Cardiovascular Pathophysiology Related to COVID-19 and Clinical Phenotypes

Subjects: Infectious Diseases

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The intricate relationship between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the cardiovascular system is an extensively studied pandemic topic, as there is an ever-increasing amount of evidence that reports a high prevalence of acute cardiac injury in the context of viral infection. In patients with Coronavirus disease 2019, COVID-19, a significant increase in serum levels of cardiac troponin or other various biomarkers was observed, suggesting acute cardiac injury, thus predicting both a severe course of the disease and a poor outcome.

Keywords: myocardial injury ; COVID-19 ; cytokines

1. The Pathophysiological Continuum between Infection and Cardiac Injury

Coronaviruses have a specific crown-like surface appearance and a structure made from four structural proteins, known as the spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins. SARS-CoV-2 enters the cell after the proteolytic cleavage of the S protein followed by its binding to the cell-surface receptor angiotensin 2 conversion enzyme (ACE 2) [1]. The latter is a membrane protein that plays a vital role in the cardiovascular and immune systems and is well expressed in the lung and heart endothelial cells, macrophages, and cardiomyocytes [2]. ACE 2 levels are higher in patients receiving treatment with medications that inhibit the renin-angiotensin-aldosterone system, such as ACE inhibitors or angiotensin receptor blockers [3]. The use of these neurohormonal modulating drugs was controversial in the early stages of the pandemic. Nevertheless, multiple studies conducted during the last two years have demonstrated that is not advisable to interrupt their chronic administration, nor to change the therapeutic class. Basically, the current consensus emphasizes that maintaining the previously prescribed treatment does not adversely affect the course of viral infection and continues to provide cardiac protection at the same time [4][5][6]. Moreover, ACE 2 has been shown to provide additional protective effects against pulmonary injury in patients with ARDS due to severe forms of COVID-19 [7].

A SARS-CoV-2 infection may both exacerbate pre-existing cardiovascular comorbidities and trigger new ones. Heart failure (HF) is among the most frequently reported cardiovascular complications related to COVID-19 infection, being diagnosed in up to 24% of patients, while venous thromboembolism was identified in 21% of cases, followed by dysrhythmias and myocarditis in 17% and 7% of patients, respectively [7][8][9][10]. The main risk factors for SARS-CoV-2-induced acute cardiac injury include smoking, male gender, and comorbidities, including diabetes mellitus, arterial hypertension, and coronary artery disease [11][12]. The imbalance between pro-inflammatory and anti-inflammatory mediators may be responsible for the development of major cardiovascular events [13]. The response to infection is governed by the adequate activity of both the innate and acquired immune systems.

Two major immunity defects are required for the onset of the critical illness in COVID-19 which is frequently associated with myocardial injury. The first is represented by a lack of initial control over the viral clearance, mainly through the innate immune system, while the second resides in the inability to regulate a balanced production of pro- and anti-inflammatory cytokines [14][15]. The innate immune response to viral infection is based on interferon types I and III. On one hand, in SARS-CoV-2 infection, interferon levels were observed to increase only in critical patients, whereas in all other positive cases the immune response was reduced and/or delayed. On the other hand, the response was quicker and more vigorous in patients hospitalized for influenza pneumonia. This particular ability of SARS-CoV-2 to elude the early innate immune response may lead to an insufficient viral clearance, followed by the development of a hyperinflammatory condition, and, in certain categories of patients, the onset of acute respiratory distress syndrome (ARDS) [16][17].

Moreover, the innate immunity may also trigger the adaptive immunity consisting of CD4+ and CD8+ T cell lymphocytes and B lymphocytes that produce neutralizing antibodies. The combined T and B cell responses contribute to SARS-CoV-2 infection resolution and a robust immunity [17]. Cytokines, predominantly produced by macrophages, mast cells, and dendritic cells, but also by B and T lymphocytes, play a central role in coordinating the immune response. A balanced synthesis of cytokines is required for an effective antiviral effect, but their excessive serum levels may cause a cytokine storm with massive collateral damage to vascular structures and alveolar barriers [18].

Cardiac troponin levels have been shown to be linearly correlated with C-reactive protein levels, indicating that acute cardiac injury may be closely related to systemic inflammation [19]. The distinctive pathogenesis of vascular damage is promoted by the presence of the cellular receptor of SARS-CoV-2 on the vascular cell's surface, contributing to endothelial dysfunction [20]. Furthermore, direct infection of the endothelial lining may lead to vasculitis and apoptosis. As a result, the exposed subendothelial surface facilitates platelet aggregation in an attempt to repair the vascular damage. However, even in the absence of direct endothelial invasion, high levels of inflammatory cytokines have the ability to impair the endothelial function by increasing the number of adhesion molecules, thus promoting thrombogenic processes [21][22][23]. Coagulopathic events include thrombin generation, platelet consumption, and increased levels of fibrinogen and the Von Willebrand factor [24]. Viral coagulopathy is manifested by venous thrombosis, usually further complicated with venous thromboembolism but also by arterial thrombosis, most commonly found in myocardial or cerebral territories. Parenteral anticoagulants, such as unfractionated heparin and low molecular weight heparins, are routinely used in the treatment of patients admitted with moderate-to-severe COVID-19, while direct oral anticoagulants are predominantly used in the ambulatory management of patients presenting a mild form of the disease [25].

