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.
SARS-CoV-2 and the cardiovascular system

Anouar Hafiane
McGill University, Canada

ABSTRACT
The coronavirus disease COVID-19 is a public health emergency caused by a novel coronavirus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). SARS-CoV-2 infection uses the angiotensin-converting enzyme 2 (ACE2) receptor, and typically spreads through the respiratory tract. Invading viruses can elicit an exaggerated host immune response, frequently leading to a cytokine storm that may be fueling some COVID-19 death. This response contributes to multi-organ dysfunction. Accumulating data points to an increased cardiovascular disease morbidity, and mortality in COVID-19 patients. This brief review explores potential available evidence regarding the association between COVID-19, and cardiovascular complications.

1. Introduction
Epidemic Corona Virus Disease 2019 (COVID-19) is gradually spreading by human-to-human transmission. The pathogen has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. In COVID-19, particular attention has been given to the role of angiotensin-(Ang)converting enzyme 2 (ACE2), and the binding site for SARS-CoV-2 cellular entry [3]. Besides severe lung involvement, invasion of the virus into circulation elicits an exaggerated host immune response, frequently leading to a cytokine storm that is associated with in-hospital death [4]. At present, there are very few evidences supporting cardiac involvement during SARS-CoV-2 infection, and they arose mainly from observational studies. Accumulating data points to the implication of the cardiovascular (CV) system on multiple levels linking COVID-19 with increased morbidity, and mortality from cardiovasculardisease (CVD). In this review article, we explore SARS-CoV-2 associated infection mechanisms with a special focus on CVD and provide an overview of this topic.

2. Structural properties
Corona viruses are miniature in size (60–140 nm in diameter) and contain a single positive-stranded ribonucleic acid (RNA), typically ranging from 26 to 32kbs in length. The SARS-CoV-2 is a novel β-coronavirus category that takes a round or elliptic pleomorphic form (Fig. 1). Metagenomics analysis from next-generation sequencing convincingly demonstrate this virus consists of six major open-reading frames (ORFs) that are common to coronaviruses, and a number of other accessory genes [5]. Further analysis indicates some of the expressed genes share less than 80% nucleotide sequence identity to earlier SARS-CoV [6]. The SARS-CoV-2 RNA genome contains 29,891 nucleotides, encoding for 9860 amino acids [6]. Although its probable origins are not completely understood, genomic analyses suggest that it probably evolved from a strain found in bats [7,8]. Similar to most other coronaviruses, the outer membrane spike glycoprotein of SARS-CoV-2, is the prime interacting protein with host cell target receptors (such as ACE2, CD26, Ezrin, cyclophilins) which are important for cell adhesion, and virulence [9]. Under an electron microscope, the SARS-CoV-2 surface morphology possesses multiple polyproteins, nucleoproteins, and membrane proteins, such as spike glycoproteins S [10]. The latter involves homotrimers protruding far from the viral surface, giving it a halo like appearance or corona as illustrated in Fig. 1.

