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.
Elevated Troponin in Patients With Coronavirus Disease 2019: Possible Mechanisms

GREGORIO TERSALVI, MD,1,2 MARCO VICENZI, MD,3,4 DAVIDE CALABRETTA, MD,5 LUIGI BIASCO, MD, PhD,6,7 GIOVANNI PEDRAZZINI, MD,1,7 AND DARIO WINTERTON, MD8

Lugano, and Lucerne, Switzerland; and Milan, Ciriè, and Monza, Italy

ABSTRACT

Coronavirus disease 2019 (COVID-19) is a pandemic that has affected more than 1.8 million people worldwide, overwhelmed health care systems owing to the high proportion of critical presentations, and resulted in more than 100,000 deaths. Since the first data analyses in China, elevated cardiac troponin has been noted in a substantial proportion of patients, implicating myocardial injury as a possible pathogenic mechanism contributing to severe illness and mortality. Accordingly, high troponin levels are associated with increased mortality in patients with COVID-19. This brief review explores the available evidence regarding the association between COVID-19 and myocardial injury. (J Cardiac Fail 2020;26:470–475)

Key Words: COVID-19, Coronavirus, SARS, Troponin, Myocardial injury, Myocarditis.

In December 2019, a series of pneumonia cases of unknown cause emerged in Wuhan, Hubei, China, with clinical presentations greatly resembling viral pneumonia.1

Deep sequencing analysis from lower respiratory tract samples indicated a novel coronavirus, which was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of April 14, 2020, a total of 1,844,863 cases of SARS-CoV-2 infection and 117,021 deaths have been confirmed by the World Health Organization.2

The most feared clinical presentation of coronavirus disease 2019 (COVID-19) is bilateral interstitial pneumonia, which may progress to acute respiratory distress syndrome. The latter occurs in approximately 3%–30% of hospitalized patients with COVID-19, depending on the cohort.1,3–8

Analyzing the first reports from China, a considerable proportion of patients (12%–28%) presented elevated cardiac troponin levels.1,6,8,9 Compared with patients with normal levels, those with elevated troponins were older and had significantly higher rates of comorbidities including hypertension, coronary artery disease (CAD), and diabetes.6 Notably, patients with higher troponin levels were more likely to be admitted to intensive care1,5 and showed higher in-hospital mortality.6,8,10–13

Acute respiratory infections as well as sepsis are often associated with an increase in troponin, which can be used as a marker of disease severity and predicts future cardiovascular events.14–16

Hypotheses on COVID-19–associated myocardial injury are consistent with previous observations relating to the outbreaks of SARS and Middle East respiratory syndrome. Several mechanisms have been proposed, which are summarized in Figure 1. In this review, we provide an overview of the available evidence regarding the possible mechanisms of myocardial injury in COVID-19.

Myocarditis

Myocarditis is an inflammatory disease of the myocardium diagnosed by established histologic, immunologic, and immunohistochemical criteria.17 Many viruses are cardio- tropic, meaning that they bind directly on molecular targets in the myocardium. Myocardial damage may be due to different mechanisms. In the initial phase of viral myocarditis, direct virus-mediated lysis of cardiomyocytes occurs.18 This process is usually followed by a robust T-cell response, which can lead to further heart injury and ventricular dysfunction.19,20

In COVID-19, particular attention has been given to the role of angiotensin-converting enzyme 2 (ACE2), the binding receptor for SARS-CoV-2 cellular entry.21 ACE2 is highly expressed in pericytes of adult human hearts, which indicates an intrinsic susceptibility of the heart to SARS-CoV-2 infection.22 SARS-CoV-2 seems to not only gain initial entry through ACE2, but also to
subsequently downregulate ACE2 expression, resulting in reduced conversion of angiotensin II (Ang-II) to angiotensin 1–7 (Ang-1–7). Ang-1–7 physiologically mediates protective cardiovascular effects in target organs.\textsuperscript{23,24} In autopsies of patients who died from the SARS outbreak in 2002, 35% of heart samples showed the presence of viral RNA in the myocardium, which in turn was associated with reduced ACE2 protein expression.\textsuperscript{25} SARS-CoV-2 may share the same mechanism with the first SARS coronavirus because the 2 viruses are highly homologous in genome.\textsuperscript{6,26,27} The consequences of ACE2 downregulation on the cardiovascular system is further expanded on.

