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Review Article

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Diagnosis and management of cardiovascular disease during the COVID-19 pandemic: epidemiology, pathophysiology and diagnosis

Abstract
Since its evolution in 2020, the severe acute respiratory syndrome coronavirus 2 causing coronavirus disease 2019 (COVID-19) has reached pandemic levels, and there have been repeated outbreaks across the globe. The aim of this article is to provide practical knowledge and guidance to aid clinicians in the diagnosis and management of cardiovascular disease (CVD) in association with COVID-19.

Keywords: Biomarkers, Cardiogenic shock, COVID-19, Myocardial injury, myocardial infarction, Myocarditis, Non-invasive imaging

INTRODUCTION

Roughly, 1 year after SARS-CoV-2 first emerged, we are now better informed about the way in which the infection interacts with the (cardiovascular) CV system. This review updates our knowledge on the specific types of (cardiovascular disease) CVD that appear to be a consequence of severe infection, which include myocardial injury, arrhythmias, heart failure (HF), vascular dysfunction, and thromboembolic disease. Possible mechanisms of CV injury are described. The document provides an update on how SARS-CoV-2 infection is diagnosed, before providing a detailed account of how CV conditions should be diagnosed in patients with COVID-19, covering the clinical presentation, the electrocardiogram (ECG), the effect of disease on cardiac biomarkers and imaging.

Epidemiology

Impact of cardiovascular comorbidities on COVID-19 outcomes

Key points

- CV comorbidities are common in patients with COVID-19.
- Presence of CVD is associated with severe COVID-19 and higher mortality.
- CV risk factors are linked with severe COVID-19 and higher mortality.

SARS-CoV-2 was first reported in Wuhan, China, on 31 December 2019. It is a new coronavirus strain that had not previously been identified in humans and causes the illness COVID-19. By 7 May 2020, 3.67 million had tested positive and >250 000 had died (1). By 22 March 2021,~124 million cases and 2.7 million deaths had been reported globally.

After the COVID-19 pandemic in Wuhan, China, the pandemic's epicenter started to shift in March 2020 to Europe, Latin America, and the USA. Numerous countries took different policy measures in an attempt to reduce the spread and the pressure on the national healthcare systems such as lockdowns, curfews and closure of non-essential stores. These measures led to a flattening of the curve and ultimately to a decrease of detected cases between May and August (2). Many countries eased their policy measures over the summer. At the end of the summer, detected cases started to gradually increase in many countries, potentially due to the reopening of many activities that have been known

to contribute to higher SARS-CoV-2 diffusion. This led to the so-called second wave in which many countries had to enforce similar or even stricter policy measures to reduce the burden of the COVID-19 pandemic.Currently, the peak of the second wave seems to be over in many European countries; however, policy measures remain strict and there are concerns that a third wave is commencing in some European countries, leading to new restrictions.

Multiple studies have demonstrated that comorbid CVD is linked to a more severe course and higher mortality of COVID-19 (3,4). The meta-analysis by Figliozzi et al. (5) showed that a history of CVD tripled the odds [odds ratio (OR) 3.15, 95% confidence interval (CI) 2.26–4.41] of the occurrence of a severe course of COVID-19, which was defined as death, severe COVID-19 infection, hospitalization in intensive care unit (ICU), and/or use of mechanical ventilation or progression of the disease. Congestive HF was identified both as a risk factor for a more severe course and increased mortality and as a possible consequence of a COVID-19 (6-8). Some meta-analyses demonstrated that patients with a history of HF have significantly poorer outcomes with higher mortality and in-hospital complications. A meta-analysis (7) concluded that the presence of HF was associated with a doubling of the odds of COVID-19 mortality.

Next to CVD, CV risk factors are associated with a higher risk for a more severe course and higher mortality.