3. Mechanisms of COVID-19 infection
COVID-19 patients presented with mild flu-like symptoms, and a few patients rapidly develop acute respiratory distress syndrome, respiratory failure, multiple organ failure, and even deaths (Table 1). In the initial step of the infection, studies support a potential interaction between SARS-CoV-2, and ACE2 receptor as a portal of infection (Fig. 2) [9,11]. ACE2 is a type 1 transmembrane protein predominantly expressed by epithelial cells of the lung [12]. When compared to other viruses that cause SARS, there are some differences in the precise amino acids belong to spike glycoprotein used to bind SARS-CoV-2 to that ACE2 receptor. Distinctly, a larger sequence difference (~55% identity) between SARS-CoV-2, and SARS-CoV was found in the S1 domain of the spike glycoprotein S (aa01–aa550) [9]. This domain is recognized for host cell target contact [9]. The receptor-binding domain (RBD) of SARS-CoV-2, and SARS-CoV interacts with ACE2 receptor [9]. Interface comparison between the RBD in SARS-CoV-2, and SARS-CoV indicates
that the most prominent alteration is the substitution of Val404 in the SARS-CoV-RBD with Lys417 in the SARS-CoV-2-RBD [11]. The high infectivity of the SARS-CoV-2 virus is in part related to new mutations in the RBD, and acquisition of a furin cleavage site. The latter mutation is inserted at the boundary of the S1/S2 subunits of the spike S-protein [13]. Moreover, the furin binding site can enhance the virus ability to internalize into cells [12]. Initially, membrane bound ACE2 proteins are cleaved by A Disintegrin And Metalloproteases 17 (ADAM17) that is upregulated by endocytosed SARS-CoV-2 spike S proteins (Fig. 2). Moreover, ACE2 contains an enzymatic domain located on the cell surface where it converts Ang II (1–9) to Ang 1–7 [14]. At this phase negative regulation of the renin-Ang system, with down regulation of ACE2 by SARS-CoV-2 may magnify the cytokine storm, resulting in an overwhelming inflammatory response (Fig. 2) [12]. In order to be active, the ACE2 complex is assembled as a stable dimer of heterodimers through interactions of the collectrin-like domain of ACE2 [11]. The resultant homodimer is able to bind two SARS-CoV-2 S protein trimers simultaneously. In this interaction, the cleavage of S protein into sub-units, S1 and S2 facilitates target cell internalization following activation of the spike protein by transmembrane protease serine 2 (TMPRSS2) [12]. The S1 subunit of S protein contains the RBD which allows coronaviruses to directly bind to the peptidase domain (PD) of ACE2 [11]. S2 likely plays a role in membrane fusion where S1 domain potentially interacts with the human CD26 that is involved in the T-cell immune response [15]. It is speculated that increased expression of ACE2 could potentially facilitate SARS-CoV-2 infection [16]. The SARS-CoV-2 binding site shows that it has improved binding stability, and potentially enhanced ACE2 receptor binding affinity [11]. Lastly, structure-based rational affinity interaction to either ACE2 or the S protein of SARS-CoV-2 provides invaluable insights into the molecular basis for coronavirus recognition, and infection. These mechanisms may uncover a potential target of novel neutralizing antibodies to suppress infection by new viruses.

4. Implication of ACE2 activity in cardiovascular complications

SARS-CoV-2 infection and its possible implication to myocarditis is still not well documented despite some case report [17]. Early data indicated that 25% of hospitalized, and treated patients in Wuhan had CVD [18]. Independent studies recognized a primary role of ACE2 in COVID-19 infection [19]. Of interest, ACE2 is localized in cardiomyocytes, cardiac fibroblasts, pericytes, vascular endothelium, and vascular smooth cells [16,20]. Whether SARS-CoV-2 can directly proliferate in the heart is unidentified. COVID-19 patients with pre-existing CVD,
hypertension, and related conditions experience disproportionately worse outcomes [21]. There are a very few pathological studies conducted on the COVID-19 patients. One of the clinical features of patients infected with SARS-CoV-2 included abnormal features such as acute cardiac injury (12%) [22]. Available clinical data revealed that 15% to 30% of the COVID-19 patients present with hypertension, and 2.5% to 15% with coronary heart disease [18,23]. Viral involvement of cardiomyocytes, and the effect of systemic inflammation seem to be the most common mechanisms responsible for cardiac injury [20] (Fig. 2). Thus, suggesting that inflammation may be a potential mechanism for myocardial injury. Various diseases including heart failure, hypertension, and diabetes are characterized by a relative ACE2-deficient state [24]. Genetic data shows that ACE2 is an essential regulator of heart function in vivo [25]. Activation of renin-Ang system, and the down-regulation of ACE2 expression play a key role in several diseases including CV pathologies (Fig. 2) [16]. Accordingly, ACE2 blockade delayed CV damage in diabetic patients [16,26]. Experimental evidence suggested a beneficial role of ACE2 in CV function [14]. Genetic manipulation of ACE2 expression points to the possible significance of this enzyme in cardiac function, and vulnerability to heart failure [14,19]. In the established heart failure, expression of ACE2 on the cell surface is downregulated; however, there is an increase in circulating ACE2 levels, and activity when compared to healthy individuals [14,27]. It is assumed that shedding of the membrane-bound ACE2 may be responsible for the increased circulating endogenous ACE2 activity in COVID-19 patients [3]. Circulating levels of soluble ACE2 are usually low to nondetectable. Soluble ACE2 would therefore not sufficiently sequester SARS-CoV-2 in the circulation to prevent viral dissemination [19]. However, the extent to which soluble ACE2 would compete for ACE2 binding to reduce viremia infection and alleviate tissue injury is unknown.