Myocarditis represents one of the most challenging diagnoses in cardiology. Suspicion rises with the number of criteria fulfilled.\textsuperscript{17} However, diagnostic certainty is based on endomyocardial biopsy or autopsy, where histologic analyses (infiltration, lymphocytes, macrophages, cellular inflammatory types) or molecular methods of viral genome identification can be performed.

To the best of our knowledge, only 3 case reports of probable COVID-19 myocarditis are available to date,\textsuperscript{28–30} but none have been proven by biopsy. A fourth case describes the autopsy of a patient with severe COVID-19 who died from sudden cardiac arrest.\textsuperscript{31} Interestingly, there were no obvious histologic changes seen in the heart tissue.

The emergency setting of many hospital facilities during the pandemic together with strict hygiene measures intended to prevent further contagion may hinder large studies on biopsy specimens in patients with COVID-19 and the performance of autopsies. At present, no convincing evidence of histologically confirmed COVID-19 myocarditis has been published.

**Microangiopathy**

SARS-CoV-2 uses ACE2 as its entry receptor, and subsequently downregulates ACE2 expression. In addition to the heart and lung, ACE2 is localized in the intestinal epithelium, vascular endothelium, and the kidneys.\textsuperscript{32,33} In the renin–angiotensin–aldosterone system, ACE2 catalyzes the conversion of Ang-II to Ang-1–7, which opposes the vasoconstrictor, proinflammatory, pro-oxidant, proproliferative, and profibrotic actions exerted by Ang-II via AT1 receptors.\textsuperscript{44} As a result, suppression of ACE2 expression and subsequent increase in Ang-II levels may represent another threat to heart and vessels in patients with COVID-19. However, the role of Ang-II/Ang-1–7 imbalance in COVID-19 is extrapolated based on limited data from a different, albeit closely related, coronavirus (SARS-CoV).

The clinical significance of this pathway in COVID-19 complications and any possible role of modulating this receptor are not yet fully known. A clinical trial testing recombinant human ACE2 as a treatment for patients with COVID-19 is currently ongoing (NCT04335136). This drug may play a double role, both by acting as a decoy and competitively decreasing viral cell entry, and by restoring ACE2 activity and its beneficial role.\textsuperscript{36}

Endothelial dysfunction, cytokine storm, oxidative stress, and Ang-II upregulation may explain the coagulopathy frequently seen in severe coronavirus disease.\textsuperscript{37} A postmortem study from Singapore\textsuperscript{38} on patients with SARS reported that 4 of 8 patients had pulmonary thromboembolic lesions and 3 patients had deep vein thrombosis. To date, there is only 1 described case of COVID-19–associated pulmonary embolism,\textsuperscript{39} but approximately one-half of patients with...
COVID-19 present high levels of d-dimer, which is associated to disease severity and higher mortality. This marked increase in d-dimer may be due to intense inflammation stimulating intrinsic fibrinolysis in the lungs with spillover into the bloodstream. Another factor that may contribute to microangiopathy is vasculitis. Several studies have linked coronavirus infection with Kawasaki disease, especially in children. Furthermore, a case series of 3 deceased SARS patients in 2003 described findings of systemic vasculitis, including edema, localized fibrinoid necrosis, and infiltration of monocytes, lymphocytes, and plasma cells into vessel walls in the heart, lung, liver, kidney, adrenal gland, and the stroma of striated muscles. It has been suggested that, in patients with COVID-19, microvascular damage occurring in the heart causes perfusion defects, vessel hyperpermeability, and vasospasm, leading to myocardial injury. Notably, a considerable proportion of critically ill patients with COVID-19 present with acute kidney injury, which is associated with worse prognosis. The mechanism may be the same, with microangiopathy of renal vessels, but there is no strong supporting evidence to date. Worsening of troponin clearance in patients with acute kidney injury could also contribute to the elevated levels in those patients.

Myocardial Infarction

Patients with preexisting CAD and those with risk factors for atherosclerotic cardiovascular disease (CVD) are at an increased risk of developing an acute coronary syndrome during acute infections, as demonstrated previously in epidemiologic and clinical studies of influenza and other acute inflammatory conditions. This outcome could result from imbalance between oxygen supply and demand in the acute setting, so that the troponin elevation may be interpreted as a type 2 myocardial infarction (MI). Reduced oxygen supply in patients with COVID-19 is typically caused by hypoxic respiratory failure, a feature that is more common in deceased patients than in patients who recover and is a marker of disease severity. In contrast, infectious states are often accompanied by fever, tachycardia, and endocrine dysregulation, which lead to a marked increase in myocardial oxygen demand. Moreover, hypoxemia also leads to excessive intracellular calcium with consequent cardiac myocyte apoptosis.