2. Acute Coronary Syndromes in the COVID-19 Pandemic: The "Perfect" Cardio-Inflammatory Symbiosis

The interplay between atherosclerotic disease and inflammation has been well-described, starting with the formation of atheroma plaque up to its erosion and rupture, with the subsequent occurrence of an acute coronary syndrome [26]. Total occlusion of a coronary artery induced by an eroded, vulnerable atherosclerotic plaque and the overlying thrombus formation might be a consequence of a hyperinflammatory environment along with the prothrombotic state induced by SARS-CoV-2 infection. This mechanism represents the basic pathophysiological substrate of ST-elevation myocardial infarction (STEMI) but also accounts for approximately 25% of cases admitted with non-ST-elevation myocardial infarction (NSTEMI) [27][28]. The real epidemiological impact of COVID-19 in patients with cardiac ischemia is mirrored by the worrisome incidence rates of myocardial infarction among SARS-CoV-2 positive cases, ranging from 1.1% to 8.9% [29][30]. The risk of developing myocardial infarction is significantly higher in the early stages of the infection, with a 5-fold increase in risk during the first 14 days of COVID-19, compared to the pre-illness period [31].

Those high figures can be explained, at least partially, by certain similarities concerning the inflammatory pathways operating both in COVID-19 and atherosclerosis. Even before the COVID-19 pandemic, the American Heart Association (AHA) suggested that viral infections could destabilize the atherosclerotic plaques, and various collagenolytic enzymes, such as matrix metalloproteinases (MMP), were becoming associated with increased plaque vulnerability [32][33]. Those MMPs can be activated by a plethora of cytokines (e.g., TNF-alpha, INF-γ, IL-1, and IL-6), thus diminishing the cohesion of the atherosclerotic plaque and consecutively increasing the risk of acute coronary syndromes [33][34]. Based on these observations, the COVID-19 pandemic again turned the spotlight on statins' pleiotropic effects, primarily based on their anti-inflammatory response, doubled by the amelioration of the endothelial function. The plaque stabilization occurs via the enhanced calcification and thickening of the fibrous cap, with inflammation playing a central role. The large JUPITER study even highlighted that patients treated with rosuvastatin presented decreased serum levels of C-reactive protein and a reduced apparition of major cardiovascular events, compared to the placebo group [35][36], while a large Swedish study claimed that previous chronic treatment with statins exhibited a modest preventive therapeutic effect on COVID-19 mortality [37]. The continuation and/or initiation of statins in COVID-19 patients may also be beneficial from the perspective of the lipid profile, as hypercholesterolemia is associated with an increased susceptibility to SARS-CoV-2 infection. It was demonstrated that high cholesterol levels are associated not only with increased density of ACE2 receptors on host cell membranes but also with a more effective interaction between the viral spike protein and the ACE2 receptors [38].

In addition, significant platelet activation occurs during the systemic inflammation associated with SARS-CoV-2 infection. This phenomenon is induced by the binding of pro-inflammatory interleukins to the platelet surface receptors, and by reducing the availability of endothelial nitric oxide. At the same time, neutrophils express adhesion molecules favoring platelet aggregation. These mechanisms, together with endothelial injury, facilitate the interaction between the platelets and the endothelial cells, thus aggravating the thromboinflammatory pathways, representing a hallmark for COVID-19 [39].

Even if mortality caused by acute myocardial infarction has reached its lowest level in the era of percutaneous coronary intervention (PCI), it still remains associated with considerable morbidity. Restoring adequate myocardial reperfusion in a timely manner limits the area of the infarction and significantly improves the outcome, regardless of the associated pathologies [40]. However, contradictorily, the resumption of blood flow to the ischemic area may lead to additional myocardial damage, a phenomenon known as reperfusion myocardial injury. This paradoxical mechanism may be responsible for the loss of up to 50% of viable myocardium and elevated cytokine levels, in addition, biochemical and metabolic changes caused by hypoxia play a core role in its occurrence [41]. A cohort study including patients over the age of 65 showed that more than three-quarters (76%) of patients who survived a first acute myocardial infarction developed HF in the next 5 years [42]. Despite modern reperfusion strategies and neurohormonal blocking therapies, the incidence of HF remains unacceptably high and there is an urgent need for better management in order to improve both survival and quality of life after myocardial infarction. However, abnormally activated immune responses during infection with SARS-CoV-2 lead to a suboptimal myocardial repair with a higher incidence of HF [43].

Type 2 myocardial infarction is caused by the imbalance between a deficient myocardial oxygen supply and an increased metabolic demand, due to specific cardiac and non-cardiac pathological conditions.

A variable association of some commonly met mechanisms in COVID-19 patients seems relevant in this context:

(1)Previously stable coronary artery disease that limits myocardial perfusion;

(2)Endothelial dysfunction in the coronary microcirculation;

(3)Significantly increased arterial hypertension resulting from elevated circulating levels of Angiotensin II and catecholamines;

(4)Hypoxemia due to acute respiratory distress syndrome (ARDS) or in situ pulmonary vascular thrombosis. In the case of sepsis, pulmonary injury, and respiratory failure, significant increases in biomarkers of overload and myocardial injury can be noticed [44][45].

