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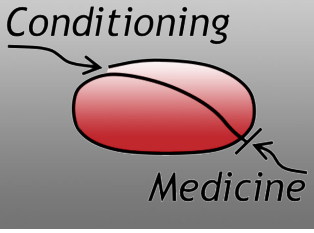

REVIEW ARTICLE | OPEN ACCESS

Cardiac manifestations of COVID-19: An update

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Abstract: In patients with coronavirus disease 19 (COVID-19), cardiac manifestations occur in 20–30% of hospitalized patients, and are associated with worse outcomes. Cardiac involvement may be detected by elevated circulating levels of cardiac biomarkers indicative of acute myocardial injury, impaired left or right ventricle function on cardiac echocardiography and cardiovascular magnetic resonance (CMR), and evidence of acute myocarditis on CMR or endomyocardial biopsy. The etiology of cardiac involvement in COVID-19 is multifactorial and diverse, and includes direct viral infection, myocarditis, cardiomyopathy, critical illness, acute pulmonary embolism, sepsis, and acute coronary syndrome, and multi-modality cardiac imaging can help determine the underlying cause. It has been recently reported that these cardiac manifestations may persist in 60-70% of patients recovering from COVID-19, although the clinical significance of these changes are not clear. The aim of this review article is to provide an update on cardiac involvement in patients with active and recovering COVID-19 with a focus on acute myocardial injury and its detection by multi-modality cardiac imaging.

Introduction

On December 31st 2019, cases of pneumonia with unknown causes were first reported in Wuhan, China (World Health Organization [WHO] - Pneumonia of unknown cause – China). The coronavirus was initially named 2019-nCoV after identification and isolation of the pathogen (Zhou et al., 2020). On January 30th 2020, the WHO declared the disease a public health emergency, and subsequently renamed the virus severe acute respiratory syndrome coronavirus (SARS-CoV-2), and named the disease coronavirus disease 19 (COVID-19) (Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV)). The total number of COVID-19 cases worldwide has reached nearly 35 million with over 1 million deaths as of October 4th 2020 (COVID-19 Map - Johns Hopkins Coronavirus Resource Center), and now a second wave of COVID-19 infection has arrived.

Although primarily a disease of the lung, cardiac manifestations of COVID-19 occur in 20–30% of hospitalized patients, and these are associated with worse outcomes (De Lorenzo et al., 2020; Shi et al., 2020). Cardiac involvement may be detected by elevated circulating levels of cardiac biomarkers indicative of acute myocardial injury (such as cardiac troponin and brain-type-natriuretic peptide [NT-pro-BNP], impaired left or right ventricle (RV) function on cardiac echocardiography and cardiovascular magnetic resonance (CMR), and evidence of acute myocarditis on CMR or endomyocardial biopsy (Guzik et al., 2020). The purpose of this article is to provide an update on cardiac involvement in active and recovering COVID-19 infection with a focus on acute myocardial injury, and its detection by multi-modality cardiac imaging.

Acute myocardial injury

Acute myocardial injury, as defined as an elevation in cardiac biomarkers (such as troponin) above the 99th percentile upper reference limit (Thygesen et al., 2019), occurs in 20 to 30% of patients at time of presentation with COVID-19 (with a greater prevalence of over 50% in patients with prior cardiovascular disease), and is associated with worse clinical outcomes (De Lorenzo et al., 2020; T. Guo et al., 2020; Shi et al., 2020). The role of cardiac troponin (cTn) as a diagnostic and prognostic marker in COVID-19 has been recently reviewed (Sandoval et al., 2020), with the etiology of acute myocardial injury divided into chronic myocardial injury (due to pre-existing

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cardiovascular disease), acute non-ischemic myocardial injury (including myocarditis, stress cardiomyopathy, critical illness, acute pulmonary embolism, and sepsis), and type I myocardial infarction (due to atherosclerotic plaque rupture) (Sandoval et al., 2020). All these factors may be triggered or exacerbated by systemic inflammation and the "cytokine storm" that accompanies COVID-19.