The occurrence of fulminant myocarditis, and cardiogenic shock seems low in patients with COVID-19 [28,29]. Despite this, a predisposition to acute cardiac complications related to underlying atherosclerotic CVD may significantly increase the severity of COVID-19 in vulnerable individuals [29]. The exact mechanism of cardiac involvement in COVID-19 is still under investigation. As presented above, one potential mechanism directing myocardial involvement is mediated by ACE2. Other mechanisms of COVID-19 morbidity related to cardiac complications are discussed below.

5. Potential therapeutic approaches based on renin-angiotensin-aldosterone system inhibition

Renin-angiotensin-aldosterone system (RAAS) inhibitors are predominantly including angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II-receptor blockers (ARBs) (Fig. 2). RAAS inhibitors are often prescribed to treat patients with hypertension, or diabetes who are infected with SARS-CoV-2 [30]. Data from experimental mouse models, revealed that injection of SARS-CoV-1 induced acute lung injury, which is limited by blocking the RA pathway [27]. Intravenous recombinant human ACE2 (rhACE2; APN01, GSK2586881) was given to healthy subjects in a randomized clinical trial phase 2 (Clinical-Trials.gov number NCT01597635) safely reduced angiotensin II levels,
is evaluated in humans with acute respiratory distress syndrome. In this trial, the observed restoration of ACE2 through the administration of (GSK2586881), appeared to attenuate acute lung injury [31]. However, this study was not adequately powered to determine changes in acute physiology or clinical outcomes [32]. Furthermore, in COVID-19 as with SARS-CoV, higher ACE2 expression might lead to a higher risk of SARS-CoV-2 infection [33,33]. Therefore, targeted disruption of ACE2 in mice caused the development of abnormal heart function [25]. Yet, increasing the expression of ACE2 may prevent, and reverse heart failure. Consequently, a therapeutic approach that will amplify the ACE2-Ang (1–7) axis could provide further protection against the progression of CVD [34]. Basing on these data, some authors have proposed an association between the use of RAAS inhibitors and COVID-19. Nevertheless, this association has been rejected due to the lack of evidence on the efficacy of this approach in reducing adverse outcomes in Covid-19 patients [35,36]. Even if RAAS inhibitors modify ACE2 levels or activity (or both) in target tissue, there are not enough clinical reports to indicate whether this would in turn facilitate greater entry of SARS-CoV-2 proteins. Further mechanistic studies are required to better define the unique interplay between SARS-CoV-2 and the RAAS network [37].

6. COVID-19 pathogenesis in relation to the cardiovascular system

SARS-CoV-2 seems to damage the heart's muscle tissue and can cause myocarditis [38]. Accordingly, after SARS-CoV-2 infection various cases of severe myocarditis with reduced systolic function have been reported [17]. Although the mechanisms of myocardial involvement in COVID-19 are still under investigation, they probably include direct viral infection, hypoxia-induced apoptosis, and cytokine storm-related cell damage in the body [4]. Excessive inflammation (IL6, TNFs, and IL-1) can further modulate the function of several cardiomyocyte ion channels, specifically K+ and Ca++ channels, leading to inflammatory cardiomyocyte channelopathies [39]. Excessive intracellular calcium promotes cardiomyocyte apoptosis [40]. Moreover, myocardial injury might represent a main driver of enhanced arrhythmic risk in these patients [41]. With the constantly evolving recognition of the interplay between COVID-19 and the CV system, available clinical data have shown that between 8 and 28% of patients with COVID-19 infections will manifest acute cardiac injury. This condition is assessed by increase in cardiac biomarkers release such as elevated troponin I (TnI), N-terminal pro-brain natriuretic peptide (NT-proBNP) or B-type natriuretic peptide (BNP) (Table 2) [22,42,43]. Evidence of myocardial injury was recommended on the basis that TnT elevation in patients with COVID-19 is significantly associated with fatal outcomes [44]. The finding of increased d-dimer levels in patients with severe COVID-19 has prompted questions regarding the existence of disseminated intravascular coagulation which may predispose patients to thrombosis risk [4]. These abnormalities may then lead to ACS [50]. Patients with COVID-19 are also at an increased risk of venous thromboembolic event (Fig. 2). The most consistent hemostatic abnormalities with COVID-19 include mild thrombocytopenia, and increased d-dimer levels (a fibrin degradation product) over 0.28 μg/L, and had a possible predictive value for the severity of SARS-COV-2 infection [49].