Moreover, infections in general, and COVID-19-associated pneumonia in particular, can unbalance the thin equilibrium between myocardial O_2 supply and consumption. The increase in the physiological demand for O_2 caused by systemic infection can be so significant that this imbalance occurs even in the absence of angiography-relevant atherosclerotic plaques. Several studies emphasized this pathway as the main mechanism of COVID-related acute cardiac injury. Essentially, vasodilation represents the main pathophysiological mechanism of the response of the cardiovascular system to sepsis. In addition, hypotension is the natural consequence of vasodilation, which can even progress to hemodynamic collapse, thus inducing or aggravating coronary hypoperfusion with subsequent acute myocardial injury through a reduced O_2 supply [46]. At the same time, in the context of sepsis, reflex tachycardia increases the myocardial oxygen demand. Of course, the presence of atheroma plaques is a risk factor for the unfavorable evolution in patients with sepsis, increasing the risk of acute myocardial injury [47][48], but COVID-19 is also highly associated with non-atherosclerotic coronary perfusion impairment, such as spasm of the coronary arteries, dissection of the coronary wall, microthrombosis in the context of the hypercoagulant state, or vasculitis-like injury of the coronary vessels [49][50]. Regardless of the intimate mechanism of COVID-19-related myocardial infarction with non-obstructive coronary arteries, the patients' prognosis is poor, with high mortality rates mainly due to the increased prevalence of severe comorbidities, such as ARDS, obesity, or congenital thrombophilia [50][51].

Under these circumstances, it is difficult to clearly differentiate between patients with acute coronary syndromes, such as unstable angina or NSTEMI, and those with acute myocarditis or myocardial injury caused exclusively by metabolic imbalances in the context of fever, tachycardia, or hypoxemia due to ARDS [45]. Those patients require an integrative diagnostic and therapeutic approach, focusing not only on SARS-CoV-2 infection and the major associated cardiovascular pathology but also on the frequently coexisting factors of poor prognosis.

3. Heart Failure in COVID-19 Patients: Different Pathways, Same Target

Patients admitted for COVID-19 may develop either an acute decompensation of a chronic, previously stable HF or a de-novo acute HF as an immediate consequence of acute cardiac injury [52]. Pathogenesis of COVID-19 cardiomyopathy is intimately related to inflammatory cytokines, referring here to diastolic dysfunction and increased myocardial stiffness mediated by interleukin-6 (IL-6), negative inotropic effects exerted by interleukin-1β (IL-1β), or myocardial fibrosis induced by IL-1β and tumor necrosis factor alfa (TNF-α). Even higher levels of those biomarkers are detected during cytokine storms in the severe forms of SARS-CoV-2 infection [53][54][55]. A significantly increased incidence of acute HF was

reported in patients deceased due to severe COVID-19, as compared to their survivor counterparts [56]. Moreover, the in-hospital mortality rate in patients presenting both acute HF and COVID-19 was extremely high, reaching up to 44.1% at the peak of the pandemic. Beyond the acute phase, COVID-19 may be responsible for HF as a long-term cardiovascular complication, but further clinical studies are required [52].

4. Myocarditis in COVID-19: Between Certainties and Controversies

The correlation between human coronaviruses and myocarditis is well-established [57]. Concerning SARS-CoV-2 infection, three pathophysiological mechanisms may contribute to myocarditis occurrence in patients with COVID-19. Firstly, it is worth mentioning the direct viral cardiomyocytes' invasion with subsequent injury accompanied by various immune mechanisms such as T cell-mediated cytotoxicity and cytokines' negative inotropic effects. Additionally, the autoimmune mechanisms triggered as a response to the release of cryptic antigens from cardiomyocytes following SARS-CoV-2-induced lesions could also enhance the development of myocarditis [58][59][60]. A very recent extensive study, including more than 100,000 subjects diagnosed with COVID-19, showed a 2 to 3-fold higher risk of myocarditis among infected patients [61], while the net prevalence of myocarditis among cases that required hospitalization was 2.4 per 1000 admissions [62]. Importantly, myocarditis was far more prevalent among non-vaccinated young males, compared to their non-vaccinated counterparts [63].

There is also evidence to support the hypothesis of molecular mimicry [64]. Necropsy studies that included endomyocardial biopsy suggest that direct viral toxicity is not the main mechanism of myocardial injury, as current evidence indicates that viral presence in the heart tissue is not necessarily associated with myocarditis [65]. Local myocardial inflammation, as well as severe systemic inflammation, can be a direct cause of myocardial injury in COVID-19 cases. It is already known that patients with sepsis-associated cardiomyopathy have an exacerbated inflammatory status that is characterized by elevated circulating levels of several cytokines, including the previously-mentioned IL-6 and TNF-α [45]. In vitro exposure to IL-6 has reduced the cardiomyocyte contractility, while recombinant TNF-α administration decreased the ejection fraction of the left ventricle in experimental models. Mechanisms of these myocytotoxic effects include the modulation of calcium channels' flows and nitric oxide synthesis which are thought to play a major role in depressing myocardial function in sepsis [45][66][67]. The reversible acute cardiac dysfunction occurring in the context of a septic environment is known as sepsis-induced cardiomyopathy (SICM). Immune response to infection leads to mitochondrial dysfunction, disruption of contractile apparatus by altering calcium balance, and myocyte apoptosis [68][69]. Increased levels of cardiac troponin (cTn) detected in SICM may also appear as a consequence of myocardial edema [70].