Myocarditis is an important cardiac complication of COVID-19, and is characterized by inflammation of heart muscle, and results from direct cell injury and T-lymphocyte–mediated cytotoxicity exacerbated by a cytokine storm (Siripanthong et al., 2020). It can manifest acutely as fulminant myocarditis presenting as cardiogenic shock (Ruan et al., 2020; Zeng et al., 2020) to asymptomatic chronic myocarditis in patients recovering from COVID-19 (Huang et al., 2020; Knight et al., 2020; Puntmann et al., 2020; Rajpal et al., 2020). Whether cardiac involvement in COVID-19 is due to direct infection of the heart by SARS-CoV-2, which gains cellular entry via angiotensin-converting enzyme 2 (ACE2) that is upregulated in cardiac disease (Chen et al., 2020; J. Guo et al., 2020; Nicin et al., 2020; Tucker et al., 2020) or is secondary to the acute systemic inflammatory response, has been the topic of ongoing investigation. Autopsy and endomyocardial biopsy case series have demonstrated the presence of SARS-CoV-2 in heart tissue (Escher et al., 2020; Lindner et al., 2020; Puelles et al., 2020; Wenzel et al., 2020; Wichmann et al., 2020), although not all reports have detected the presence of SARS-CoV-2 in heart tissue (Sala et al., 2020; Xu et al., 2020). In the autopsy series, SARS-CoV-2 was detected in myocardial tissue of 17/22 (77%) (Puelles et al., 2020), 5/12 (41%)(Wichmann et al., 2020), and 24/39 (61%) patients (Lindner et al., 2020), with the detection rate lower in the series of endomyocardial biopsies from 104 COVID-19 patients with suspected myocarditis or unexplained heart failure, where SARS-CoV-2 was only detected in 5 patients (Escher et al., 2020). One case report in a COVID-19 patient with fulminant myocarditis detected low-grade inflammation and SARS-CoV-2 in infiltrating macrophages but not in cardiomyocytes or endothelial cells in endomyocardial biopsy (Tavazzi et al., 2020). In another case report of a 27-year-old patient with COVID-19 who had severe lung injury and cardiac dysfunction, SARS-CoV-2 was detected in cardiomyocytes, and this was associated with cytotoxic effects (focal loss of myofibrils) (Bojkova et al., 2020). In vitro studies have demonstrated cardiotoxic effects of SARS-CoV-2 in induced pluripotential stem cell (iPSC)-derived cardiomyocytes, and infection was dependent on cathepsins and ACE-2, and was blocked by remdesivir (Bojkova et al., 2020). In contrast, in a case report of a young COVID-19 patient presenting with a delayed multisystem inflammatory syndrome (also reported as Kawasaki-like disease) associated with acute heart failure, there was evidence of fulminant lymphocytic myocarditis on endomyocardial biopsy, but SARS-CoV-2 was not detected in heart tissue, suggesting in this case that the myocarditis was secondary to the pro-inflammatory response, rather than a direct viral cytopathic effect (Bonnet et al., 2020). Another case series has reported widespread endothelial inflammation in different organs including the heart (Varga et al., 2020), which taken together with the evidence of high ACE-2 expression in the pericytes (which line blood vessels) (Chen et al., 2020), may provide the basis for the described systemic vascular effects of active COVID-19 infection (Varga et al., 2020).

A number of case reports have been published describing acute myocarditis in patients with COVID-19, and the major findings in 14 of these articles have been summarized by Sawalha et al. (2020) as follows: Male 58%, median age 50 yrs, 50% had no co-morbidity, 15% had hypertension, electrocardiogram (ECG) findings were variable, cTn was elevated in 91% of cases, echocardiography showed reduced cardiac function in 60%, and 42% showed evidence of pericardial effusion, and global hypokinesis was seen in 25% of cases. In terms of management, endotracheal intubation was performed in the majority of cases, and glucocorticoids were most commonly used in the reatment of myocarditis (58%). The majority of patients survived to discharge (81%).

