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COVID and Cardiovascular Disease: What We Know in 2021

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Abstract

Purpose of Review Coronavirus disease 2019 (COVID-19) has been the cause of significant global morbidity and mortality. Here, we review the literature to date of the short-term and long-term consequences of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection on the heart.

Recent Findings Early case reports described a spectrum of cardiovascular manifestations of COVID-19, including myocarditis, stress cardiomyopathy, myocardial infarction, and arrhythmia. However, in most cases, myocardial injury in COVID-19 appears to be predominantly mediated by the severity of critical illness rather than direct injury to myocardium from viral particles. While cardiac magnetic resonance imaging remains a powerful tool for diagnosing acute myocarditis, it should be used judiciously in light of low baseline prevalence of myocarditis. Guiding an athletic patient through return to play (RTP) after COVID-19 infection is a challenging process. More recent data show RTP has been a safe endeavor using a screening protocol. "Long COVID" or post-acute sequelae of SARS-CoV-2 infection has also been described. The reported symptoms span a large breadth of cardiopulmonary and neurologic complaints including fatigue, palpitations, chest pain, breathlessness, brain fog, and dysautonomia including postural tachycardia syndrome (POTS). Management of POTS/dysautonomia primarily centers on education, exercise, and salt and fluid repletion.

Summary Our understanding of the impact of COVID-19 on the cardiovascular system is constantly evolving. As we enter a new age of survivorship, additional research is needed to catalogue the burden of persistent cardiopulmonary symptoms. Research is also needed to learn how acute management may alter the likelihood and prevalence of this chronic syndrome.

Keywords COVID-19 · Cardiovascular disease · SARS-CoV2 · Return to play · Long COVID

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Introduction

In the year 2020, the Coronavirus disease 2019 (COVID-19) was the third leading cause of death with an estimated 345,323 deaths in the USA [1]. Perhaps more than any other communicable disease, COVID-19 has captivated the cardiology community due to its apparent links with cardiovascular disease (CVD) [2•, 3–5]. The novelty of the virus led to early reliance on small case reports and theoretical explanations to explain and predict the impact on CVD. Now, more than a year since the pandemic's onset, more mature studies have emerged that refine our understanding of the interplay between COVID-19 and the heart.

Early in the pandemic, patients with cardiovascular comorbidities proved most vulnerable to severe infection [3, 6]. The specificity of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) for the angiotensin-converting enzyme-2 (ACE-2) protein fueled further concerns about injury to the cardiovascular system [3, 7] and triggered fears about concurrent use of drugs including angiotensin-

converting enzyme inhibitors and angiotensin receptor blockers [8•]. Early case reports described a spectrum of cardiovascular manifestations of COVID-19 infection, including myocarditis, stress cardiomyopathy, myocardial infarction (MI), and arrhythmia [9–12]. In combating a novel disease, the cardiology community deployed its most advanced technology including cardiac magnetic resonance imaging (CMR) which has characterized acute and chronic consequences of SARS-CoV-2 infection [13, 14], but often the findings have left clinicians with more questions than answers.

Now more than a year since the first reported cases in 2020, the global community finds itself at a critical point in the timeline of the pandemic. With survivors outnumbering those infected and with vaccines in distribution, further attention can be paid to the long-term cardiovascular effects of COVID-19. Nonetheless, as surges continue across the world owing to new variants and a lag in vaccine distribution, the medical community must remain apprised of the latest evidence-based management of acute COVID-19 infection.

Our understanding of the impact of COVID-19 on the cardiovascular system is constantly evolving. The rapid pace of the pandemic and the body of research it has spawned requires clinicians to adapt management in real time. Herein, we review the latest literature through April 1, 2021 to refine our current understanding of the acute and long-term consequences of COVID-19 infection on the cardiovascular system. In acute infection, we revisit our current understanding of mechanisms of myocardial injury in COVID-19 infection, the prognostic implications of troponin elevation, and indications for CMR in diagnosis and management. In resolved infection, we review considerations for special populations such as athletes regarding safe return to play, as well as those with lingering cardiopulmonary symptoms colloquially known as "long COVID." We conclude by proposing future areas of investigation for the interaction between COVID-19 and CVD.

Part I: Acute Infection

Mechanisms of Cardiac Injury in COVID-19

Cardiac troponin is a highly specific test for myocardial injury, which can be measured by conventional or high-sensitivity assays. Notably, an elevated troponin (defined as being above the 99th percentile of upper reference limit) does not necessarily equate to an MI. According to the 4th universal definition, the criteria for an MI requires a rise/fall pattern of troponin with at least one value above the 99th percentile along with other symptoms or signs of ischemia [15]. A type 1 MI occurs from an acute plaque rupture/erosion event, which has also been seen in the setting of other viral infections [4, 16], whereas a type 2 MI is from "demand ischemia" in the context

of an oxygen demand/supply mismatch stemming from stressors such as hypoxia, hypoperfusion, and tachycardia, which can occur in COVID-19, as well as other critical illnesses. Both types of MIs have been reported in COVID-19 [2•]. However, paradoxically, there was an approximate 20% reduction in ST-elevation myocardial infarction (STEMI) rates during the COVID-19 pandemic. Alternate mechanisms behind this STEMI reduction have been postulated, but the leading concern was that patients were avoiding hospital care for fear of contracting the virus. Beyond acute MI, troponin elevation can accompany a number of other COVID-19 cardiovascular presentations including viral myocarditis, indirect cardiac injury from cytokine storm, stress cardiomyopathy, heart failure (HF), pulmonary embolism, and arrhythmias, or reflect pre-existing CVD or cardiac structural abnormalities [17•, 18].