However, it remains unclear to what extent myocarditis is caused by direct viral myocardial damage or is just a consequence of systemic inflammation.

5. Stress Cardiomyopathy: An Additional Trigger

The incidence of stress cardiomyopathy (also known as tako-tsubo cardiomyopathy) during the COVID-19 pandemic appears to follow an increasing trend, with psychological distress and anxiety having a core role in its onset. Incriminated mechanisms include the sympathetic activation causing catecholamine-induced myocardial stunning and microvascular dysfunction that is transient and more frequently observed in elderly women [71]. It is worth mentioning that a study showed that this hypercatholaminergic condition due to cytokine storm in critical patients (from ICU departments) induces a significantly increased blood pressure, compared to non-critical patients (145 mmHg vs. 122 mmHg; $p < 0.001$); interestingly, this hypertensive pattern in patients with severe forms of COVID-19 is actually associated with an improved prognosis, a lower need for inotropic support, and a decreased risk of developing cardiogenic shock or multiple organ dysfunction [72].

6. Right Ventricular Failure: A Key Element in the Hemodynamics of COVID-19 Patients

The right ventricle (RV) represents an essential component in the hemodynamic homeostasis of patients with COVID-19, an acute RV dysfunction being considered a factor of poor prognosis. Several mechanisms have a complementary role in RV injury [73][74]:

- Pulmonary hypertension induced by vasoactive mediators;
- Pulmonary vasoconstriction due to hypoxemia;
- Vascular remodeling;
- Microthrombi in pulmonary vessels due to inflammatory cytokines;

- Mechanical compression due to atelectasis, interstitial edema, or associated pleural effusion.

Moreover, in ICU-admitted patients due to a severe course of COVID-19, persistent ventilation with elevated positive expiratory pressures leads to a significantly increased RV afterload, thus inducing additional mechanical strain in a cavity with rather thin walls and further reducing an already impaired cardiac output [74]. This pathophysiological chain of events is clearly expressed by the rise of serum concentrations for several biomarkers, such as NT-proBNP, ST2, or GDF-15 molecules, that express various mechanisms suggestive not only of myocardial dysfunction but also of inflammation or oxidative stress, conditions that are commonly found in infected patients [75][76][77].

References

1. Jackson, C.B.; Farzan, M.; Chen, B.; Choe, H. Mechanisms of SARS-CoV-2 entry into cells. Nat. Rev. Mol. Cell. Biol. 2022, 23, 3–20.
2. Guzik, T.J.; Mohiddin, S.A.; Dimarco, A.; Patel, V.; Savvatis, K.; Marelli-Berg, F.; Madhur, M.S.; Tomaszewski, M.; Maffia, P.; D'Acquisto, F.; et al. COVID-19 and the cardiovascular system: Implications for risk assessment, diagnosis, and treatment options. Cardiovasc. Res. 2020, 116, 1666–1687.
3. Zheng, Y.Y.; Ma, Y.T.; Zhang, J.Y.; Xie, X. COVID-19 and the cardiovascular system. Nat. Rev. Cardiol. 2020, 17, 259–260.
4. Zhosbøl, E.L.; Butt, J.H.; Østergaard, L.; Andersson, C.; Selmer, C.; Kragholm, K.; Schou, M.; Phelps, M.; Gislason, G.H.; Gerds, T.A.; et al. Association of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use With COVID-19 Diagnosis and Mortality. JAMA 2020, 324, 168–177.
5. Zhang, P.; Zhu, L.; Cai, J.; Lei, F.; Qin, J.J.; Xie, J.; Liu, Y.M.; Zhao, Y.C.; Huang, X.; Lin, L.; et al. Association of Inpatient Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers with Mortality Among Patients with Hypertension Hospitalized With COVID-19. Circ. Res. 2020, 126, 1671–1681.
6. Guo, T.; Fan, Y.; Chen, M.; Wu, X.; Zhang, L.; He, T.; Wang, H.; Wan, J.; Wang, X.; Lu, Z. Cardiovascular Implications of Fatal Outcomes of Patients with Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020, 5, 811–818.
7. Imai, Y.; Kuba, K.; Rao, S.; Huan, Y.; Guo, F.; Guan, B.; Yang, P.; Sarao, R.; Wada, T.; Leong-Poi, H.; et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 2005, 436, 112–116.
8. Chen, T.; Wu, D.; Chen, H. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: Retrospective study. BMJ 2020, 368, m1091.
9. Lu, Y.F.; Pan, L.Y.; Zhang, W.W.; Cheng, F.; Hu, S.S.; Zhang, X.; Jiang, H.Y. A meta-analysis of the incidence of venous thromboembolic events and impact of anticoagulation on mortality in patients with COVID-19. Int. J. Infect. Dis. 2020, 100, 34–41.
10. Liu, K.; Fang, Y.Y.; Deng, Y.; Liu, W.; Wang, M.F.; Ma, J.P.; Xiao, W.; Wang, Y.N.; Zhong, M.H.; Li, C.H.; et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin. Med. J. 2020, 133, 1025–1031.
11. Abate, S.M.; Mantefardo, B.; Nega, S.; Chekole, Y.A.; Basu, B.; Ali, S.A.; Taddesse, M. Global burden of acute myocardial injury associated with COVID-19: A systematic review, meta-analysis, and meta-regression. Ann. Med. Surg. 2012, 68, 102594.
12. Li, X.; Guan, B.; Su, T.; Liu, W.; Chen, M.; Bin-Waleed, K.; Guan, X.; Gary, T.; Zhu, Z. Impact of cardiovascular disease and cardiac injury on in-hospital mortality in patients with COVID-19: A systematic review and meta-analysis. Heart 2020, 106, 1142–1147.
13. Kilic, T.; Ural, D.; Ural, E.; Yumuk, Z.; Agacdiken, A.; Sahin, T.; Kahraman, G.; Kozdag, G.; Vural, A.; Komsuoglu, B. Relation between proinflammatory to anti-inflammatory cytokine ratios and long-term prognosis in patients with non-ST elevation acute coronary syndrome. Heart 2006, 92, 1041–1046.
14. Paludan, S.R.; Mogensen, T.H. Innate immunological pathways in COVID-19 pathogenesis. Sci. Immunol. 2022, 7, eabm5505.
15. Metkus, T.S.; Sokoll, L.J.; Barth, A.S.; Czarny, M.J.; Hays, A.G.; Lowenstein, C.J. Myocardial Injury in Severe COVID-19 Compared with Non-COVID-19 Acute Respiratory Distress Syndrome. Circulation 2021, 143, 553–565.
16. Galani, I.E.; Rovina, N.; Lampropoulou, V.; Triantafyllia, V.; Manioudaki, M.; Pavlos, E. Untuned antiviral immunity inCOVID-19 revealed by temporal type I/III interferon patterns and flu comparison. Nat. Immunol. 2021, 22, 32–40.
17. Sette, A.; Crotty, S. Adaptive immunity to SARS-CoV-2 and COVID-19. Cell 2021, 184, 861–880.
18. Fajgenbaum, D.C.; June, C.H. Cytokine Storm. N. Engl. J. Med. 2020, 383, 2255–2273.