Cardiac imaging and COVID-19

Cardiac imaging of confirmed or suspected COVID-19 patients can be challenging given the potential logistics of access, and risk of COVID-19 infection among healthcare personnel. Due to its portability and accessibility, echocardiography (especially point-of-care ultrasound [POCUS]) is often the initial imaging modality of choice for assessing cardiac involvement in confirmed or suspected COVID-19 patients (Cameli et al., 2020). Invasive coronary angiography or coronary CT angiography may be used when there is a strong suspicion for obstructive coronary artery disease (CAD), and CMR imaging may be considered to evaluate other causes of non-ischemic acute myocardial injury, although the latter may not be accessible or readily available (Rudski et al., 2020).

In a prospective study of 100 hospitalized COVID-19 patients, echocardiography was abnormal in 68% of patients with the predominant findings being RV dilatation (39% of patients), impaired left ventricle (LV) diastolic function (16%), and LV systolic dysfunction (10%) (Szekely et al., 2020). A global prospective survey undertaken in April 2020 of cardiac echocardiography findings in 1216 patients across six continents with known or suspected COVID-19 reported cardiac abnormalities in 50% of patients undergoing echocardiography for clinical indications, and imaging changed management in one-third of patients (Dweck et al., 2020). Independent predictors of LV abnormalities (incidence 39%) were elevated circulating natriuretic peptides (OR 2.96) and cTn (OR 1.69), and the severity of COVID-19 symptoms were independently associated (OR 3.19) with RV abnormalities (incidence 33%). Severe ventricular dysfunction or tamponade occurred in 15% of patients, and in those without pre-existing cardiac disease, the echocardiogram was abnormal in 46%, and 13% had severe disease (Dweck et al., 2020). Echocardiography criteria indicative of acute myocarditis include increased wall thickness (due to myocardial edema), chamber dilation, and pericardial effusion in the background of ventricular systolic dysfunction, although CMR can provide more specific evidence for the presence of myocarditis. It has been recommended that cardiac assessment by echocardiography should be reserved for those with clinical indications, or may be considered in those with elevated cardiac biomarkers such as troponin or natriuretic peptides to evaluate cardiac involvement (Skulstad et al., 2020).

CMR in confirmed, suspected, and recovering COVID-19 patients

CMR is the non-invasive imaging modality of choice for structural and functional evaluation of the heart, which in addition provides unique information on myocardial tissue characterization, and has been used to evaluate cardiac involvement in active, suspected, and recovering COVID-19 patients, but is limited in its accessibility and availability when compared to echocardiography. CMR is able to differentiate myocardial infarction, myocarditis, and Takotsubo cardiomyopathy, and should be considered in patients that are well enough to be scanned and in whom establishing a clear diagnosis will change management. Potential clinical indications for performing CMR in this setting are varied and include acute and chronic myocarditis, pericarditis, left and right heart failure, acute and chronic coronary syndromes, Takotsubo cardiomyopathy, pulmonary hypertension, acute

vasculitis, myocardial infarction with normal coronary arteries (MINOCA), and hyperinflammatory syndrome with Kawasaki-like features in children and adolescents. Recommendations have been published to provide guidance on safe CMR scanning and clinical CMR protocols for confirmed, suspected, and recovering COVID-19 patients (Allen et al., 2020; Han et al., 2020; Kelle et al., 2020). These guidelines should help ensure consistency between registries and clinical studies evaluating the role of CMR in patients with COVID-19. Overall, it is recommended that standard CMR protocols should be used, based on the clinical indication as per normal practice, and in patients with known or suspected COVID-19, CMR should focus on the specific clinical question and focus on ventricular function and myocardial tissue characterization.