The prevalence of cardiac injury, as measured by an elevated cardiac troponin, on the order of 20–40% among the first reported patients with severe (hospitalized) COVID-19 attracted the attention of the cardiology and medical community at large [6, 17•, 18–23, 24•, 25]. As the virology of SARS-CoV-2 was further elucidated, its interaction with the ACE2 protein found on cardiomyocytes supported the physiologic plausibility of direct cardiac viral injury [7]. A precedent had been established by a related coronavirus, SARS-CoV-1, causing the first SARS outbreak in Asia, whereby viral RNA in cardiac tissue had been isolated [26]. Furthermore, individuals with CVD, such coronary artery disease (CAD) and HF [27, 28], and those with CVD risk factors including hypertension, diabetes, and obesity [27, 29–31] proved more susceptible to severe infection, heightening concerns that the heart may be a direct viral target and rendered more vulnerable if compromised.

With respect to the etiology of myocardial injury in COVID-19, our understanding has evolved since the onset of the outbreak. Larger histopathologic studies have challenged early frameworks of cardiac injury, demonstrating the prevalence of myocarditis and direct viral toxicity to myocytes to be exceedingly rare [32••, 33]. In one of the largest cardiac autopsy series to date, Lindner and colleagues demonstrated that while viral RNA was isolated in cardiac tissue, in situ hybridization localized the site of infection not to cardiomyocytes, but rather the interstitium and infiltrating macrophages [32••]. Additionally, there were zero confirmed cases of myocarditis by the Dallas criteria. Other pathologic studies have also failed to document direct cardiomyocyte infection [33, 34].

Notably, as features of the novel coronavirus were rapidly catalogued early in the pandemic, little was done to compare against appropriate control groups. Recent research has situated COVID-19 in the context of the broader critical care landscape. Metkus and colleagues compared troponin elevation in COVID-19 acute respiratory distress syndrome (ARDS) versus non-COVID-19 ARDS among nearly 250

intubated patients across a large hospital system and demonstrated that myocardial injury was actually *less* common in COVID-19 than non-COVID-19 ARDS, after accounting for the degree of critical illness and organ dysfunction [35••]. Patients with COVID-19 had worse oxygenation and hemodynamics, reinforcing indirect cardiac injury secondary to critical illness as the more likely mechanism at play [36]. These findings are further reinforced by high rates of myocardial injury seen in other systemic infections beyond COVID-19, including sepsis, documented in the critical care literature [37–39].

While other cardiac manifestations including myocarditis, stress cardiomyopathy, and MI have been described in COVID-19 and should not be discounted [2, 9–12], situating COVID-19 in the context of other critical illness has recalibrated our understanding of myocardial injury to recognize more prevalent mechanisms such as hypoxemia and hemodynamic compromise (Fig. 1).

Although myocardial injury in COVID-19 may not be unique to the virus, the degree of critical illness that it can cause speaks to unique pathogenic attributes. The responsible mechanism is likely related to its ability to stimulate a robust inflammatory response. In studies of myocardial injury in COVID-19, predictors of troponin elevation consistently demonstrated associations with inflammatory markers, including C-reactive protein (CRP), D-dimer, ferritin, and fibrinogen [19, 35••, 40]. Pathology studies have supported this

relationship by demonstrating greater expression of cytokines with higher viral loads [32••]. While the hyper-inflammatory phase inflicts much of the respiratory and circulatory compromise mediating indirect myocardial injury in severe infection, inflammation is previously known to directly mediate CVD, as seen in atherosclerosis and other hyper-inflammatory states including sepsis and hemophagocytic lymphohistiocytosis (HLH) [41]. Cardiomyocytes express receptors to cytokines including tumor necrosis factor and interleukin-6, the effects of which can reduce inotropy secondary to alterations in catecholamine signaling and cause cytotoxic injury [42]. Moreover, cytokines alter the vascular endothelium to promote inflammatory migration and can cause endothelitis, microthrombi, and microvascular injury which have been described in COVID-19 [34].