Diabetes mellitus and COVID-19 are linked in numerous ways. COVID-19 seems to exacerbate the underlying pathophysiology of hyperglycemia in people with diabetes (9). Increased severity and higher mortality rates of COVID-19 are also observed in obese patients (5-7). A pooled analysis including 399 461 diagnosed patients concluded that obese individuals were more at risk of COVID-19 positivity for hospitalization ICU admission and for mortality (9). Chronic kidney disease is another comorbidity that is associated with a more severe course of COVID-19. Lower estimated glomerular filtration rates were associated with greater hazard ratios for mortality from COVID-19 (10,11). Hypertension is one of the most common comorbidities among COVID-19 patients (12). Multiple meta-analyses concluded that the presence of hypertension significantly increased the odds for a severe course of COVID-19 or mortality though relations with obesity, substantially more prevalent in the presence of hypertension, should be further clarified.

Case fatality is highest in older age groups. A meta-analysis including 611 583 patients highlighted the determinant effect of age on mortality. The highest mortality occurs in patients aged ≥80 years in whom mortality was 6 times higher than in younger patients. This underlines the fact that increasing age is the dominant risk factor for a severe course of COVID-19 (13,14). Multinational cohort analyses will give more insights into the prevalence and risk of CV comorbidities in COVID-19. There are several potential mechanisms explaining why the course of the disease is more severe in patients with underlying CV risk factors and CVD.

Cardiovascular manifestations and clinical course of COVID-19

Key points

- COVID-19 has comparable cardiac manifestations to previous outbreaks of other coronaviruses.
- Cardiac manifestations are associated with worse outcomes of COVID-19.
- Long-term manifestations of COVID-19 are unclear, so extensive follow-up is needed.

Previous coronavirus outbreaks such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) were associated with a significant burden of CV morbidity. Common CV complications in SARS were hypotension, myocarditis, arrhythmias, and sudden cardiac death. Diagnostic workup during SARS infection revealed electrocardiographic changes, subclinical left ventricular (LV) diastolic impairment, and troponin elevation.

The presence of acute cardiac injury, vascular dysfunction, and thrombosis in patients with COVID-19 raises important questions about potential long-term CV effects. At this moment, it remains unclear if COVID-19 leads to persistent myocardial injury and/or if it is associated with increased long-term risk for developing coronary artery disease and HF. Extensive (cardiac) follow-up of COVID-19 patients is needed to mitigate the potential long-term adverse physical and mental health effects. Multi-ethnic long-ranging longitudinal observational studies will be critical to elucidate the duration and severity of health consequences attributable to COVID-19.

Arrhythmias are a common manifestation of CVD in patients with COVID-19 (15). Brady arrhythmias specific to COVID-19 have not been described. Data on the frequency of malignant arrhythmias such as ventricular tachycardias (VTs) and atrial fibrillation (AF) in COVID-19 patients are still limited. Small clinical studies estimate the incidence of new-onset AF between 3.6% and 6.7% in patients with COVID-19. A Danish nationwide registry study published [17,18] that the diagnosis of new-onset AF was 47% lower during the first 3 weeks of the national lockdown compared with the same period of the previous year, perhaps for the same reasons that led to a reduction in hospital admissions for ACSs.

Pathophysiology—mechanism of disease in relation to the cardiovascular system

Key points

- The pathophysiology of coronavirus infection involves SARS-CoV-2 binding to the host angiotensin-converting enzyme 2 (ACE2) receptor to mediate entry into cells. ACE2 is expressed in the lungs, heart and vessels.
- CVD associated with COVID-19 likely involves

dysregulation of the ACE/ACE2 system due to SARS-CoV-2 infection and due to comorbidities, such as hypertension.

- SARS-CoV-2 directly infects human cardiomyocytes (native and induced pluripotent stem cell-derived) in an ACE2- and cathepsin-dependent manner. These effects can be inhibited by the antiviral drug remdesivir.
- CVD comorbidity in COVID-19 may be either primary or secondary due to acute lung injury, leading to increased cardiac workload (particularly relevant in HF).
- Other molecules such as neuropilin-1 can facilitate SARS-CoV-2 cell entry and infectivity, although the significance of this process for CVD is unclear.
- A cytokine storm, originating from an imbalance of T-cell activation with dysregulated release of interleukin (IL)-6, IL-17, and other cytokines, may contribute to CVD in COVID-19. IL-6 targeting is being tested therapeutically.
- Immune system activation along with immunometabolism alterations may result in plaque instability, contributing to the development of acute coronary events.