In patients with active or suspected COVID-19, CMR has been used to diagnose the presence of acute myocarditis. Criteria for using CMR to diagnose acute myocarditis have been published (Friedrich et al., 2009), and recently updated (Ferreira et al., 2018). For patients with clinically suspected myocarditis (Caforio et al., 2013), the originally proposed CMR criteria consistent with myocardial inflammation, included at least two of the following criteria (Friedrich et al., 2009): (1) Regional or global myocardial signal intensity on T2-weighted imaging due to myocardial edema and infiltration of inflammatory cells (>2:1 myocardium to skeletal muscle ratio); (2) Increased global myocardial signal intensity on early gadolinium enhancement (EGE) imaging for hyperemia and capillary leak (EGE ratio >4:1 myocardium to skeletal muscle ratio); and (3) focal non-ischemic late gadolinium enhancement (LGE) due to cardiomyocyte injury and necrosis with replacement interstitial fibrosis and scar formation. On LGE imaging, myocarditis lesions are usually patchy, subepicardial, and midwall, and are often localized to basal to mid-inferolateral LV walls. A recent update aimed at improving the diagnostic accuracy of CMR further has added the role of pixel-wise myocardial mapping to the diagnostic criteria for acute myocarditis (Ferreira et al., 2018). The updated guidelines propose 'at least one T2-based criterion (global or regional increase of myocardial T2 relaxation time or an increased signal intensity in T2-weighted CMR images), with at least one T1-based criterion (increased myocardial T1, extracellular volume [ECV], or LGE)' (Ferreira et al., 2018). Supportive diagnostic criteria include pericardial effusion on cine CMR images or high signal intensity of the pericardium in LGE images, T1-mapping or T2-mapping, and systolic LV wall motion abnormalities on cine CMR images (Ferreira et al., 2018). It is important to note that although having both a positive T2-based and T1-based marker increases specificity for diagnosing acute myocardial inflammation, the presence of only one of these, may still support a diagnosis of acute myocardial inflammation but with less specificity (Ferreira et al., 2018). In acute myocarditis, the inflammatory response is accompanied by myocardial inter- and intracellular edema, which causes prolongation of both T1 and, especially, T2 relaxation times in the myocardium (Ferreira et al., 2018). These CMR changes can be detected by T2-weighted images (as regional or global signal hyperintensity), and increases in T1 and T2 relaxation times on pixel-wise T1 and T2 mapping sequences, respectively, although the increase in myocardial T1 values is less specific for myocardial edema as it is also elevated in areas of interstitial fibrosis (Ferreira et al., 2018). A previous study in acute myocarditis has shown that elevations of T2 relaxation values were more diagnostic for chronic myocarditis when compared to T1 values (Lurz et al., 2016). Myocardial inflammation may also be detected by increases in ECV, which can be estimated using T1 maps acquired pre- and post-administration of gadolinium and adjusting for the hematocrit value (Radunski et al., 2014).

There have been a number of published case reports describing cardiac involvement in patients with COVID-19, with elevated serum biomarkers and changes in CMR suggestive of acute myocarditis (Doyen et al., 2020; Kim et al., 2020) that fulfill the updated CMR criteria for the diagnosis of myocarditis (Ferreira et al., 2018). The presence of cardiac manifestations of acute myocarditis on CMR have been reported in both young and aged patients with COVID-19 and even in the absence of respiratory symptoms or lung involvement (Inciardi et al., 2020; Paul et al., 2020). In these case reports cardiac manifestations of COVID-19 have included impaired LV function, acute myocardial edema (as evidenced by increase LV wall thickness and mass index), increased signal intensity on T2-weighted imaging, elevated T1 and T2 relaxation times on mapping), non-ischemic LGE, and pericardial effusion (Esposito et al., 2020). In one case report of a patient who underwent endomyocardial biopsy, diffuse T-lymphocytic inflammatory infiltrates with huge interstitial edema and limited foci of necrosis, and no replacement fibrosis was detected, suggesting an acute inflammatory process, as evidenced by myocardial edema on T2-weighted and T2-mapping CMR (Sala et al., 2020).

