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Emerging cardiological issues during the COVID-19 pandemic

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1 | INTRODUCTION

Today the modern world is facing an unprecedented health crisis. The COVID-19 pandemic is putting extensive strain on healthcare systems hospitals and medical workers worldwide. Epidemiological data are emerging that COVID-19 patients with cardiac risk factors or pre-existing cardiac conditions are at increased risk for complications and mortality from COVID-19. As we just begin to understand the pathophysiology underlying the disease the involvement of the heart whether through direct myocardial infection and damage or due to cardiac complications is already evident. Also the current therapy for COVID-19 using antiviral agents (hydroxy) chloroquine and other off-label used medications is not without risk for cardiac side effects. Furthermore the pandemic puts stress on the organization of cardiac health care both for COVID-19 patients and for the acute and chronic care of cardiac patients in which patient as well as physician-related delays in treatment could potentially lead to harm.

2 | EPIDEMIOLOGICAL DATA, ARE CARDIAC PATIENTS AT HIGHER RISK?

Is there a relation between cardiac risk factors or cardiac injury and the mortality risk in COVID-19? Early reports from China[1] indeed show markedly elevated mortality rates in patients with hypertension, diabetes and pre-existing coronary artery disease (up to 10-fold in the latter) compared to patients without underlying health conditions. In a recent report of Shi et al,[2] hospitalized COVID-19 patients in Wuhan, China, presenting with elevated high-sensitive cardiac troponin I levels had a higher frequency of complications such as ARDS (58.5% vs 14.7%) and acute kidney injury (8.5% vs 0.3%), required more invasive mechanical ventilation (22% vs 4.2%) and had a significant increase in in-hospital mortality than patients without cardiac injury (51.2% vs 4.5%). The percentage of hospitalized COVID-19 patients with elevated troponins is in the range of 20%-28%[2,3] and in patients with pre-existing cardiovascular disease with elevated troponins the mortality can be as high as 69.4%.[3] These data indicate that patients with cardiac risk factors or pre-existing coronary artery disease are at high risk during this COVID-19 pandemic and that cardiac injury is an important predictor of adverse outcomes.

3 | UNDERSTANDING THE CARDIAC MANIFESTATIONS OF COVID-19

The pathophysiological mechanisms by which the SARS-CoV-2 virus affects the heart seem to be diverse in nature (Figure 1). As already mentioned, in a substantial amount of hospitalized COVID-19 patients signs of acute myocardial injury are evident from the rise in cardiac biomarkers. This rise in troponin levels is sometimes, but not always, accompanied by ECG changes and LV dysfunction on echocardiography (Table 1).