The host receptor through which SARS-CoV-2 enters cells to trigger infection is ACE2 (Figure 1). ACE2 is a multifunctional protein. Its primary physiological role is the enzymatic conversion of angiotensin (Ang) II to Ang-(1–7), and Ang I to Ang-(1–9), which are CV protective peptides. In the context of COVID-19, however, ACE2 is also involved in SARS through its function as the coronavirus receptor. Virus entry into lung alveolar epithelial cells is facilitated by high levels of expression of ACE2 in these cells, which lead to enhanced binding of the SARS-CoV-2 spike protein through processes involving cell surface associated transmembrane protein serine 2 (TMPRSS2) or proprotein convertase furin (Figure 1). Interestingly, the recently identified neuropilin 1 (NRP1) can greatly enhance infectivity when co-expressed with ACE2 and TMPRSS2 (17-19). The role of NRP1 appears to be SARS-CoV-2 specific and has not been seen with SARS-CoV.7 Within the host cell cytoplasm, the viral genome RNA is released and replicates leading to newly formed genomic RNA, which is processed into virion-containing vesicles that fuse with the cell membrane to release the virus. SARS-CoV-2 is spread mainly through the respiratory tract by droplets, respiratory secretions and direct contact. The ACE/ACE2 seems to be disrupted by SARS-CoV-2 infection, which likely plays a pathogenic role in severe lung injury and respiratory failure in COVID-19.In addition to the lungs, ACE2 is highly expressed in the heart, blood vessels and gastrointestinal tract. Other receptors can also facilitate the entry of SARS-CoV-2.

COVID-19 is primarily a respiratory disease, but—as noted in Sections Impact of cardiovascular comorbidities on COVID-19 outcomes and Cardiovascular manifestations and clinical course of COVID-19—many patients also have CVD, such as hypertension and obesity, acute myocardial injury and myocarditis (Figure 2).This may be secondary to the lung disease, since acute lung injury itself leads to increased cardiac workload and can be problematic especially in patients with pre-existing HF. CVD may also be a primary phenomenon considering the important pathophysiological role of the renin–angiotensin system (RAS)/ACE2 in the CV system and the fact that ACE2 is expressed in human heart, vascular cells, and pericytes. In vitro studies have demonstrated that SARS-CoV-2 directly infects human-induced pluripotent stem cell-derived cardiomyocytes in an ACE2- and cathepsin-dependent manner. These effects can be inhibited by the antiviral drug remdesivir. It is important to note that while biologically able to inhibit cardiomyocyte effects in vitro, remdesivir does not improve overall mortality, initiation of ventilation, or duration of hospital stay. SARS-CoV-2-induced pathways within cardiomyocytes are related to viral response and interferon inflammatory signalling, apoptosis, and oxidative stress.