By definition, a type 2 MI can occur with or without underlying CAD. However, considering the higher prevalence of elevated troponin in patients with COVID-19 with previous CVD, it is possible that the type 2 MI when underlying stable coronary disease is unmasked by the acute infection.

Type 1 MI, caused by plaque rupture with thrombus formation, may also be precipitated by COVID-19. Circulating cytokines released during a severe systemic inflammatory stress could lead to atherosclerotic plaque instability and rupture. In addition, the suppression of ACE2 expression and Ang-II increase may elevate cardiovascular risk through mechanisms such as oxidative stress, endothelial dysfunction, and vasoconstriction. Moreover, because ACE2 is expressed in vascular endothelial cells, direct viral vascular infection leading to plaque instability may also play a role in type 1 MI in patients with COVID-19.

The occurrence of acute coronary syndrome and MI in infected patients during the first SARS outbreak has been described. However, there are very scarce data about symptoms and electrocardiogram changes related to MI in COVID-19. Chest pain has been broadly reported and is also associated with cardiac injury, but it has a very low specificity owing to the primary lung disease (ie, pleuritic pain). Interestingly, Guo et al reported that on admission no patients showed evidence of acute MI. No data regarding electrocardiogram changes on larger groups have been published to date.

Cytokine Storm

Severe lung inflammation and impaired pulmonary gas exchange in COVID-19 has been suggested to be due to upregulation of proinflammatory cytokines. In healthy subjects, Ang-1–7 limits the synthesis of proinflammatory and profibrotic cytokines. Thus, downregulation of ACE2 by SARS-CoV-2, with a consequent decrease in Ang-1–7 levels, may magnify the cytokine storm, resulting in an overwhelming inflammatory response. Cytokines have been extensively studied in patients with heart failure owing to their role in inflammatory modulation, myocyte stress or stretch, myocyte injury and apoptosis, fibroblast activation, and extracellular matrix remodeling.

In the study by Guo et al, plasma troponin levels had a significant positive linear correlation with plasma high-sensitivity C-reactive protein levels, indicating that myocardial injury may be closely associated with inflammatory pathogenesis during the progress of the disease. In addition to their direct effects on cardiomyocytes, high levels of circulating cytokines also lead to functional reprogramming of endothelial cells, endothelial dysfunction, and atherogenesis. In fact, endothelial cells are thought to play a primary role in the inflammatory response in viral infections.

Thus, systemic inflammatory response with cytokine storm is a plausible cause of myocardial injury in the late phases of disease, usually associated with acute respiratory distress syndrome, multiorgan failure, and mortality. Overall, high cytokine levels may represent the key player of myocardial injury in COVID-19, being related to direct myocardial injury, endothelial dysfunction, destabilization of coronary plaque, and microthrombogenesis.

Future Perspectives

Troponin represents a useful marker of disease progression and prognosis in COVID-19. As noted by Guo et al, the 16% of their patients with underlying CVD but normal troponin levels had a relatively favorable outcome. Therefore, myocardial biomarkers should be evaluated in patients with CVD who develop COVID-19 for risk stratification purposes to potentially lead to earlier and more aggressive interventions.
Numerous therapies have been proposed worldwide to reduce COVID-19-associated morbidity and mortality. Some are antiviral drugs acting directly on SARS-CoV-2, with conflicting results to date. Other ongoing trials are testing immunomodulating agents, aimed at decreasing the excessive inflammatory response that characterizes severe disease progression. Because evidence of inflammatory cell infiltration has been reported in the alveoli of patients with acute respiratory distress syndrome associated with SARS-CoV-2 infection, this finding could justify the use of corticosteroids in patients with COVID-19. Another therapeutic possibility is drugs or biologics that act on the cytokine storm, especially targeting IL-1 and IL-6. Further observations on myocardial enzyme curves and imaging studies in patients treated with those drugs are needed to correlate immunomodulation with myocardial protection in COVID-19.