7. Inflammation and CV complications in COVID-19

Rise in inflammation in the myocardium can result in CV complications, such as myocarditis, heart failure, cardiac arrhythmias, and acute coronary syndrome (ACS) (Fig. 2) [17]. However, elevated high sensitivity TnT with other inflammatory vascular biomarkers (d-dimer, ferritin, IL-6, and lactate dehydrogenase) may rise the possibility that these changes are specific effects of the virus, reflects a cytokine storm, or is merely an isolated myocardial injury (Table 2). As an example of this statement, one case reported a man presenting with chest pain, and ST-segment elevation without coronary obstruction as well as elevated cardiac biomarkers (TnT serum levels > 10 ng/mL, NT-proBNP > 21,000 pg/mL) [40]. Another study found IL-6 over 4.3 pg/mL, and d-dimer (a fibrin degradation product) over 0.28 μg/L, and had a possible predictive value for the severity of SARS-COV-2 infection [49]. The finding of increased d-dimer levels in patients with severe COVID-19 has prompted questions regarding the existence of disseminated intravascular coagulation which may predispose patients to thrombosis risk [4]. These abnormalities may then lead to ACS [50]. Patients with COVID-19 are also at an increased risk of venous thromboembolic event (Fig. 2). The most consistent hemostatic abnormalities with COVID-19 include mild thrombocytopenia, and increased d-dimer levels [51]. Thus, demonstrating a promise to hold prognostic value of d-dimers in COVID-19 patients [52]. However, the reason behind elevated d-dimer levels whether is thrombosis/hypercoagulability or proinflammatory response remains unclear until now.

More recently, inflammatory response, hypoxic abnormalities, and...
electrolytic disturbance are found to be one of the physiologic sequelae of COVID-19 leading to arrhythmic risk. Notably, heart palpitation was reported as one of the most common initial symptoms in 137 patients presenting with COVID-19 (7.3%) [41]. In addition, the elevation of serum Ang exhibits a direct correlation to the viral load, and lung injury [53]. At this point, plasma levels of angiotein II may offer a novel method of predicting disease severity [52]. Indeed, activation of ADAM-17 by Ang II, and SARS-CoV-2 binding leads to a loss of membrane-bound ACE2, and its release into the circulation (Fig. 2). However, intracellular ACE levels are not depleted [54]. These conditions limit the effects of Ang II diverse in tissues, culminating in CV, renal, and lung diseases. Higher plasma ACE2 levels were associated with a history of atrial fibrillation, and coronary artery bypass graft, and elevated heart rate specially in man [14]. Moreover, reduced ACE2 levels in plasma was associated with higher left ventricular ejection fraction, and systolic blood pressure [55].

In summary, there is a mounting evidence implicating an excessive cytokine storm with the pathophysiology of severe COVID-19, where systemic inflammatory potentiates/complicates the coexisting CV in these patients [56]. Such complications included hypertension, heart failure, myocardial injury, and atherosclerosis [57]. In these patients, the pathogenic mechanism that produces CV complications seem to be remarkably complex.

8. Conclusion

Significance of the SARS-CoV-2 infection in the CV system is reflected through incidences of acute myocardial injury, arrhythmias, ACS, sepsis, septic shock, viral myocarditis, and heart failure. Myocardial injury underscore significant association with fatal outcomes, whereas the prognosis of patients with underlying CVD but without myocardial injury seems quite favorable. We speculate that while COVID-19 disease begins with respiratory condition, it hastily involves the CV system through an imbalance of the renin-Angle system, which possibly complicates the clinical course through the inflammatory response, endothelial dysfunction, and microvascular damage where inflammation may be associated with myocardial injury. However, additional study of these mechanisms is clearly needed and may influence the search for ways to prevent myocardial complications. More evidence from laboratories, and clinical research is needed to learn more about the impact of COVID-19 on the CV system.

Funding

This research received no funding.

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.