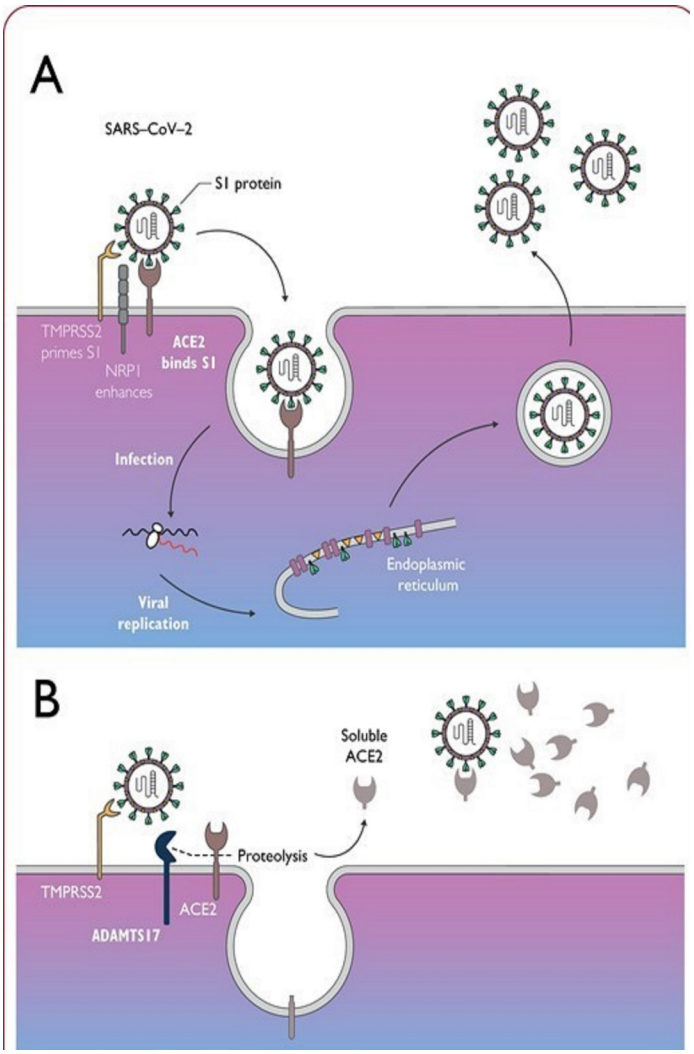

Figure 1. Critical role of ACE2 in the regulation of SARS-CoV-2 infection in ACE2-expressing cellsa (A) and ACE2 reduced surface expression by ADAMTS17 (B)

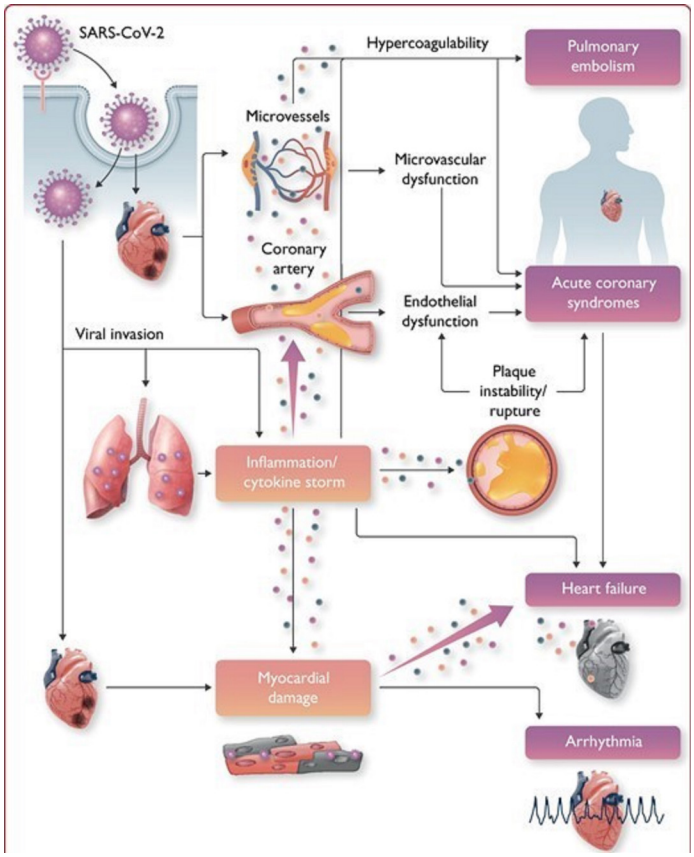

Figure 2. Cardiovascular involvement in COVID-19—key manifestations and hypothetical mechanisms

Diagnosis of cardiovascular conditions in COVID-19 patients

Clinical presentation

Chest pain

Key points

- Chest pain and breathlessness are frequent symptoms in COVID-19.
- Chronic and ACS presentations can be associated with respiratory symptoms.

Chest pain or tightness is common in patients with active COVID-19. It is usually poorly localized and associated with breathlessness due to underlying pneumonia. Associated profound hypoxemia together with tachycardia may result in chest pain and electrocardiographic changes suggestive of myocardial ischemia. When biomarkers are elevated in conjunction with ECG changes, type 2 MI may be suggested. Patients with ACS do, however, experience typical symptoms related to ischemia when they have COVID-19. The presence of a COVID-19 can make the differential diagnosis more difficult, as shortness of breath and respiratory symptoms may be present and may precede or precipitate cardiac signs and symptoms.