Echocardiography has further refined our understanding of myocardial damage in COVID-19, detailing certain functional patterns of injury [14]. Szekely and colleagues found right ventricular (RV) dysfunction to be the most common echocardiographic abnormality in a series of 100 hospitalized COVID-19 patients, among nearly 40%, with RV deterioration most associated with clinical decompensations [43]. RV dysfunction was also the most common abnormality seen in a multi-center international cohort of over 300 hospitalized patients with COVID-19, around 26% [44]. A full spectrum of dysfunction was seen in both studies, however, including global and regional left ventricular (LV) systolic dysfunction,

Fig. 1 Symbolic pie chart illustrating common causes of indirect myocardial injury and more rare causes of direct myocardial injury in COVID-19 infection
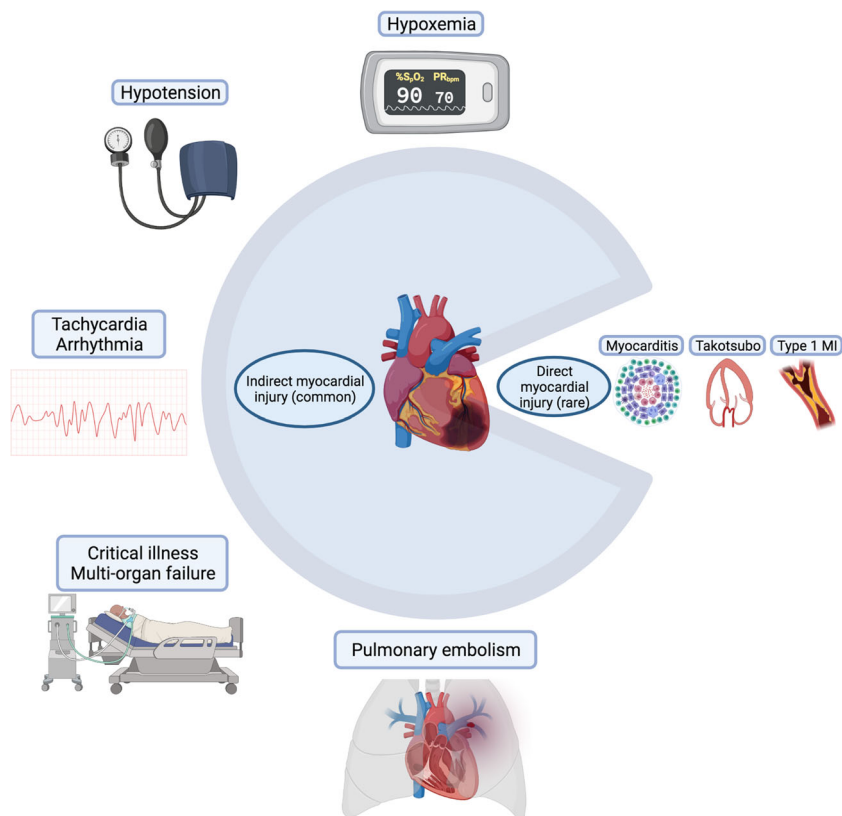
diastolic dysfunction, and pericardial effusions. The preva-
lence of RV dysfunction speaks to COVID-19 being a pre-
dominantly respiratory pathogen with a tendency for deep
venous thrombosis and pulmonary embolism, all of which
can compromise pulmonary vascular resistance and increase
RV loading conditions. Use of speckle-tracking echocardiog-
raphy found reduced basal longitudinal strain to be present in
52% of patients in one single-center study; patients who were
obese, Black patients, or patients with hypertension and dia-
betes were more likely to present with this functional pattern
[45]. Future studies are needed to determine whether these
functional changes are unique to COVID-19 or also seen in
other forms of ARDS and critical illness.

Troponin Elevation: Prognostic Implications

Mechanism of injury aside, detectable troponin elevation
carries prognostic value in acute COVID-19 infection. Shi
and colleagues were among the first to report higher mortality
in those with troponin elevation from a single-center cohort in
Wuhan, finding a threefold to fourfold risk of death [19].
Later, Lombardi and colleagues validated these findings in a
multi-center cohort in Italy with over 600 patients, albeit with
a more attenuated hazard ratio of 1.7 [25]. In one of the most
diverse cohorts studied with over 2000 patients admitted to a
New York City hospital system, Smilowitz and colleagues
illustrated that the risk of death was twofold higher among
patients with troponin elevation [46]. Importantly, the degree
of troponin elevation was associated with more severe critical
illness (defined as ICU admission, need for mechanical ven-
tilation, discharge to hospice, or death). While these seminal
studies defined troponin elevation as greater than the 99th
percentile of the upper limit of normal, Qin and colleagues
illustrated that troponin elevation in COVID-19 infection
was associated with mortality even at thresholds 19–50% low-
er than those traditionally used in clinical settings [47].

Moreover, risk for mortality and adverse outcomes appears
continuous with the degree of troponin elevation; higher tro-
ponin continues to amplify risk, providing clinicians with a
quantitative not just qualitative risk assessment for patients
[24•]. As such, measuring troponin for hospitalized COVID-
19 patients has been integrated into routine clinical practice
and management algorithms. For hospitals, it serves to fore-
cast trajectory and identify patients that may require more
intensive resources particularly in times of scarcity [48].
Several society guidelines including the World Health
Organization and the Chinese Clinical Guidance for
COVID-19 recommend measuring troponin for all admitted
patients, while others including the American College of
Cardiology (ACC) recommend testing when clinically indi-
cated [22].