An important question that needs further research is how to select which active and suspected COVID-19 patients should undergo CMR imaging to detect cardiac involvement. Recommendations have been published to guide the use of multi-modality cardiac imaging including CMR in patients with active or suspected COVID-19 in the acute stage (Rudski et al., 2020). The current guidelines suggest that CMR should be considered in different clinical scenarios (Rudski et al., 2020): (1) COVID-19 patient with suspected acute coronary syndrome who has equivocal symptoms in whom MINOCA or myocarditis is suspected (no history of CAD); (2) the COVID-19 patient with hemodynamic instability (shock or hypotension) in whom POCUS or formal echocardiogram shows LV dysfunction or diffuse/non-coronary regional wall motion abnormalities, and myocarditis is suspected; (3) the COVID-19 patient with new LV dysfunction without hemodynamic instability in whom echocardiogram shows diffuse/non-coronary regional wall motion abnormalities, and myocarditis is suspected (Rudski et al., 2020). For COVID-19 patients with new LV dysfunction at time of presentation, the current guidelines suggest repeating cardiac imaging (using either echocardiogram or CMR) should be considered at 2 to 6 months following discharge to assess for myocardial recovery, and guideline-directed medical therapy should be optimized (Rudski et al., 2020).

Cardiac involvement in patients recovering from COVID-19

Case reports have described CMR evidence of myocarditis at 2 to 3 weeks after recovery from COVID-19 with myocardial edema and non-ischemic LGE detected on CMR (Beşler & Arslan, 2020; Sardari et al., 2020). In this regard, CMR performed in patients recovering from COVID-19 have detected persistent cardiac involvement with residual LV dysfunction and ongoing myocardial inflammation, in a substantial number of patients (Huang et al., 2020; Knight et al., 2020; Puntmann et al., 2020; Rajpal et al., 2020). In a small study of 26 recovered COVID-19 patients with ongoing cardiac symptoms but no troponin elevation, CMR imaging at a median of 47 days following onset of COVID-19 symptoms revealed abnormal CMR findings in 58% of patients comprising myocardial edema (in 54%) and scarring detected by LGE (in 31%) with associated changes in RV functional parameters including ejection fraction (EF), cardiac index and stroke volume (Huang et al., 2020). In addition, there was evidence of increased global T1, T2, and ECV values in COVID-19 patients when compared to control subjects (Huang et al., 2020). In a larger prospective observational cohort study of 100 patients with prior

COVID-19 infection but no cardiac symptoms (67 who had recovered at home and 33 who had required hospitalization), hs-cardiac tronopin T (TnT) was elevated in 71% of the patient cohort. When compared to a cohort of healthy control subjects (N=50) and risk factor-matched controls (N=57), post-COVID-19 patients had lower LV ejection fraction, higher LV volumes, higher LV mass, and increased native T1 and T2 relaxation times on CMR performed at a median of 71 (IQR: 64-92) days (Puntmann et al., 2020). Abnormal CMR findings were observed in 78% of post-COVID-19 patients and included elevated myocardial native T1 values (N=73), myocardial native T2 values (N=60), myocardial LGE (N=32), and pericardial enhancement (N=22) (Puntmann et al., 2020). Levels of hs-cTnT were shown to correlate with native T1 mapping and native T2 mapping, and native T1 and T2 values were most predictive for COVID-19–related myocardial pathology (Puntmann et al., 2020). In another series of recovering COVID-19 patients (N=29) with myocardial injury and troponin elevation of unknown etiology, convalescent CMR at 46 days post-COVID-19 diagnosis showed non-ischemic myocarditis-like LGE in 45% of patients, but interestingly, there was no evidence of myocardial edema in this series (Knight et al., 2020). Finally, a recent study has evaluated the role of CMR in detecting myocardial inflammation in 26 competitive athletes recovering from COVID-19 infection (none of whom were hospitalized or received anti-viral therapy), 27% having had mild symptoms (sore throat, shortness of breath, myalgias, fever), and the others being asymptomatic (Rajpal et al., 2020). There were no diagnostic ST/T wave changes on ECG, and ventricular volumes and function assessed by echocardiography were normal, and none of the athletes had elevated serum troponin I levels (Rajpal et al., 2020). CMR performed at 11 to 53 days after end of quarantine, detected evidence of myocarditis in 15% of subjects (elevated T2 values [59ms versus 51ms] and non-ischemic LGE), and an additional 31% of subjects had LGE without T2 elevation (Rajpal et al., 2020). These findings suggest that CMR may be used to risk stratify competitive athletes recovering from COVID-19 infection with respect to the presence of myocardial inflammation or injury, in order to guide the safe return of athletes to competitive sports. In a retrospective preprint study of 22 collegiate athletes with prior COVID-19 infection but minimal symptoms with normal cardiac function, ECG, and troponin levels, CMR performed at 53 days demonstrated a lower rate of cardiac involvement with non-ischemic LGE or myocarditis in 3 subjects (14%) (Clark et al., 2020).