19. Wu, C.; Hu, X.; Song, J.; Du, C.; Xu, J.; Yang, D.; Chen, D.; Zhong, M.; Jiang, J.; Xiong, W.; et al. Heart injury signs are associated with higher and earlier mortality in coronavirus disease 2019 (COVID-19). medRxiv 2002.

20. Huertas, A.; Montani, D.; Savale, L.; Pichon, J.; Tu, L.; Parent, F.; Guignabert, C.; Humbert, M. Endothelial cell dysfunction: A major player in SARS-CoV-2 infection (COVID-19)? Eur. Respir. J. 2020, 56, 2001634.

21. Koupenova, M.; Clancy, L.; Corkrey, H.A.; Freedman, J.E. Circulating platelets as mediators of immunity, inflammation, and thrombosis. Circ. Res. 2018, 122, 337–351.

22. Varga, Z.; Flammer, A.J.; Steiger, P.; Haberecker, M.; Andermatt, R.; Zinkernagel, A.S.; Mehra, M.R.; Schuepbach, R.A.; Ruschitzka, F.; Moch, H. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020, 395, 1417–1418.

23. Koupenova, M.; Kehrel, B.E.; Corkrey, H.A.; Freedman, J.E. Thrombosis and platelets: An update. Eur. Heart J. 2017, 38, 785–791.

24. Gómez-Mesa, J.E.; Galindo-Coral, S.; Montes, M.C.; Muñoz Martin, A.J. Thrombosis and Coagulopathy in COVID-19. Curr. Probl. Cardiol. 2021, 46, 100742.

25. Kipshidze, N.; Dangas, G.; White, C.J.; Kipshidze, N.; Siddiqui, F.; Lattimer, C.R.; Carter, C.A.; Fareed, J. Viral Coagulopathy in Patients with COVID-19: Treatment and Care. Clin. Appl. Thromb. Hemost. 2020, 26, 1076029620936776.

26. Wolf, D.; Ley, K. Immunity and Inflammation in Atherosclerosis. Circ. Res. 2019, 124, 315–327.

27. Cohen, M.; Visveswaran, G. Defining and managing patients with non-ST-elevation myocardial infarction: Sorting through type 1 vs other types. Clin. Cardiol. 2020, 43, 242–250.

28. Eposito, L.; Cancro, F.P.; Silverio, A.; Di Maio, M.; Iannece, P.; Damato, A.; Alfano, C.; De Luca, G.; Vecchione, C.; Galasso, G. COVID-19 and Acute Coronary Syndromes: From Pathophysiology to Clinical Perspectives. Oxid. Med. Cell. Longev. 2021, 2021, 4936571.