The association between troponin elevation and mortality
spurred debate whether myocardial injury is a mediator or a

marker of adverse outcomes. In their comparison between
COVID and non-COVID ARDS, Metkus and colleagues
demonstrated that troponin elevation was no longer associated
with mortality after controlling for age, sex, and, importantly,
multiorgan system dysfunction [35••]. Moreover, Giustino
and colleagues have suggested that the presence of troponin
elevation alone may not be sensitive enough to detect clinical-
ly meaningful myocardial injury [44]. In a retrospective,
multi-center international study of echocardiographic findings
in over 300 hospitalized patients with COVID-19, only those
with troponin elevation and echocardiographic abnormalities,
not troponin elevation alone, had significantly higher risk of
in-hospital mortality [44]. These findings suggest that myo-
cardial injury evidenced by detectable troponin, akin to other
markers including lactate, creatinine, and bilirubin, is often the
consequence, rather than the cause of, critical illness and re-
flects the frailty of the underlying substrate.

Role of Cardiac Magnetic Resonance Imaging

The pathophysiologic plausibility of COVID-19 causing di-
rect myocardial infection and early case reports invoking
myocarditis led to increased interest in use of CMR, now the
preferred non-invasive diagnostic modality for acute myocar-
ditis [49]. The first case reports of myocarditis in acute
COVID-19 infection reported prevalence of about 7% [50,
51]; however, these studies were flawed by inconsistent diag-
nostic criteria and limited sample sizes. As discussed previ-
ously in the context of histopathologic studies, the prevalence
of myocarditis in COVID-19 is now appreciated to be ex-
tremely rare, and larger retrospective multi-center cohort stud-
ies have found it to be 1% or less [52]. Recognizing the low
pre-test probability of COVID-19 myocarditis and consider-
ing more likely causes of myocardial injury inform the appro-
priate use of CMR. In particular with CMR, the lengthier
examination time and logistics required to accommodate
exams in intubated patients (including transitioning patients
to and from scanner-safe ventilators) increase exposure risk
for healthcare workers [53].

Subsequently, society guidelines for appropriate use of
CMR during COVID-19 infection have emphasized the con-
sideration of alternative diagnoses and recommended use only
when findings will alter management. The Society of
Cardiovascular Magnetic Resonance (SCMR) endorses the
use of CMR in COVID-19 infection when results have imme-
diate procedural implications, including but not limited to re-
vascularization, valvular interventions, necessary ablations,
immunosuppression, or concern for malignancy requiring car-
diothoracic surgery [54]. When new LV dysfunction or clin-
ical symptoms (e.g., chest pain, arrhythmia) raise concern for
myocarditis, an expert panel from the ACC recommends
CMR only after CAD has been ruled out by angiography or
less invasive modalities such as coronary computed

tomography angiography (CCTA), because the pre-test probability of ischemia is much more likely than acute myocarditis [55•]

There may be even greater interest in CMR for the surveillance of survivors following acute infection. Huang and colleagues were the first to demonstrate myocardial edema and fibrosis, evidenced by abnormal T1/T2 signaling and late gadolinium enhancement (LGE), respectively, in a small sample of 26 patients who continued to report cardiac symptoms 50 days from symptom onset [56]. Later, in a prospective cohort study of 100 unselected patients (i.e., did not necessarily present with cardiac symptoms), Puntmann and colleagues demonstrated ongoing myocardial inflammation in 60% of patients at a median follow-up of 71 days [13]. These findings raised alarm for long-term consequences for the general population (of note, two-thirds of the participants were not hospitalized) as well as select individuals, namely athletes, to be explored in the subsequent section. Importantly, these studies did not examine clinical outcomes related to these findings which remains an important area of investigation. Moreover, additional work is needed to compare myocardial injury following COVID-19 infection with controls beyond healthy individuals, because similar CMR findings have been described following other infectious syndromes such as sepsis [57]. Recommendations for CMR in COVID-19 infection are summarized in Fig. 2.

Part II: Resolved Infection

COVID-19 and Return to Play for Athletes

The question of when a competitive athlete can return to play (RTP) after COVID-19 infection poses an urgent and important challenge to the field of cardiology. The urgency is driven by the fact that athletic organizations, from the professional to the recreational, were some of the first to return to full speed during the pandemic. This collective rush to return began with little data on how to do so safely after an infection. The importance was clear, as myocarditis is a potential sequela of COVID-19 infection and a cause of death in young athletes [58]. Exercising with an active myocarditis can lead to increased inflammation and a proarrhythmogenic milieu. Furthermore, the athletic heart can have abnormalities in size, function, and response to exercise that make it challenging to distinguish from the inflamed or injured heart [59]. Intense exercise can lead to transient elevations in troponins and imaging findings suggestive of cardiac fatigue and myocardial inflammation [60]. With thousands of athletes eager to return to action, how to do so safely became a central issue in the field of cardiology throughout the pandemic.

