Nature Medicine* Brief Communication. DOI:10.1038/s41591-020-0868-6.
- [13] Rawnsley A. How the coronavirus sneaks into your body. *mail. google.com*. April 25, 2020. [https://mail.google.com/mail/u/0?ik=c19f\\_dj3d4f8&view](https://mail.google.com/mail/u/0?ik=c19f_dj3d4f8&view).
- [14] Lim Y, Ng Y, Tam J, Liu D. Human coronaviruses: a review of virus-host interactions. *Diseases* 2016;4:3. <https://doi.org/10.3390/diseases4030026>.
- [15] Wang Q, Zhang Y, Wu L, Niu S, Song C, Zhang Z, et al. Structural and functional basis of SARS-CoV-2 entry by using human ACE1. *Cell* 2020. <https://doi.org/10.1016/j.cell.2020.03.045>. S0092-8674(20)30338-X.
- [16] Tian S, Hu W, Niu L, Liu H, Xu H, Xiao S-Y. Pulmonary pathology of early phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. *J Thor Oncol* 2020. <https://doi.org/10.1016/j.jtho.2020.02.010>.
- [17] Hagen P, Scholz D, Edwards W. Incidence and size of patent foramen ovale during first ten decades of life. *Mayo Clin Proc* 1984;59:17–20.
- [18] Wilmsmurst PT, de Belder MA. Patent foramen ovale in adult life. (Editorial). *Brit Heart J* 1994;718:209–12.
- [19] Liew J, Stevens J, Slatore C. Refractory hypoxemia in a patient with submassive pulmonary embolism and an intracardiac shunt. *Permanent J* 2018;22:17–061. <https://doi.org/10.7812/TOO/120061>.
- [20] Giannis D, Ziogas I, Gianni P. J Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. *Clin Virol* 2020;127:104362. <https://doi.org/10.1016/j.jcv.2020.104362>.
- [21] Wichmann D, Sperhake J-P, Lutgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19. *A prospective cohort study. Annals* 2020.
- [22] Carsana L, Sonzogni A, Nasr A, Rossi R, Pellegrinelli A, Zerbi P, et al. Pulmonary post-mortem findings in a large series of COVID-19 cases from Northern Italy. *medRxiv* 2020. <https://doi.org/10.1101/2020.04.19.2005462>.
- [23] Poissy J, Goutay J, Caplan M, Parmentier E, Duburcq T, Lasalle F et al. Pulmonary Embolism in COVID-19 patients: awareness of an increased prevalence. DOI:10.1161/CirculationAHA.120.047430.
- [24] Grillet F, Behr J, Calame P, Aubry S, Delabrousse E. Acute pulmonary embolism associated with COVID-19 pneumonia detected by pulmonary CT angiography. *Radiology* 2020. <https://doi.org/10.1148/radiol.2020201544>.
- [25] Fox S, Akmatbekov A, Harbert J, Li G, Brown J, Vander Heide R. Pulmonary and cardiac pathology in Covid-19: the first autopsy series from New Orleans. *medRxiv* preprint DOI:10.1101/2020.04.06.20050575.
- [26] Gralinski LE, Bankhead III A, Jeng S, Menachery VD, Proll S, Belisle SE, Matzke M, Webb-Robertson B-J, Luna ML, Shukla AK, Ferris MT, Bolles M, Chang J, Aicher L, Waters KM, Smith RD, Metz TO, Law GL, Katze MG, McWeeney S, Baric RS, Dermody TS. Mechanisms of severe acute respiratory syndrome coronavirus-induced acute lung injury. *mBio* 2013;4(4). <https://doi.org/10.1128/mBio.00271-13>.
- [27] Wang J, Hajjizadeh N, Moore E, et al. Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): a case series.

- J Thromb Hemostasis 2020. <https://doi.org/10.1111/jth.14828>.
- [28] Cha AE. Young and middle aged people, barely sick with COVID-19, are dying from strokes. *Washington Post* 2020.