References

[1] J. Ojii, F. Li, Z.-L. Shi, Origin and evolution of pathogenic coronaviruses, Nat. Rev. Microbiol. 17 (3) (2019) 181–192, https://doi.org/10.1038/s41579-018-0118-9.
[2] A.E. Gorbakleya, S.C. Baker, R.S. Baric, R.J. de Groot, C. Drosten, A.A. Gulyaeva, et al., The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2, Nat. Microbiol. 5 (4) (2020) 536–544, https://doi.org/10.1038/s41564-020-0695-z.
[3] J. Guo, Z. Huang, L. Lin, J. Lv, Coronavirus Disease 2019 (COVID-19) and Cardiovascular Disease: A Viewpoint on the Potential Influence of Angiotein- Converting Enzyme Inhibitors/Angiotein Receptor Blockers on Onset and Severity of Severe Acute Respiratory Syndrome Coronavirus 2 Infection, J Am Heart Assoc. 9 (7) (2020), https://doi.org/10.1161/JAHA.120.016219.
[4] R.J. Jose, A. Manuel, COVID-19 cytokine storm: the interplay between inflammation and coagulation. The Lancet. Respir. Med. 8 (6) (2020), https://doi.org/10.1016/S2213-2600(20)30126-2 e47–e47.
A. A. Divani, S. Andalib, M. Di Napoli, S. Lattanzi, M.S. Hussain, J. Biller, et al., A. Hafiane

Januzz JL. Troponin and BNP Use in COVID-19. American College of Cardiology

F.Zhou, T.Yu, R.Du, G.Fan, Y.Liu, Z.Liu, et al., Clinical course and risk factors for

T.Guo, Y.Fan, M.Chen, X.Wu, L.Zhang, T.He, et al., Cardiovascular implications

E.Driggin, M.V.Madhavan, B. Bikdeli, T.Chuich, J.Laracy, G. Bondi-Zoccai, et al.,

H. Hu, F. Ma, X. Wei, Y. Fang, Coronavirus fulminant myocarditis saved with glu-

corticoid and human immunoglobulin, Eur. Heart J. (2020), https://doi.org/10.1002/ehj.21005.

M. Aboughdir, T. Kirwin, A. Abdullah, B. Wang, Prognostic value of Cardiovascular biomarkers in COVID-19: A review. Viruses. 12 (5) (2020), https://doi.org/10.3390/v12050527.

A.N. Kochi, A.P. Taglialac, G.B. Forleo, M.G. Fassini, C. Tondo, Cardiac and ar-
rhythmia complications in patients with COVID-19, J Cardiovasc Ultrasound 31 (5) (2020) 1003–1008, https://doi.org/10.1111/jce.14479.

K.B. Pedersen, H. Chodavarapu, C. Porretta, L.K. Robinson, E. Lazartigues, Dynamics of ADAM17-Mediated Shedding of ACE2 Applied to Pancreatic Islets of Male db/db Mice, Endocrinology 156 (12) (2015) 4411–4425, https://doi.org/10.1210/en.2015-1556.

L.E. Sama, A. Ravera, B.T. Santema, H. van Goor, J.M. ter Maaten, J.G.F. Cleland, et al., Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin–angiotensin–aldosterone inhibitors, Eur. Heart J. 41 (19) (2020) 1810–1817, https://doi.org/10.1093/eurheartj/ehaa373.

D. Zhang, R. Guo, L. Lei, H. Liu, Y. Wang, Y. Wang, et al., COVID-19 infection induces readily detectable morphological and inflammation-related phenotypic changes in peripheral blood monocytes, the severity of which correlates with patient outcome, medRxiv (2020), https://doi.org/10.1101/2020.05.22.20052555.

B. Long, W.J. Brady, A. Koyfman, M. Gottlieb, Cardiovascular complications in COVID-19, The American journal of emergency medicine. 38 (7) (2020) 1504–1507, https://doi.org/10.1016/j.ajem.2020.04.048.

D. Zheng, R. Guo, L. Lei, H. Liu, Y. Wang, Y. Wang, et al., COVID-19 infection induces readily detectable morphological and inflammation-related phenotypic changes in peripheral blood monocytes, the severity of which correlates with patient outcome, medRxiv (2020), https://doi.org/10.1101/2020.05.22.20052555.