In May of 2020, the ACC's Sports and Exercise Cardiology Section issued its first set of RTP recommendations [61]. For those athletes that experienced a symptomatic infection, they recommended a 2-week rest period after symptom resolution, a cardiac evaluation (electrocardiogram, echocardiogram, or high-sensitivity troponin), and additional cardiac imaging with any abnormalities. If myocarditis was detected, clinicians were referred to existing American Heart Association (AHA)/ACC myocarditis guidelines which recommend abstaining from athletics for 3–6 months [62]. Six months later, the Section updated and expanded these guidelines to include specific recommendations based on age and detailed troponin and CMR screening recommendations [63]. An Expert Consensus Statement followed, both of which recommended against the use of CMR-based screening of all athletes with prior COVID-19 infection [64].

The use of CMR in the RTP setting received much attention. Published in September of 2020, Rajpal and colleagues performed CMR in 26 competitive athletes and found that 4 (15%) had CMR findings suggestive of myocarditis and 8 additional athletes (30.8%) exhibited LGE without T2 elevation suggestive of prior myocardial injury [65]. Brito and colleagues then published a study of imaging findings (echocardiography and CMR) of 54 student athletes who were recovering from COVID-19 infection [66]. They concluded that more than 1 in 3 previously healthy college athletes recovering from COVID-19 infection showed imaging features of resolving pericardial inflammation. These studies are limited in their size and lack of a control group or clinical endpoints, but they raised the alarm further for RTP safety, particularly at the collegiate level.
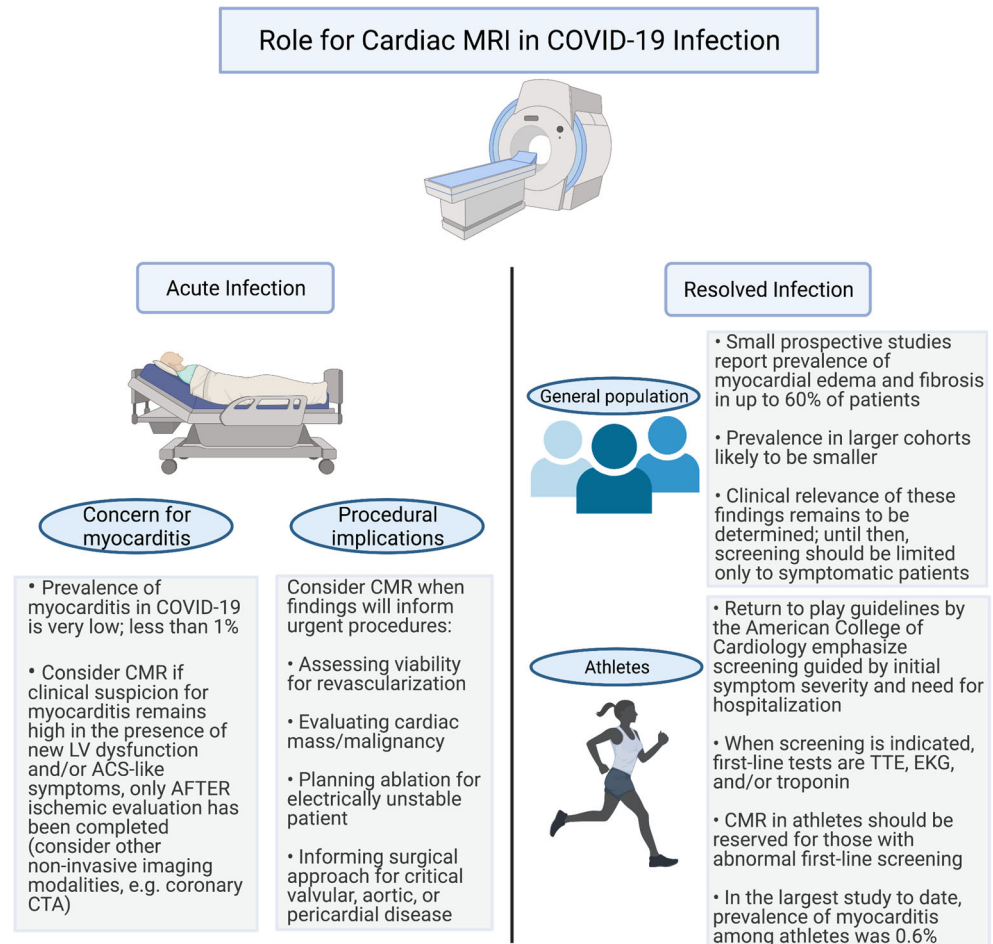
Fortunately, more recent registry data shows the national RTP has been a safe endeavor. A study of 789 professional athletes that underwent a RTP cardiac testing protocol after COVID-19 infection found imaging evidence of inflammatory heart disease in 5 athletes (0.6%) [67••]. The cardiac screening protocol included troponin, ECG, and transthoracic echocardiogram; CMR or stress echocardiography was pursued only in athletes with abnormal initial cardiac screening. No adverse cardiac events occurred in athletes who underwent cardiac screening and returned to play.

Guiding a patient through the return to athletics after COVID-19 infection is a challenging process. COVID-19 data evolves rapidly, sports cardiology is a relatively nascent field, and the athletic heart is a unique substrate. This combines to produce more uncertainty than clear answers when approaching the return to play. However, as time has passed and more data emerged, that return, when guided by the current screening recommendations, can be done safely.

