COVID-19 in patients with cardiovascular diseases

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Abbreviated title: COVID-19 in cardiovascular diseases

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A novel coronavirus of zoonotic origin emerged in China at the end of December 2019, spreading rapidly throughout the country [1, 2], and is affecting a large number of countries at the time this editorial was written (early March 2020). The infection, called Coronavirus Disease 2019 (COVID-19), is caused by a virus officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the World Health Organization. SARS-CoV-2 is an enveloped RNA beta-coronavirus with a phylogenetic similarity to another known coronavirus, SARS-CoV, which caused an outbreak of SARS in 2003 [3]. While the epidemiological and clinical characteristics of COVID-19 are not yet fully determined, first evidence indicates important consequences for the cardiovascular system and implications for cardiologists [4].

First, early case reports suggest that patients with previous or underlying cardiovascular diseases are at higher risk for developing severe symptoms if infected with SARS-CoV-2. In a report on 138 patients with COVID-19 hospitalized in Wuhan (Hubei province, China) [5], 64 (46.4%) had one or more coexisting medical conditions, mostly cardiovascular or cerebrovascular. Hypertension was present in 31.2%, diabetes in 10.1%, and cardiovascular disease in 14.5% of patients [5]. Interestingly, these proportions were significantly higher in patients with the most severe forms of COVID-19 (i.e. requiring hospitalization in an intensive care unit), with hypertension in 58.3%, diabetes in 22.2%, cardiovascular disease in 25.0% and cerebrovascular disease in 16.7% [5]. Similarly, while the true overall mortality rate of COVID-19 is still undetermined, and is estimated (based on a crude mortality ratio) at between 3% and 4%, it could be higher in older patients (>60 years) or patients with pre-existing comorbid conditions such as cardiovascular disease (10.5%), diabetes (7.3%) or hypertension (6.0%) [6]. While the disease can present as a pulmonary disease, the case-fatality rate for patients with underlying cardiovascular disease is greater (10.5%) than in patients with underlying chronic respiratory disease (6.3%) [4].

Second, whereas COVID-19 typically presents with symptoms of lower tract respiratory infection, a significant proportion of patients experience cardiovascular symptoms at initial presentation [7]. These symptoms notably include palpitations and chest tightness. In addition, it is likely that SARS-CoV-2 can cause myocardial damage. In different reports, an increase in high-sensitivity cardiac troponin I (cTnI) was noted in 10–20% of patients infected with COVID-19 [5, 8]. In China, an estimated 11.8% of patients who died from COVID-19 presented substantial heart damage, with elevated levels of cTnI or cardiac arrest during hospitalization, without having any pre-existing

cardiovascular disease [7]. The exact conditions leading to acute myocardial injury are still unclear, but could be linked to either acute myocarditis or acute coronary syndrome, as previously experienced with the Middle East respiratory syndrome-related coronavirus (MERS-CoV) [7]. It was notable that classical symptoms and presentation of acute myocardial infarction can be overshadowed in the context of COVID-19, leading to a potential delay in diagnosis [4].

Overall, these first data indicate a level of interaction between SARS-CoV-2 and the cardiovascular system, either by a direct or an indirect mechanism. SARS-CoV and SARS-CoV-2 infections are triggered by binding of the virus' spike protein to angiotensin-converting enzyme 2 (ACE2) [9]. ACE2 is a membrane-bound zinc metallopeptidase involved in the cleavage of angiotensin. ACE2 is highly expressed in the lungs but also in the heart, where it is localized to macrophages, vascular endothelium, smooth muscle and myocytes [10]. Intriguingly, ACE2 expression is increased post-myocardial infarction [10] and in patients with diabetes [11], two populations that are at higher risk of developing severe forms of COVID-19. ACE2 also regulates important cardiovascular and metabolic functions, including regulation of blood pressure and glycaemia [12, 13]. Whether SARS-CoV-2 directly affects the cardiovascular system by targeting ACE2-expressing cells remains to be explored. Another possibility involves an indirect effect of the immune response to SARS-CoV-2 on the myocardium and the vessels. It is likely that severe forms of COVID-19 involve a cytokine storm, which may play a role in coronary plaque instability, as previously observed with SARS-CoV [14, 15]. In addition, patients infected with SARS-CoV or SARS-Cov-2 typically present with lymphopaenia [5, 8], a condition that has been associated with the development of atherosclerosis and adverse cardiovascular outcomes [16].

The situation of the COVID-19 outbreak is rapidly evolving, with uncertain clinical and physiopathological profiles. However, the first case reports indicate that COVID-19 has important effects on the heart and the vessels, which should be known by the cardiovascular community.

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Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References

[1] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382:727-33.

[2] Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med. 2020.

[3] Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020.

[4] Madjid M, Solomon S, Vardeny O. ACC Clinical Bulletin: Cardiac Implications of Novel Coronavirus (COVID-19). In: Committee ASaQ, editor. USA: ACC; 2020.

[5] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020.

[6] Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020.

[7] Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol. 2020.

[8] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.

[9] Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020.

[10] Burrell LM, Risvanis J, Kubota E, Dean RG, MacDonald PS, Lu S, et al. Myocardial infarction increases ACE2 expression in rat and humans. Eur Heart J. 2005;26:369-75; discussion 22-4.

[11] Soro-Paavonen A, Gordin D, Forsblom C, Rosengard-Barlund M, Waden J, Thorn L, et al. Circulating ACE2 activity is increased in patients with type 1 diabetes and vascular complications. J Hypertens. 2012;30:375-83.

[12] Bindom SM, Lazartigues E. The sweeter side of ACE2: physiological evidence for a role in diabetes. Mol Cell Endocrinol. 2009;302:193-202.

[13] Jiang F, Yang J, Zhang Y, Dong M, Wang S, Zhang Q, et al. Angiotensin-converting enzyme 2 and angiotensin 1-7: novel therapeutic targets. Nat Rev Cardiol. 2014;11:413-26.

[14] Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017;39:529-39.

[15] Tsui KL, Leung TC, Yam LY, So LK, Poon E, Lung KC, et al. Coronary plaque instability in severe acute respiratory syndrome. Int J Cardiol. 2005;99:471-2.

[16] Nunez J, Sanchis J, Bodi V, Nunez E, Mainar L, Heatta AM, et al. Relationship between low lymphocyte count and major cardiac events in patients with acute chest pain, a non-diagnostic electrocardiogram and normal troponin levels. Atherosclerosis. 2009;206:251-7.