29. Katsoularis, I.; Fonseca-Rodríguez, O.; Farrington, P.; Lindmark, K.; Connolly, A.-M.F. Risk of acute myocardial infarction and ischaemic stroke following COVID-19 in Sweden: A self-controlled case series and matched cohort study. Lancet 2021, 398, 599–607.

30. Shaw, P.; Senguttuvan, N.B.; Raymond, G.; Sankar, S.; Mukherjee, A.G.; Kunale, M.; Kodiveri Muthukaliannan, G.; Baxi, S.; Mani, R.R.; Rajagopal, M.; et al. COVID-19 Outcomes in Patients Hospitalised with Acute Myocardial Infarction (AMI): A Protocol for Systematic Review and Meta-Analysis. COVID 2022, 2, 138–147.

31. Modin, D.; Claggett, B.; Sindet-Pedersen, C.; Lassen, M.C.H.; Skaarup, K.G.; Jensen, J.U.S.; Fralick, M.; Schou, M.; Lamberts, M.; Gerds, T.; et al. Acute COVID-19 and the Incidence of Ischemic Stroke and Acute Myocardial Infarction. Circulation 2020, 142, 2080–2082.

32. Min, C.K.; Cheon, S.; Ha, N.Y.; Sohn, K.M.; Kim, Y.; Aigerim, A.; Kim, Y.S.; Shin, H.M.; Choi, J.Y.; Inn, K.S.; et al. Comparative and kinetic analysis of viral shedding and immunological responses in MERS patients representing a broad spectrum of disease severity. Sci. Rep. 2016, 6, 25359.

33. Sagris, M.; Theofilis, P.; Antonopoulos, A.S.; Tsioufis, C.; Oikonomou, E.; Antoniades, C.; Crea, F.; Kaski, J.C.; Tousoulis, D. Inflammatory Mechanisms in COVID-19 and Atherosclerosis: Current Pharmaceutical Perspectives. Int. J. Mol. Sci. 2021, 22, 6607.

34. Guizani, I.; Fourti, N.; Zidi, W.; Feki, M.; Allal-Elasmi, M. SARS-CoV-2 and pathological matrix remodeling mediators. Inflamm. Res. 2021, 70, 847–858.

35. Kattoor, A.J.; Pothineni, N.V.K.; Palagiri, D.; Mehta, J.L. Oxidative Stress in Atherosclerosis. Curr. Atheroscler. Rep. 2017, 19, 42.

36. Ridker, P.M.; Danielson, E.; Fonseca, F.A.; Genest, J.; Gotto, A.M.; Kastelein, J.J.; Koenig, W.; Libby, P.; Lorenzatti, A.J.; MacFadyen, J.G.; et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N. Engl. J. Med. 2008, 359, 2195–2207.

37. Bergqvist, R.; Ahlqvist, V.H.; Lundberg, M.; Hergens, M.P.; Sundström, J.; Bell, M.; Magnusson, C. HMG-CoA reductase inhibitors and COVID-19 mortality in Stockholm, Sweden: A registry-based cohort study. PLoS Med. 2021, 18, e1003820.

38. Tang, Y.; Hu, L.; Liu, Y.; Zhou, B.; Qin, X.; Ye, J.; Shen, M.; Wu, Z.; Zhang, P. Possible mechanisms of cholesterol elevation aggravating COVID-19. Int. J. Med. Sci. 2021, 18, 3533–3543.

39. Theofilis, P.; Sagris, M.; Antonopoulos, A.S.; Oikonomou, E.; Tsioufis, C.; Tousoulis, D. Inflammatory Mediators of Platelet Activation: Focus on Atherosclerosis and COVID-19. Int. J. Mol. Sci. 2021, 22, 11170.

40. Keeley, E.C.; Boura, J.A.; Grines, C.L. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: A quantitative review of 23 randomised trials. Lancet 2003, 361, 13–20.

41. Broch, K.; Anstensrud, A.K.; Woxholt, S.; Sharma, K.; Tøllefsen, I.M.; Bendz, B.; Aakhus, S.; Ueland, T.; Amundsen, B.H.; Damås, J.K.; et al. Randomized Trial of Interleukin-6 Receptor Inhibition in Patients with Acute ST-Segment Elevation Myocardial Infarction. J. Am. Coll. Cardiol. 2021, 77, 1845–1855.

42. Ezekowitz, J.A.; Kaul, P.; Bakal, J.A.; Armstrong, P.W.; Welsh, R.C.; McAlister, F.A. Declining in-hospital mortality and increasing heart failure incidence in elderly patients with first myocardial infarction. J. Am. Coll. Cardiol. 2009, 53, 13–20.

43. Halade, G.V.; Lee, D.H. Inflamation and resolution signaling in cardiac repair and heart failure. eBioMedicine 2022, 79, 103992.

44. Lala, A.; Johnson, K.W.; Januzzi, J.L.; Russak, A.J.; Paranjpe, I.; Richter, F.; Zhao, S.; Somani, S.; Van Vleck, T.; Vaid, A.; et al. Mount Sinai COVID Informatics Center. Prevalence and Impact of Myocardial Injury in Patients Hospitalized with COVID-19 Infection. J. Am. Coll. Cardiol. 2020, 76, 533–546.