Long COVID

As healthcare workers and researchers are continuing to learn, triage, and treat the acute cardiovascular risks of COVID-19,

Fig. 2 Review of the role and indications for cardiac magnetic resonance (CMR) imaging in acute and resolved infection, both in the general population and more specifically in athletes. Abbreviations: LV left ventricular, ACS acute coronary syndrome, CCTA coronary computed tomography angiography, TTE transthoracic echocardiography, EKG electrocardiogram

Role for Cardiac MRI in COVID-19 Infection

Acute Infection

Resolved Infection

Concern for myocarditis

- Prevalence of myocarditis in COVID-19 is very low; less than 1%

- Consider CMR if clinical suspicion for myocarditis remains high in the presence of new LV dysfunction and/or ACS-like symptoms, only AFTER ischemic evaluation has been completed (consider other non-invasive imaging modalities, e.g. coronary CTA)

Procedural implications

Consider CMR when findings will inform urgent procedures:

- Assessing viability for revascularization

- Evaluating cardiac mass/malignancy

- Planning ablation for electrically unstable patient

- Informing surgical approach for critical valvular, aortic, or pericardial disease

General population

- Small prospective studies report prevalence of myocardial edema and fibrosis in up to 60% of patients

- Prevalence in larger cohorts likely to be smaller

- Clinical relevance of these findings remains to be determined; until then, screening should be limited only to symptomatic patients

Athletes

- Return to play guidelines by the American College of Cardiology emphasize screening guided by initial symptom severity and need for hospitalization

- When screening is indicated, first-line tests are TTE, EKG, and/or troponin

- CMR in athletes should be reserved for those with abnormal first-line screening

- In the largest study to date, prevalence of myocarditis among athletes was 0.6%

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many outpatient providers are being inundated by patients with persistent symptoms after acute infection, known in popular media as "long COVID" [68]. With greater recognition of this ongoing syndrome, researchers have established the following definitions: *post-acute COVID syndrome (PACS)* for persistent symptoms after 3 weeks and *chronic COVID* after 12 weeks [69, 70]. The National Institutes of Health has also referred to "long COVID" as *post-acute sequelae of SARS-CoV-2 infection (PASC)* [71]. The reported symptoms span a large breadth of cardiopulmonary and neurologic complaints including fatigue, palpitations, chest pain, breathlessness, brain fog, and dysautonomia [69, 70, 72–75].

Researchers have been studying the persistent effects of COVID-19 since the early days of the pandemic. Of a cohort of 143 discharged patients in Italy from April 2020, 87% reported ongoing fatigue and dyspnea at 60 days [76]. Halpin and colleagues in the United Kingdom (UK) demonstrated that patients requiring intensive care unit–level care were more likely than general ward patients to report persistent symptoms of fatigue (72% verses 60.3%) and breathlessness (65.6% vs 42.6%) after discharge [72]. Another larger cohort in Michigan found that 159 of 488 (33%) patients endorsed ongoing cardiopulmonary symptoms including cough

and dyspnea at 60 days [77•]. This study was limited by a large number of patients (greater than 50%) being lost to follow-up.

While early studies estimated the prevalence of long COVID to be between 30 and 80%, they were limited by a primary focus on hospitalized patients. Within a non-hospitalized cohort of 272 individuals across the USA, 35% reported not being at baseline at 14–21 days after COVID-19 diagnosis [73]. New studies are using mobile technology to allow responders to directly monitor and report their symptoms for both acute and long-term tracking of symptoms [78, 79]. While older individuals with multiple comorbidities are at higher risk of long COVID, approximately 20% of young individuals, ages 18–34 and without comorbid conditions, also continued to report ongoing symptoms at 14–21 days [73].

With regards to specific cardiovascular symptoms, approximately 20% of individuals reported chest pain and 14% reported palpitations at 60 days [76, 80]. Inflammation and increased metabolic and myocardial demand are thought to contribute to persistent cardiovascular symptoms as this has been seen in other severe coronavirus infections such as SARS [75, 81, 82]. A rising number of patients and case studies are also

noting a relationship between COVID-19 and postural tachy-cardia syndrome (POTS) [83•]. POTS is characterized by change in heart rate with positional change, often accompanied by palpitations and decreased exercise tolerance [83•]. POTS has been previously linked to post-viral illness, but the exact mechanism is unknown [84, 85]. One hypothesis connecting POTS with COVID-19 builds on its known inter-action with the ACE2 protein expressed on neurons. Researchers hypothesize that this can disrupt the normal reg-ulation of blood pressure mediated by ACE2, leading to hy-potension and dysautonomia [74, 85]. Management of POTS and dysautonomia primarily centers on education, exercise, and salt and fluid repletion. Agents such as midodrine can improve vascular tone, while beta-blockers and ivabradine can help manage palpitations [86]. The prevalence, features, and management principles of long COVID are summarized in Fig. 3.