COVID-19 patients may present with cough, dyspnea, and ARDS.

Electrocardiogram

Key points

- The same ECG diagnostic criteria for cardiac conditions apply in patients affected by SARS-CoV-2 infection and in the general population.

So far, no specific ECG changes have been described in patients with SARS-CoV-2 infection and non-specific ST-T abnormalities are observed in up to 30% of patients with SARS-CoV-2 pneumonia (10). Although we assume that the overall minimal level of myocardial injury associated with the infection (see the following section on biomarkers) does not translate into characteristic ECG manifestations in many patients, a systematic review on COVID-19 myocarditis described ST-segment abnormalities (mostly specific) in 71% of patients.

Biomarkers

Biomarker elevation suggesting cardiovascular conditions in patients with COVID-19

Cardiac troponin T/I

COVID-19 is viral pneumonia that may result in severe systemic inflammation and ARDS, and both conditions have profound effects on the heart (20). There is a quantitative marker of cardiomyocyte injury, the concentrations of cardiac troponin T/I in a patient with COVID-19 should be seen as the combination of the presence/extent of pre-existing cardiac disease and/or the acute injury related to COVID-19 (8).

Cohort studies from patients hospitalized with COVID-19 have shown that 5–40% of patients had elevations >ULN in cardiac troponin T/I, and this finding was more common in patients admitted to the ICU and among those who died (21). Concentrations remained in the normal range in the majority of survivors. In non-survivors, troponin levels progressively increased in parallel with the severity of COVID-19 and the development of ARDS

B-type natriuretic peptide/N-terminal pro B-type natriuretic peptide

B-type natriuretic peptide/NT-pro BNP as quantitative biomarkers of hemodynamic myocardial stress and HF is frequently elevated among patients with severe (22,23) inflammatory and/or respiratory illnesses. Experience in patients with COVID-19 is limited (24,25). Very likely, the experience from other cases of pneumonia can be extrapolated to COVID-19.

As quantitative markers of hemodynamic stress and HF, the concentrations of BNP/NT-pro BNP in a patient with COVID-19 should be seen as the combination of the presence/extent of pre-existing cardiac disease and/or the acute hemodynamic stress related to COVID-19. At least to some extent, the release of BNP/NT-pro BNP seems to be associated with the extent of right ventricular (RV) hemodynamic stress (Figure 3).