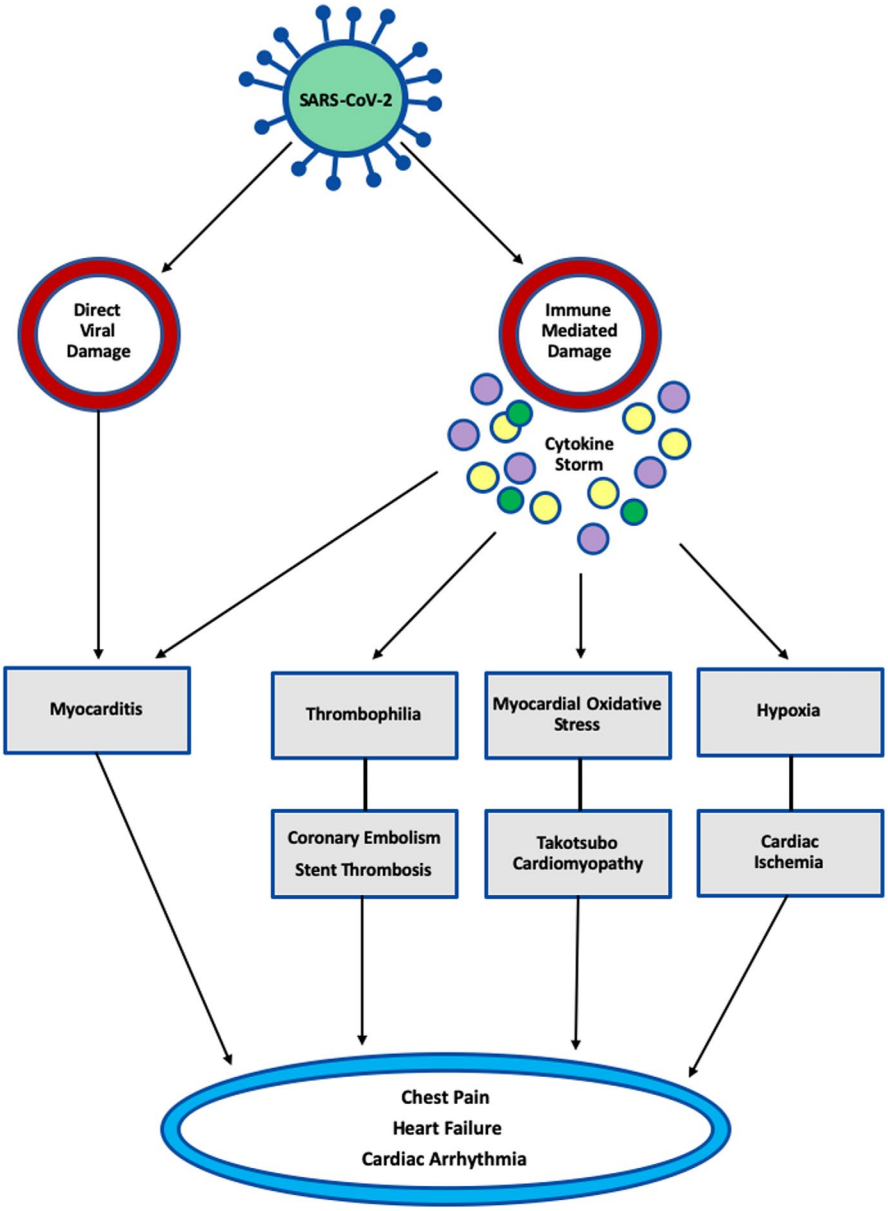

FIGURE 1 Pathophysiological mechanisms by which the SARS-CoV-2 virus affects the heart

As with other viral conditions such as influenza and SARS-CoV,[4] direct myocardial infection of the virus can lead to an acute form of viral myocarditis (1 in 3 patients presenting with SARS during the Toronto outbreak). Also, the release of inflammatory cytokines on itself can also lead to a form of myocarditis, resulting in a takotsubo-like clinical picture.[5,6] And although underlying coronary artery disease is present in a substantial number of patients, acute occlusion of the coronary vasculature seems relatively uncommon. In early reports from Italy, about 60% of COVID-19 patients referred to the cathlab for typical chest pain with troponin rise presented with normal coronary arteries. Other groups also have reported this clinical picture, that is ST-segment elevation myocardial injury in nonobstructive coronary artery disease (MINOCA). In data from 6 New York hospitals, only 8 out of 18 patients presenting with ST-elevation on the initial ECG had evidence of obstructive coronary disease on angiography or regional wall-motion abnormalities on echocardiography.[7] MINOCA could be due to microvascular dysfunction, coronary thrombosis or embolism, plaque disruption of coronary dissection or vasospasm. In this regard, a higher incidence of coronary embolism has been reported, which probably relates to the prothrombotic state of COVID-19 patients, in whom a rise in D-dimers is commonly seen. This higher incidence of arterial thrombotic complications in COVID-19 was recently reported to be as high as 3.7% in critically ill patients on the intensive care unit, making a strong case for—probably high dose—thrombosis prophylaxis in these patients.[8] On the other hand, cfr. the aforementioned New York study, true obstructive myocardial infarctions do occur, as many patients with COVID-19 present with underlying cardiovascular disease or cardiac risk factors. In general, these patients present with higher median troponin and D-dimer levels than patients with noncoronary myocardial injury.[7] To further complicate the clinical picture, also other forms of

TABLE 1 Differentiating characteristics of COVID-19 and other COVID-19-related or COVID-19-unrelated cardiac disease

	Troponin	CK	LDH	BNP	D-dim	CRP	ECG	TTE	Angio
COVID-19	nl or ↑*	nl or↑*	nl or↑*	nl or↑*	nl or↑*	↑↑	Possible ST-T abn		
ACS/STEMI	↑↑	↑	↑	nl or ↑	nl or ↑	nl or ↑	Typical ST-T abn	Regional wall-motion abn	Obstructive coronary disease
Myocarditis	↑	nl or ↑	↑	nl or ↑	nl or ↑	↑↑	Diffuse ST-T abn, conduction abn	nl or nonspecific	nl
Congestive Heart Failure	nl or ↑	nl	nl or ↑	↑↑	nl or ↑	nl or ↑	Possible ST-T abn	LV dysfunction, elevated LVEDP	nl
Takotsubo	↑	nl or ↑	nl	↑	nl	nl or ↑	Typical ST-T abn	Apical dyskinesia, basal hyperkinesia	Typical apical ballooning
Hypoxia	nl or ↑	nl	↑	nl	nl	nl or ↑	Possible ST-T abn	nl or nonspecific	nl or nonspecific
Pulmonary Embolism	nl or ↑	nl	↑	nl or ↑	↑↑	nl	Possible ST-T abn	Elevated PAP, RV dysfunction	nl

Note: Differentiating characteristics are highlighted in red.

Abbreviations: Abn, abnormality; LV, left ventricle; LVEDD, left ventricular end diastolic pressure; nl, normal; PAP, pulmonary artery pressure; RA, right atrium; RV, right ventricle.

*Associated with worse outcome if elevated.

stress-induced cardiomyopathy, such as takotsubo, hypoxia-induced cardiac injury, MOF or pulmonary embolism can result in a rise of cardiac troponin. These conditions can mimic, whether by symptoms or by changes in the baseline ECG, a true myocardial infarction.

In the setting of viral myocarditis, concomitant pericarditis has been reported in COVID-19 patients, leading to pericardial effusion and occasionally cardiac tamponade. Furthermore, myocarditis can lead to acute heart failure, life-threatening cardiac arrhythmias such as ventricular tachycardia or sudden cardiac death. For instance, in some rapidly progressive cases of COVID-19 in younger patients, myocarditis leading to fulminant heart failure and cardiogenic shock probably plays an important role in the underlying disease process.