45. Giustino, G.; Pinney, S.P.; Lala, A.; Reddy, V.Y.; Johnston-Cox, H.A.; Mechanick, J.I.; Halperin, J.L.; Fuster, V. Coronavirus and cardiovascular disease, myocardial injury, and arrhythmia: JACC focus seminar. J. Am. Coll. Cardiol. 2020, 76, 2011–2023.

46. Manolis, A.S.; Manolis, A.A.; Manolis, T.A.; Melita, H. COVID-19 and Acute Myocardial Injury and Infarction: Related Mechanisms and Emerging Challenges. J. Cardiovasc. Pharmacol. Ther. 2021, 26, 399–414.

47. Pergola, V.; Cabrelle, G.; Previtero, M.; Fiorencis, A.; Lorenzoni, G.; Dellino, C.M.; Montonati, C.; Continisio, S.; Masetto, E.; Mele, D.; et al. Impact of the “atherosclerotic pabulum” on in-hospital mortality for SARS-CoV-2 infection. Is calcium score able to identify at-risk patients? Clin. Cardiol. 2022, 45, 629–640.

48. Greer, J.R. Pathophysiology of cardiovascular dysfunction in sepsis. BJA Educ. 2015, 15, 316–321.

49. Basso, C.; Leone, O.; Rizzo, S.; De Gaspari, M.; van der Wal, A.C.; Aubry, M.C.; Bois, M.C.; Lin, P.T.; Maleszewski, J.J.; Stone, J.R. Pathological features of COVID-19 associated myocardial injury: A multicentre cardiovascular pathology study. Eur. Heart J. 2020, 41, 3827–3835.

50. Shamsi, F.; Hasan, K.Y.; Hashmani, S.; Jamal, S.F.; Ellaham, S. Review Article—Clinical Overview of Myocardial Infarction Without Obstructive Coronary Artey Disease (MINOCA). J. Saudi. Heart. Assoc. 2021, 33, 9–15.

51. Sheikh, A.B.; Ijaz, Z.; Javed, N.; Upadyay, S.; Shekhar, R. COVID-19 with non-obstructive coronary artery disease in a young adult. J. Community Hosp. Int. Med. Perspect. 2021, 11, 111–114.

52. Italia, L.; Tomasoni, D.; Bisegna, S.; Pancaldi, E.; Stretti, L.; Adamo, M.; Metra, M. COVID-19 and Heart Failure: From Epidemiology During the Pandemic to Myocardial Injury, Myocarditis, and Heart Failure Sequelae. Front. Cardiovasc. Med. 2021, 8, 713560.

53. Nguyen, N.; Nguyen, H.; Ukoha, C.; Hoang, L.; Patel, C.; Ikram, F.G.; Acharya, P.; Dhillon, A.; Sidhu, M. Relation of interleukin-6 levels in COVID-19 patients with major adverse cardiac events. Bayl. Univ. Med. Cent. Proc. 2021, 3, 6–9.

54. Rad, F.; Dabbagh, A.; Dorgalaleh, A.; Biswas, A. The Relationship between Inflammatory Cytokines and Coagulopathy in Patients with COVID-19. J. Clin. Med. 2021, 10, 2020.

55. Song, Y.; Gao, P.; Ran, T.; Qian, H.; Guo, F.; Chang, L.; Wu, W.; Zhang, S. High Inflammatory Burden: A Potential Cause of Myocardial Injury in Critically Ill Patients With COVID-19. Front. Cardiovasc. Med. 2020, 7, 128.

56. Timpau, A.S.; Miftode, R.; Petris, A.O.; Costache, I.I.; Miftode, I.L.; Rosu, F.M.; Anton-Paduraru, D.T.; Leca, D.; Miftode, E.G. Mortality Predictors in Severe COVID-19 Patients from an East European Tertiary Center: A Never-Ending Challenge for a No Happy Ending Pandemic. J. Clin. Med. 2021, 11, 58.

57. Siripanthong, B.; Nazarian, S.; Muser, D.; Deo, R.; Santangeli, P.; Khanji, M.Y.; Cooper, L.T., Jr.; Chahal, C.A.A. Recognizing COVID-19-related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management. Heart Rhythm 2020, 17, 1463–1471.

58. Dabbagh, M.F.; Aurora, L.; D’Souza, P.; Weinmann, A.J.; Bhargava, P.; Basir, M.B. Cardiac tamponade secondary to COVID-19. J. Am. Coll. Cardiol. 2020, 2, 1326–1330.

59. Fernandes, F.; Ramires, F.J.A.; Fernandes, F.D.; Simões, M.V.; Mesquita, E.T.; Mady, C. Pericardial Affections in Patients with COVID-19: A Possible Cause of Hemodynamic Deterioration. Arq. Bras. Cardiol. 2020, 115, 569–573.

60. Imazio, M.; Spodick, D.H.; Brucato, A.; Trinchero, R.; Adler, Y. Controversial issues in the management of pericardial diseases. Circulation 2010, 121, 916–928.

61. Priyadarshni, S.; Westra, J.; Kuo, Y.F.; Baillargeon, J.G.; Khalife, W.; Raji, M. COVID-19 Infection and Incidence of Myocarditis: A Multi-Site Population-Based Propensity Score-Matched Analysis. Cureus 2022, 14, e21879.