Another important issue in this disease is prevention of thrombotic complications. As noted, severe COVID-19 has been associated with high levels of d-dimer as a marker of a general prothrombotic state. Based on the immunothrombosis model, which highlights a bidirectional relationship between the immune system and thrombin generation, blocking thrombin by heparin may dampen the inflammatory response. Furthermore, heparin also has an anti-inflammatory function, which may be relevant in this setting. Several publications have demonstrated this property and some of the described mechanisms include binding to inflammatory cytokines, inhibition of neutrophil chemotaxis and leukocyte migration, neutralization of the positively charged peptide complement factor C5a, and sequestration of acute phase proteins. A systematic review concluded that, in the clinical setting, heparin can decrease the level of inflammatory biomarkers but stressed the need for more data from larger studies.

**Conclusions**

Elevated troponin levels are frequent in patients with COVID-19 and significantly associated with fatal outcomes. Several mechanisms may explain this phenomenon: viral myocarditis, cytokine-driven myocardial damage, microangiopathy, and unmasked CAD.

At present, none of these mechanisms have been definitely proven to be the main driver of troponin elevation and/or myocardial damage in patients with COVID-19. However, we posit that, although COVID-19 initially presents as a primarily respiratory condition, it quickly involves the cardiovascular system through an imbalance of the renin–angiotensin–aldosterone system mediated by ACE2 depletion. This mechanism may complicate the clinical course mediated through the inflammatory response, endothelial dysfunction and microvascular damage.

Additional study of these mechanisms is clearly needed and may influence the search for ways to prevent myocardial damage (eg, immunomodulating drugs). Given the impact of myocardial damage in the pathophysiology and prognosis of patients with COVID-19, the inclusion of cardiovascular end points in ongoing drug trials is essential.

It is reasonable to triage patients with COVID-19 according to the presence of underlying CVD and evidence of myocardial injury for prioritized treatment and even more aggressive treatment strategies in an effort to decrease mortality.

**References**

1. 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.
2. World Health Organization. Coronavirus disease 2019 (COVID-19) situation report – 85. Available at: https://relief-web.int/report/world/coronavirus-disease-2019-covid-19-situation-report-85-14-april-2020.
3. Guan W, Ni Z, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020 Feb 28. [Epub ahead of print].
4. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13.
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 Feb 7. [Epub ahead of print].
6. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020 Mar 27. [Epub ahead of print].
7. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020 March 25. [Epub ahead of print].
8. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective study. Lancet 2020;395:1054–62.
9. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020 Feb 20. [Epub ahead of print].
10. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020 Mar 26. [Epub ahead of print].
11. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020 March 3. [Epub ahead of print].
12. He XW, Lai JS, Cheng J, Wang MW, Liu YJ, Xiao ZC, et al. [Impact of complicated myocardial injury on the clinical outcome of severe or critically ill COVID-19 patients]. Zhonghua Xue Yan Hua Za Zhi 2020;48:E011.
13. Wang L, He W, Yu X, Hu D, Bao M, Liu H, et al. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. J Infect 2020 Mar 30. [Epub ahead of print].
14. Long B., Long D.A., Tannenbaum L., Koyfman A. An emergency medicine approach to troponin elevation due to causes other than occlusion myocardial infarction. Am J Emerg Med. [Epub ahead of print].
15. Frencken JF, van Baal L, Kappen TH, Donker DW, Horn J, van der Poll T, et al. Myocardial injury in critically ill patients with community-acquired pneumonia: A cohort study. Ann Am Thorac Soc 2019;16:606–12.
16. Menéndez R, Méndez R, Aldás I, Reyes S, Gonzalez-Jimenez P, España PP, et al. Community-acquired pneumonia patients at risk for early and long-term cardiovascular events are identified by cardiac biomarkers. Chest 2019;156:1080–91.

17. Caforio ALP, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2013;34:2636–48. 2648a–8d.

18. Maekawa Y, Ozoumian M, Opavsky MA, Liu PP. Connecting the missing link between dilated cardiomyopathy and viral myocarditis: virus, cytoskeleton, and innate immunity. Circulation 2007;115:5–8.

19. Lawson CM. Evidence for mimicry by viral antigens in animal models of autoimmune disease including myocarditis. Cell Mol Life Sci CMLS 2000;57:552–60.