- [29] Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, Zhang Qi, Shi X, Wang Q, Zhang L, Wang X. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature* 2020;581(7807):215–20. <https://doi.org/10.1038/s41586-020-2180-5>.
- [30] Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 in SARS coronavirus-induced lung injury. *Nat Med* 2005;11(8):875–9. <https://doi.org/10.1038/nm1268>.
- [31] Turner AJ. ACE2 cell biology, regulation and physiological functions. Chap 25: The protective arm of the renin-angiotensin system (RAS). DOI:10.1016/8978-0-12-801364-9.00025-0.
- [32] Li F, Li W, Farzan M, Harrison S. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. *Science* 2005;309(5742):1864–8. <https://doi.org/10.1126/Science.1116480>.
- [33] Towler P, Staker B, Prasad S, Menon S, Tang J, Parsons T, et al. ACE2 X-ray structures reveal a large hinge-bending motion important for inhibitor binding and catalysis. *J Biol Chem* 2004;279(17):17996–8007. Epub 2004 Jan 30.
- [34] Imai Y, Kuba K, Rao S, Huan Yi, Guo F, Guan B, Yang P, Sarao R, Wada T, Leong-Poi H, Crackower MA, Fukamizu A, Hui C-C, Hein L, Uhlig S, Slutsky AS, Jiang C, Penninger JM. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* 2005;436(7047):112–6. <https://doi.org/10.1038/nature03712>.
- [35] Wang Y, Li X, Liu W, Gan M, Zhang Lu, Wang J, Zhang Z, Zhu A, Li F, Sun J, Zhang G, Zhuang Z, Luo J, Chen D, Qiu S, Zhang Li, Xu D, Mok CKP, Zhang F, Zhao J, Zhou R, Zhao J. Discovery of a subgenotype of human coronavirus NL63 associated with severe lower respiratory tract infection in China, 2018. *Emerging Microbes Infect* 2020;9(1):246–55. <https://doi.org/10.1080/22221751.2020.1717999>.
- [36] Graves M, Kiratli P, Mozley D. Scintigraphic diagnosis of a right to left shunt in end-stage lung disease. *Respir Med* 2003;97(5):549–54. <https://doi.org/10.1053/rmed.2003.1481>.
- [37] Maeda S, Katsura H, Chida K, Imai T, Kuboki K, Watanabe C, et al. Lack of correlation between p pulmonale and right atrial overload in chronic obstructive airways disease. *Brit Heart J* 1991;65(3):132–6. <https://doi.org/10.1136/hrt.65.3.132>.
- [38] Rotzinger D, Beigelman-Aubry C, von Garnier C, Qanadli S. Pulmonary embolism in patients with COVID-19: time to change the paradigm of computed tomography. *Thromb Res* 2020. <https://doi.org/10.1016/j.thrombres.2020.04.011>.
- [39] Zhang T-T, Cheng G-S, Wang J, Wang X-Y, Xie X-G, Du Y-J, et al. Platypnea-orthodeoxia syndrome in a patient with a pre-existing patent foramen ovale successfully treated with an atrial septal occluder. *J Geriatr Cardiol* 2015;12(3):323–5.
- [40] Brawn M, Frankender D. Transcatheter closure of PFO in patients with cerebral ischemia. *J Am Coll Cardiol*. 2002;39:2019–25.
- [41] Coro A, Boone Y, Mallabiabarrena I, Augstburger M, Tozzi P, Ferrari E, et al. Myocardial and pulmonary effects of aqueous oxygen with acute hypoxia. *Ann Thorac Surg* 2004;78(3):956–60.
- [42] Spears J. Reperfusion microvascular ischemia after prolonged coronary occlusion: implications and treatment with local supersaturated oxygen delivery. *Hypoxia (Auckl)* 2019;7:65–79. <https://doi.org/10.2147/HP.S217955>. eCollection 2019.
- [43] Clements JA, Fisher HK. The oxygen dilemma. (Editorial) *New England J Med* 1970;282:976.