62. Ammirati, E.; Lupi, L.; Palazzini, M.; Hendren, N.S.; Grodin, J.L.; Cannistraci, C.V.; Schmidt, M.; Hekimian, G.; Peretto, G.; Bochaton, T.; et al. Prevalence, Characteristics, and Outcomes of COVID-19-Associated Acute Myocarditis.

Circulation 2022, 145, 1123–1139.

63. Singer, M.E.; Taub, I.B.; Kaelber, D.C. Risk of Myocarditis from COVID-19 Infection in People Under Age 20: A Population-Based Analysis. medRxiv 2022.
64. Imazio, M.; Gaita, F. Diagnosis and treatment of pericarditis. Heart 2015, 101, 1159–1168.
65. Lindner, D.; Fitzek, A.; Bräuninger, H.; Aleshcheva, G.; Edler, C.; Meissner, K.; Scherschel, K.; Kirchhof, P.; Escher, F.; Schultheiss, H.P.; et al. Association of Cardiac Infection With SARS-CoV-2 in Confirmed COVID-19 Autopsy Cases. JAMA Cardiol. 2020, 5, 1281–1285.
66. Kažukauskienė, I.; Baltrūnienė, V.; Jakubauskas, A.; Žurauskas, E.; Maneikienė, V.V.; Daunoravičius, D.; Čelutkienė, J.; Ručinskas, K.; Grabauskienė, V. Prevalence and prognostic relevance of myocardial inflammation and cardiotropic viruses in non-ischemic dilated cardiomyopathy. Cardiol. J. 2022, 29, 441–453.
67. Natanson, C.; Eichenholz, P.W.; Danner, R.L. Endotoxin and tumor necrosis factor challenges in dogs simulate the cardiovascular profile of human septic shock. J. Exp. Med. 1989, 169, 823–832.
68. L'Heureux, M.; Sternberg, M.; Brath, L.; Turlington, J.; Kashiouris, M.G. Sepsis-Induced Cardiomyopathy: A Comprehensive Review. Curr. Cardiol. Rep. 2020, 22, 35.
69. Ehrman, R.R.; Sullivan, A.N.; Favot, M.J.; Sherwin, R.L.; Reynolds, C.A.; Abidov, A.; Levy, P.D. Pathophysiology, echocardiographic evaluation, biomarker findings, and prognostic implications of septic cardiomyopathy: A review of the literature. Crit. Care 2018, 22, 112.
70. Vasques-Nóvoa, F.; Laundos, T.L.; Madureira, A.; Bettencourt, N.; Nunes, J.P.L.; Carneiro, F.; Paiva, J.A.; Pinto-do-Ó, P.; Nascimento, D.S.; Leite-Moreira, A.F.; et al. Myocardial Edema: An Overlooked Mechanism of Septic Cardiomyopathy? Shock 2020, 53, 616–619.
71. Salah, H.M.; Mehta, J.L. Takotsubo cardiomyopathy and COVID-19 infection. Eur. Heart J. Cardiovasc. Imaging 2020, 21, 1299–1300.
72. Sisti, N.; Valente, S.; Mandoli, G.E.; Santoro, C.; Sciaccaluga, C.; Franchi, F.; Cameli, P.; Mondillo, S.; Cameli, M. COVID-19 in patients with heart failure: The new and the old epidemic. Postgad. Med. J. 2021, 97, 175–179.
73. Park, J.F.; Banerjee, S.; Umar, S. In the eye of the storm: The right ventricle in COVID-19. Pulm. Circ. 2020, 10, 2045894020936660.
74. Miftode, R.S.; Petriș, A.O.; Onofrei Aursulesei, V.; Cianga, C.; Costache, I.I.; Mitu, O.; Miftode, I.L.; Șerban, I.L. The Novel Perspectives Opened by ST2 in the Pandemic: A Review of Its Role in the Diagnosis and Prognosis of Patients with Heart Failure and COVID-19. Diagnostics 2021, 11, 175.
75. Alserawan, L.; Peñacoba, P.; Orozco Echevarría, S.E.; Castillo, D.; Ortiz, E.; Martínez-Martínez, L.; Moga Naranjo, E.; Domingo, P.; Castellví, I.; Juárez, C.; et al. Growth Differentiation Factor 15 (GDF-15): A Novel Biomarker Associated with Poorer Respiratory Function in COVID-19. Diagnostics 2021, 11, 1998.
76. Miftode, R.S.; Constantinescu, D.; Cianga, C.M.; Petris, A.O.; Timpau, A.-S.; Crisan, A.; Costache, I.I.; Mitu, O.; Anton-Paduraru, D.T.; Miftode, I.L.; et al. A Novel Paradigm Based on ST2 and Its Contribution towards a Multimarker Approach in the Diagnosis and Prognosis of Heart Failure: A Prospective Study during the Pandemic Storm. Life 2021, 11, 1080.
77. Kaufmann, C.C.; Ahmed, A.; Burger, A.L.; Muthspiel, M.; Jäger, B.; Wojta, J.; Huber, K. Biomarkers Associated with Cardiovascular Disease in COVID-19. Cells 2022, 11, 922.