20. Badorff C, Knowlton KU. Dystrophin disruption in enterovirus-induced myocarditis and dilated cardiomyopathy: from bench to bedside. Med Microbiol Immunol (Berl) 2004;193:121–6.

21. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger 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;181: 271–80.e8.

22. Chen L, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. Cardiovasc Res 2020 mar 20. [Epub ahead of print].

23. Patel VB, Zhong J-C, Grant MB, Oudit GY. Role of the ACE2/angiotensin 1-7 axis of the renin-angiotensin system in heart injury. Circ Res 2016;118:1313–26.

24. Vadugananathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin—angiotensin—aldosterone system inhibitors in patients with Covid-19. N Engl J Med 2020;382:1653–9.

25. Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, Penninger JM, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur J Clin Invest 2009;39:618–25.

26. Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci 2020;63:457–60.

27. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus (SARS-CoV-2) outbreak in Wuhan, China: a study of 41 cases. N Engl J Med 2020;382:727–33.

28. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020 March 27. [Epub ahead of print].

29. Zeng JH, Liu Y-X, Yuan J, Wang FX, Wu WB, Li JX, et al. First case of COVID-19 infection with fulminant myocarditis complication: case report and insights. Life Sci 2020 March 11. https://doi.org/10.1016/j.preprints.202003.0180.v1. [Epub ahead of print] 11 March 2020.

30. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis treated with glucocorticoid and human immunoglobulin. Eur Heart J 2020 Mar 16. [Epub ahead of print].

31. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020;8:420–2.

32. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 2004;203:631–7.

33. Tikellis C, Bernardi S, Burns WC. Angiotensin-converting enzyme 2 is a key modulator of the renin-angiotensin system in cardiovascular and renal disease. Curr Opin Nephrol Hypertens 2011;20:62–8.

34. Kuster GM, Pfister O, Burkard T, Zhou Q, Twerebold R, Haaf P, et al. SARS-CoV-2: should inhibitors of the renin–angiotensin system be withdrawn in patients with COVID-19? Eur Heart J 2020 Mar 20. [Epub ahead of print].

35. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med 2020;46:586–90.

36. Guo J, Huang Z, Lin L, Lv J. Coronavirus disease 2019 (COVID—19) and cardiovascular disease: a viewpoint on the potential influence of angiotensin—converting enzyme inhibitors/angiotensin receptor blockers on onset and severity of severe acute respiratory syndrome coronavirus 2 infection. J Am Heart Assoc 2020;9:e016219.

37. Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. J Thromb Thrombolysis 2020 Apr 3. [Epub ahead of print].

38. Chong PY, Chui P, Ling AE, Franks TJ, Tai DY, Leo YS, et al. Analysis of deaths during the severe acute respiratory syndrome (SARS) epidemic in Singapore: challenges in determining a SARS diagnosis. Arch Pathol Lab Med 2004;128:195–204.

39. Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association? Eur Heart J 2020 Mar 30. [Epub ahead of print].

40. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost JTH 2020;18:844–7.

41. Idell S. Coagulation, fibrinolysis, and fibrin deposition in acute lung injury. Crit Care Med 2003;31:S213–20.

42. Chang L-Y, Lu C-Y, Shao P-L, Lee PL, Lin MT, Fan TY, et al. Viral infections associated with Kawasaki disease. J Formos Med Assoc Taiwan Yi Zhi 2014;113:148–54.

43. Shirato K, Imada Y, Kawase M, Nakagaki K, Matsuyma S, Taguchi F. Possible involvement of infection with human coronavirus 229E, but not NL63, in Kawasaki disease. J Med Virol 2014;86:2146–53.

44. Giray T, Bıçer S, Küçük Ö, Cöl D, Yalvaç Z, Gürol Y, et al. Four cases with Kawasaki disease and viral infection: aetiolog or association. Infecz Med 2016;24:340–4.

45. Ding Y, Wang H, Shen H, Li Z, Geng J, Han H, et al. The clinical pathology of severe acute respiratory syndrome (SARS) in patients from China J Pathol 2004;200:282–9.

46. Chen Y, Li Y, Liu X, et al. Potential pathophysiological mechanisms underlying COVID-19-induced myocardial injury. Chin J Pathophysiol 2020;36:573–6.