As expected, the magnitude of elevations in T1, T2, and ECV values in these studies of recovering COVID-19 patients were relatively small in these recovery CMR imaging studies (Huang et al., 2020; Puntmann et al., 2020), when compared to the published case reports of acute myocarditis associated with COVID-19 (Kim et al., 2020), suggesting a chronic ongoing myocardial inflammatory process in the recovering COVID-19 patients. The significance of these persistent CMR findings in patients recovering from COVID-19 on clinical outcomes remains unclear, and needs to be determined. In addition, further studies are needed to evaluate the evolution of CMR changes in patients recovering from COVID-19. The natural course of myocarditis secondary to COVID-19 is not known, but with other viral infections the acute phase of viral myocarditis lasts only for a few (1 to 3) days, and is characterized by cardiomyocyte necrosis induced by virus replication, which results in the activation of the humoral and cellular immunologic response, which in some patients may persist for several weeks or months (chronic post-infectious autoimmune myocarditis). Whether this is the cause for the persisent myocardial inflammatory changes observed in patients recovering from COVID-19 is not known.

There is limited guidance on cardiac imaging of patients recovering from COVID-19. This is particularly important given that 50 to 70% of recovering COVID-19 patients appear to have evidence of ongoing myocardial inflammation (Huang et al., 2020; Knight et al., 2020; Puntmann et al., 2020; Rajpal et al., 2020), and may be potentially at risk of cardiac arrhythmias. In this regard, insights may be provided by the Chief Scientist Office Cardiovascular and Pulmonary Imaging in SARS Coronavirus disease-19 (CISCO-19) study, which will use multi-modality cardiac imaging (CMR and cardiac CT coronary angiography) performed at 28 days to evaluate cardiac and clinical outcomes in patients with COVID-19 (Mangion et al., 2020).

Conclusion

Cardiac manifestations occur in 20 to 30% of hospitalized patients with COVID-19, and are associated with worse outcomes. They can be detected by elevations in cardiac biomarkers (such as troponin), cardiac dysfunction on echocardiography or CMR, and evidence of myocarditis on CMR or endomyocardial biopsy. The etiology of cardiac involvement in COVID-19 is multifactorial and includes direct viral infection, myocarditis, cardiomyopathy, critical illness, acute pulmonary embolism, sepsis, and acute coronary syndrome, and multi-modality cardiac imaging can help determine the underlying cause. In 60 to 70% of cases, CMR evidence of chronic inflammation may persist for several weeks in patients recovering from COVID-19 infection. Further studies are needed to evaluate the time-course of cardiac involvement in COVID-19 patients especially in the recovery period in terms of the clinical significance of the observed cardiac involvement detected on CMR.

Acknowledgement

Sang-Ging Ong is supported by National Institutes of Health grant R00 HL130416 and R01 HL148756. Derek Hausenloy is supported by the British Heart Foundation (CS/14/3/31002), Duke-National University Singapore Medical School, Singapore Ministry of Health's National Medical Research Council under its Clinician Scientist-Senior Investigator scheme (NMRC/CSA-SI/0011/2017) and Collaborative Centre Grant scheme (NMRC/CGAug16C006). This article is based upon work from COST Action EU-CARDIOPROTECTION CA16225 supported by COST (European Cooperation in Science and Technology).

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