With 20–30% of outpatient individuals and up to 80% of hospitalized patients having persistent symptoms, the onus is now on providers and researchers to recognize and manage the persistent burden of COVID-19 infection. Many recover slowly on their own through anticipatory guidance and light exercise. However, the British Thoracic Society has established guidelines to follow up all patients regardless of severity at 12 weeks with a chest X-ray and clinical assess-ment to evaluate any need for further testing [87]. Those with severe COVID-19 are recommended to follow up earlier at 4–6 weeks to evaluate need for further testing as well as multi-disciplinary rehabilitation [75]. Serial electrocardiograms and echocardiograms can be used to monitor those with persistent cardiac symptoms, although advanced imaging should be discussed on a case-by-case basis.

Conclusion

It has been some time since the global medical community has confronted a novel disease of pandemic proportions. Unraveling the mysteries of COVID-19 has been an exercise in diligent science and experimentation. The latest observational, patholog-ic, imaging, and clinical studies have clarified the short-term and long-term impacts of COVID-19 on the cardiovascular system and updated our understanding in a number of ways.

Fig. 3 Review of the prevalence of long COVID, definitions and symptomatic manifestations, and current principles of management for potential COVID/postural orthostatic tachycardia syndrome overlap
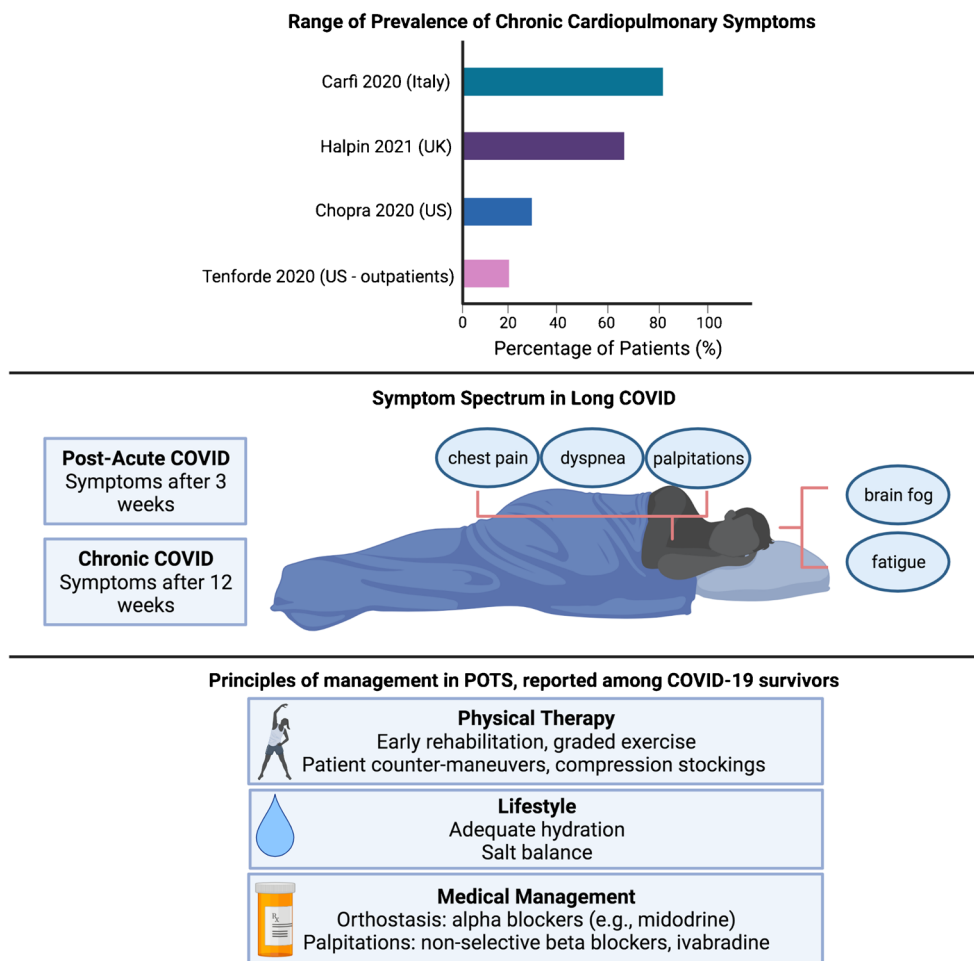
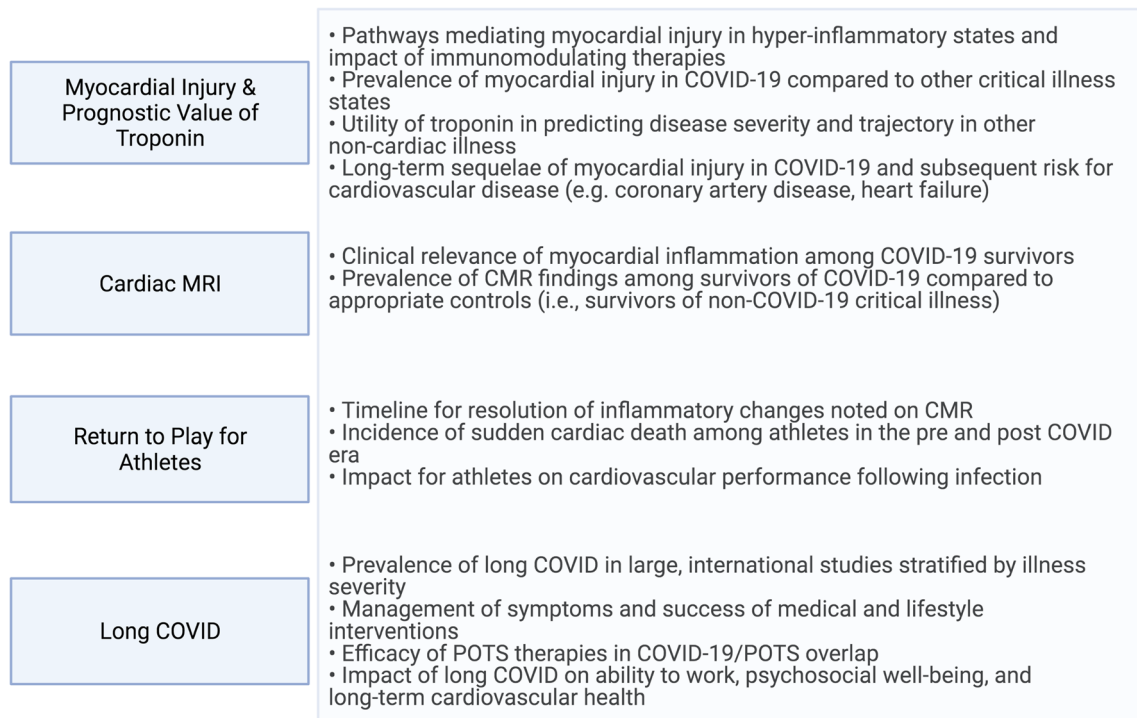## Areas for Future Investigation: COVID-19 and Cardiovascular Disease