47. Zheng Y-Y, Ma Y-T, Zhang J-Y, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol 2020;17:259–60.

48. Pan X, Xu D, Zhang H, Zhou W, Wang LH, Cui XG. Identification of deaths during the severe acute respiratory syndrome coronavirus 2 infection. JAMA Cardiol 2020 Mar 31. [Epub ahead of print].

49. Madjid M, Miller CC, Zarubaev VV, Marinich IG, Kiseol OF, Lobzin YV, et al. Influenza epidemics and acute respiratory disease activity are associated with a surge in autopsy-confirmed coronary heart disease death: results from 8 years of autopsies in 34 892 subjects. Eur Heart J 2007;28:1205–10.

50. Nguyen JL, Yang W, Ito K, Matte TD, Shaman J, Kinley PL. Seasonal influenza infections and cardiovascular disease mortality. JAMA Cardiol 2016;1:274.

51. Kwong JC, Schwartz KL, Campitelli MA, Chung H, Crowcroft NS, Karnauchow T, et al. Acute myocardial infarction after laboratory-confirmed influenza infection. N Engl J Med 2018;378:345–53.
52. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. N Engl J Med 2004;351:2611–8.

53. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J 2018;72:2231–64.

54. Bonow RO, Fonarow GC, O’Gara PT, Yancy CW. Association of coronavirus disease 2019 (COVID-19) with myocardial injury and mortality. JAMA Cardiol 2020 Mar 27. [Epub ahead of print].

55. Peiris J, Chu C, Cheng V, Chan KS, Hung IF, Poon LL, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet 2003;361:1767–72.

56. Xiong T-Y, Redwood S, Prendergast B, Chen M. Coronaviruses and the cardiovascular system: acute and long-term implications. Eur Heart J 2020 Mar 18. [Epub ahead of print].

57. Peiró C, Moncada S. Substituting angiotensin-(1-7) to prevent lung damage in SARS-CoV2 infection? Circulation 2020 Apr 3. [Epub ahead of print].

58. Stanciu AE. Cytokines in heart failure. Advances in clinical chemistry. New York: Elsevier; 2019. p. 63–113.

59. Kofler S, Nickel T, Weis M. Role of cytokines in cardiovascular diseases: a focus on endothelial responses to inflammation. Clin Sci Lond Engl 1979 2005;108:205–13.

60. Mirzaei H, Ferns GA, Avan A, et al. Cytokines and MicroRNA in coronary artery disease. Advances in clinical chemistry. New York: Elsevier; 2019. p. 47–70.

61. Teijaro JR, Walsh KB, Cahalan S, Fremgen DM, Roberts E, Scott F, et al. Endothelial cells are central orchestrators of cytokine amplification during influenza virus infection. Cell 2011;146:980–91.

62. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. N Engl J Med 2020 Mar 18. [Epub ahead of print].

63. Conti P, Gallenga CE, Tette G, Caraffa A, Ronconi G, Younes A, et al. How to reduce the likelihood of coronavirus-19 (CoV-19 or SARS-CoV-2) infection and lung inflammation mediated by IL-1. J Biol Regul Homeost Agents 2020 Mar 31. [Epub ahead of print].

64. Zhang C, Wu Z, Li J-W, Zhao H, Wang GQ. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents 2020 Mar 29. [Epub ahead of print].

65. Gaertner F, Massberg S. Blood coagulation in immunothrombosis—At the frontline of intravascular immunity. Semin Immunol 2016;28:561–9.

66. Thachil J. The versatile heparin in COVID-19. J Thromb Haemost 2020 Apr 2. [Epub ahead of print].

67. Young E. The anti-inflammatory effects of heparin and related compounds. Thromb Res 2008;122:743–52.

68. Li J-P, Vlodavsky I. Heparin, heparan sulfate and heparanase in inflammatory reactions. Thromb Haemost 2009;102:823–8.

69. Esmon CT. Targeting factor Xa and thrombin: impact on coagulation and beyond. Thromb Haemost 2014;111:625–33.

70. Poterucha TJ, Libby P, Goldhaber SZ. More than an anticoagulant: do heparins have direct anti-inflammatory effects? Thromb Haemost 2017;117:437–44.

71. Mousavi S, Moradi M, Khoshidahmad T, et al. Anti-inflammatory effects of heparin and its derivatives: a systematic review. Adv Pharmacol Sci 2015;2015:507151.