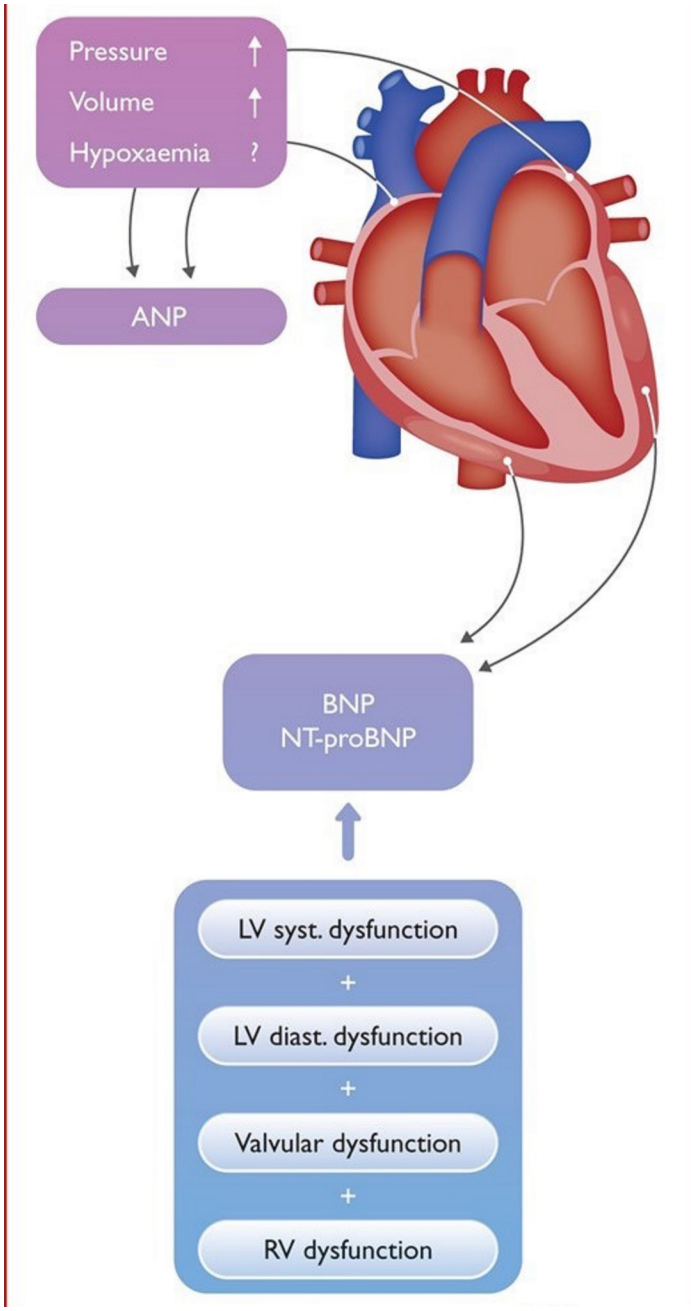

Figure 3. Haemodynamic determinants of natriuretic peptides. ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; LV, left ventricular; NT-proBNP, N-terminal proBNP; RV, right ventricular

Non-invasive imaging

- Do not perform routine cardiac imaging in patients with suspected or confirmed COVID-19.
- COVID-19-positive and -negative patients should not cross in the waiting area/scanner area, etc.
- Prevent contamination from patients to other patients, to imagers and imaging equipment.
- Perform imaging studies in patients with suspected or confirmed COVID-19 only if the management is likely to be impacted by the results.
- Re-evaluate which imaging technique is best for your patients both in terms of diagnostic yield and infectious risk for the environment.
- The imaging protocols should be kept as short as possible.
- Transthoracic and transoesophageal echocardiography

Key points

- Avoid performing transthoracic, transesophageal and stress echocardiograms in patients in which test results are unlikely to change the management strategy.
- Transoesophageal echocardiography (TOE) carries increased risks of spread of COVID-19 due to exposure of HCP to aerosolization of large viral load and should not be performed if an alternative imaging modality is available.
- In COVID-19-infected patients, the echocardiogram should be performed focusing solely on the acquisition of images needed to answer the clinical question to reduce patient contact with the machine and the HCP performing the test.
- Point of care focused ultrasound (POCUS), focused cardiac ultrasound study (FoCUS), and critical care echocardiography performed at the bedside are effective options to screen for CV complications of COVID-19.

Computed tomography

Key points

- Cardiovascular CT should be performed in hospitalized patients only with indications in which imaging results will likely impact management.
- Coronary computed tomography angiography (CCTA) may be the preferred non-invasive imaging modality to diagnose CAD since it reduces the time of exposure for patients and personnel.
- Cardiac CT may be preferred to TOE to rule out left atrial appendage and intracardiac thrombus prior to cardioversion.
- In patients with respiratory distress, chest CT is recommended to evaluate imaging features typical of COVID-19.
- Check renal function when contrast is indicated.

CONCLUSION

In COVID-19 patients with clinical presentation compatible with CVD, three main entities should be considered:

- Patients with COVID-19 can present with cardiac events that can be favored by the infection or unrelated. These include ACS, acute HF, arrhythmias, venous thromboembolic events, CS, and cardiac arrest. Those syndromes require a quick diagnosis and management and should not be

overlooked due to the presence of COVID-19.

- Infection-related cardiac injury can also lead to a clinical presentation suggestive of cardiac event and should also be considered as a differential diagnosis.
- Patients with COVID-19 can present with symptoms mimicking CV events, including chest pain, dyspnea, and shock, even in the absence of cardiac injury.

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