Myocardial Injury & Prognostic Value of Troponin	• Pathways mediating myocardial injury in hyper-inflammatory states and impact of immunomodulating therapies • Prevalence of myocardial injury in COVID-19 compared to other critical illness states • Utility of troponin in predicting disease severity and trajectory in other non-cardiac illness • Long-term sequelae of myocardial injury in COVID-19 and subsequent risk for cardiovascular disease (e.g. coronary artery disease, heart failure)
Cardiac MRI	• Clinical relevance of myocardial inflammation among COVID-19 survivors • Prevalence of CMR findings among survivors of COVID-19 compared to appropriate controls (i.e., survivors of non-COVID-19 critical illness)
Return to Play for Athletes	• Timeline for resolution of inflammatory changes noted on CMR • Incidence of sudden cardiac death among athletes in the pre and post COVID era • Impact for athletes on cardiovascular performance following infection
Long COVID	• Prevalence of long COVID in large, international studies stratified by illness severity • Management of symptoms and success of medical and lifestyle interventions • Efficacy of POTS therapies in COVID-19/POTS overlap • Impact of long COVID on ability to work, psychosocial well-being, and long-term cardiovascular health

Fig. 4 Suggestions for future areas of investigation in the domains explored in this review. Abbreviations: POTS postural orthostatic tachycardia syndrome, CMR cardiac magnetic resonance

Myocardial injury in COVID-19 appears to be predominantly mediated by the severity of critical illness rather than direct injury to myocardium from viral particles. While myocardial injury is not unique to COVID-19 and is seen elsewhere in the critical care literature in sepsis and ARDS, the hyper-inflammatory response precipitated by COVID-19 is a unique hallmark and may mediate the more severe clinical courses seen as compared with other viruses. If anything, COVID-19 has reinforced the critical interaction between inflammation and CVD and should spur future work in this field. While myocardial injury in the form of troponin elevation is prevalent and prognostic in acute COVID-19 infection, recent studies suggest that troponin elevation is a marker of disease severity and the underlying substrate, rather than an independent mediator of outcomes.

While CMR remains a powerful tool for diagnosing acute myocarditis, it should be used judiciously in light of the low baseline prevalence established in studies to date, as well as risk of exposure to healthcare personnel. Studies are needed to understand the clinical relevance of persistent inflammatory signals seen in survivors and how this may compare or contrast with those recovering from other common viruses or critical illness. CMR may have a more focused role in providing recommendations for at-risk populations such as athletes; however, it should rarely be the first-line modality and imaging findings alone should not serve as the basis for diagnosing acute myocarditis.

Lastly, as we enter a new age of survivorship, additional research is needed to catalogue the burden of persistent cardiopulmonary symptoms which have significant implications for patient well-being and global economies regarding ability to return to work. Research is also needed to confirm whether existing therapies for dysautonomia including POTS are effective in the long COVID population, and how acute management may alter the likelihood and prevalence of this chronic syndrome. Future areas of investigation across the domains explored in this review are outlined in Fig. 4.

While questions remain and will continue to emerge regarding COVID-19 and CVD, the pandemic has proven that the scientific community is exceptionally committed and capable of providing these critical answers.

Declarations

Conflict of Interest   The authors declare no competing interests.

Human and Animal Rights and Informed Consent   This article does not contain any studies with human or animal subjects performed by any of the authors.

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