Also, as in other acute inflammatory of infectious states, COVID-19 can worsen the condition of known heart failure patients leading to cardiac decompensation. In some patients, COVID-19 induces "de novo" atrial fibrillation or it can destabilize patients with paroxysmal or permanent atrial fibrillation.

4 | ISSUES REGARDING CARDIOVASCULAR MEDICATION AND ANTI-COVID-19 TREATMENT

As the SARS-CoV-2 uses the ACE2 receptor as entry point for intracellular invasion, concerns were raised for the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). Data supporting this were derived from animal studies. However, human studies did not show consistent results.[9] Nevertheless, some clinicians have advocated restrictions on the use of ACEIs or ARBs in the setting of COVID-19.[10] This hypothesis is probably premature and several groups and international societies have warned against withholding ACEIs/ARBs in patients because of the risk of adverse outcomes, including worsening of heart failure.[11] Moreover, in animal studies of SARS-CoV-1 and ARDS, ACE2 and ARB treatment (losartan) improved the acute lung injury[12,13] and clinical studies in COVID-19 patients with these agents are currently active and recruiting patients (NCT04287686 and NCT04312009 or NCT04311177, respectively). The debate is currently going even in the opposite direction as it was recently reported that the in-hospital mortality proved to be significantly lower in patients receiving ACE inhibitors, with ARBs posing no potential harm.[14] In another study, the potential association between the use of RAAS blockers and the susceptibility for COVID-19 was refuted in a multivariable analysis, showing that the higher frequency of ACEI/ARBs in COVID-19 patients was due to the higher prevalence of cardiovascular disease in these patients.[15]

Concerning the use of (hydroxy)chloroquine (with or without azithromycin) as a first-line treatment option in hospitalized COVID-19 patient, there is a significant chance of QTc prolongation and subsequent arrhythmias such as torsade de pointes and other fatal ventricular arrhythmias. We caution to initiate this treatment in patients with underlying congenital long QT syndrome or patients with acquired forms

of long QT. ECG with QTc measurement before the initiation of (hydroxy)chloroquine, azithromycin or antiviral drugs such as lopinavir/ritonavir is absolutely necessary, certainly in patients with concomitant use of known QT prolonging medications such as antiarrhythmic drugs (eg amiodarone, sotalol or flecainide), antipsychotics, anticonvulsants, antidepressants, antibiotics, antiemetics, antifungal, antiviral or antimalarial drugs.[16] Regular repeat ECGs during therapy, for example every 2 days or more frequently if QTc is elevated, or continuous ECG monitoring is warranted. Hypokalaemia has to be avoided and actively corrected. Discontinuation of the medication is required when QTc exceeds 500ms or when torsade de pointes or other ventricular tachyarrhythmias occurs.

5 | INCREASED STRESS ON CARDIOVASCULAR CARE STRUCTURES

The COVID-19 pandemic is putting our healthcare structures under a lot of pressure. In hospitals there are competing needs between COVID-19 and non-COVID-19 patients for ICU beds and ventilators, medical staff and nurses have to be redeployed on dedicated COVID-19 wards and we are witnessing shortages in medical (protective) equipment and medications. There is a high risk for infection of medical personnel and further transmission to our patients, co-workers and families. This leads to disruption of standard medical care and increases physical and mental stress in healthcare workers. Elective procedures and patient visits have to be postponed, and there is a higher threshold for admitting patients or doing invasive procedures. For instance, in the cathlab, due to the high risk of infection of cathlab staff, urgent PCI is restricted in most centres to patients with ST-elevation myocardial infarction (STEMI) or highly instable patients. In some, there is even a revival of thrombolysis as first-line therapy in the setting of STEMI. Moreover, patients are anxious to visit doctors, emergency wards and hospitals, leading to patient delay, discontinuation of medication and a high risk of serious complications. Furthermore, medical students and fellows, by interference with normal education and training programmes, will be affected, as is medical research by disturbance of ongoing clinical trials.

We are currently also uncertain of the long-term effects on cardiac prognosis of patients affected by the virus as viral myocarditis can lead to devastating and long-lasting effects on ventricular function. In this way, it is possible that we will witness a second wave of the COVID-19 pandemic, this time presenting as patients with a dilated cardiomyopathy and chronic congestive heart failure. Although it is still too early to draw definite conclusions in this regard, preliminary case reports on imaging of left ventricular function after acute myocarditis or acute takotsubo syndrome in the setting of COVID-19 are somewhat reassuring with general recovery of function and absence of myocardial scar or necrotic foci.[5,17]

In conclusion, the COVID-19 pandemic has important implications for the cardiovascular care of our patients, whether by putting our patients at increased risk or by affecting the way we treat or care for our patients. All these issues are currently of great concern and as long as the virus stays endemic and in the absence of a vaccine or effective antiviral treatment, this will probably continue to have a marked impact on our daily practice.

CONFLICT OF INTEREST

The authors have no conflicts to declare.

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