Exercise After Acute Myocarditis
When and How to Return to Sports

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KEYWORDS

• Myocarditis • Return to play • Arrhythmia • Virus • Mitochondria • Sex differences • Exercise • Cardiac magnetic resonance imaging

KEY POINTS

- Myocarditis is an inflammation of the myocardium with the most feared consequence being sudden cardiac death owing to arrhythmia.
- Cardiac MRI is an important diagnostic and prognostic tool for cases of symptomatic myocarditis.
- Guidelines recommend return to play following myocarditis no sooner than 3 to 6 months in addition to follow-up testing, which may include repeat cardiac MRI.

BACKGROUND

Sudden cardiac death (SCD) associated with sports participation is a tragic event, and much has been done to better understand and prevent this occurrence. Early studies evaluating SCD in athletes implicated hypertrophic cardiomyopathy as the most common cause of SCD in the United States.[1] However, more recent studies involving international data and the military have found normal autopsies in the majority of cases raising the possibility of yet undefined channelopathies and arrhythmia as a significant cause of SCD.[2–11] To date, approximately 6% to 14% of SCD events in athletes are attributed to myocarditis.[6,12] However, autopsy, which is needed to identify myocarditis, is not consistently performed, and the contribution of myocarditis to SCD may be underestimated. The mechanism by which myocarditis causes SCD in athletes is attributed to both focal cellular electrical instability and ischemia leading to polymorphic ventricular tachycardia or sometimes heart block.[13] National and international societies provide recommend timelines for return to play (RTP) after acute myocarditis to mitigate the risk of SCD.

DISCUSSION

Definition and Epidemiology

Myocarditis is an inflammation of the myocardium that occurs primarily in response to infectious agents but can also be caused by noninfectious insults, such as autoimmune disorders and/or inherited cardiomyopathies. Viral illnesses are most implicated with acute myocarditis worldwide except for *Trypanosoma cruzi* infection, leading to Chagas disease in South America. Adenovirus and enterovirus are the most likely infectious causes in the United States with parvovirus B-19 and human herpesvirus 6 currently most implicated in Europe.[14–16] More recently, SARS-CoV-2 and the messenger RNA (mRNA) vaccines used against the virus have been linked to the development of myocarditis.

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Myocarditis is defined as probable, possible, and definite based on the combination of symptoms and diagnostic test results. Possible myocarditis is defined with a high degree of certainty based on the following: (1) cardiac symptoms (dyspnea, chest pain, palpitations, syncope); (2) elevated cardiac troponin (cTn); (3) abnormal electrocardiogram (ECG) (diffuse T-wave inversions, ST-segment elevations without reciprocal ST-segment depressions, prolongation of the QRS duration), and/or abnormal echocardiogram (left ventricular wall motion abnormalities in a noncoronary distribution); and (4) abnormal cardiac magnetic resonance (CMR) imaging findings, such as late gadolinium enhancement (LGE) in a nonischemic pattern with prolonged native T1 and T2 relaxation times.[17] Possible myocarditis is defined when cardiac symptoms, elevated cTn, and abnormal ECG and/or echocardiographic findings are present with the absence of CMR or endomyocardial biopsy (EMB) evidence or the inability to perform CMR or EMB.[17] Definite myocarditis is defined by compatible histopathologic findings from endomyocardial or surgical biopsy or from autopsy specimens. When an acute pericarditis clinical syndrome and elevated troponin occur together, the condition is termed myopericarditis. Myocarditis specifically after vaccination may be defined according to the Brighton or Centers for Disease Control and Prevention criteria.[18,19]

Lake Louise criteria (LLC) help define CMR abnormalities for the diagnosis of myocarditis. LLC include CMR evidence of the following: (1) myocardial edema on T2-mapping sequences showing regional or global increases in native T2 and/or T2 signal intensity; (2) nonischemic myocardial injury with abnormal regional or global increases in native T1 or extracellular volume and/or regional LGE. Supportive findings on CMR that are not sufficient in themselves for diagnosis include the following: (1) pericardial effusion detected on cine CMR images; (2) pericardial inflammation with LGE, T1 or T2 mapping; and/or (3) LV wall motion abnormalities.[20]

Recently, several large cohort studies in athletes used the LLC to determine cardiac involvement by CMR to help define and identify cases of COVID-19 myocarditis. One study evaluating the risk of developing myocarditis after SARS-CoV-2 infection in young ($\leq$20 years of age) otherwise healthy people found the incidence to be around 450 per million cases.[21] When CMR imaging was used as a screening tool to evaluate for cardiac involvement in acute and subacute COVID-19, approximately 2.3% of athletes had findings that met the updated 2018 LLC for clinical myocarditis.[22,23] Although the LLC was originally developed for the diagnosis of myocarditis in symptomatic patients, these criteria were adapted to ascertain whether athletes had definite, probable, or possible myocarditis after COVID-19, despite many asymptomatic athletes. There was high variability among studies for the presence of cardiac involvement and of methods used to quantify and report myocardial tissue characterization. The studies used nonstandardized methods for CMR identification of cardiac involvement, and cardiac abnormalities did not meet LLC for myocarditis. Many of these studies did not include control groups of uninfected athletes for comparison. For post–vaccine myocarditis, the Centers for Disease Control and Prevention recently reported 1226 cases of probable myocarditis/pericarditis and 323 confirmed myocarditis/pericarditis cases after approximately 300 million COVID-19 mRNA vaccine doses, supporting a very rare occurrence of myocarditis/pericarditis associated with mRNA vaccine administration.[24]

Last, it is worthwhile to discuss autoimmune myocarditis and the potential for inherited cardiomyopathies to progress to fulminant myocarditis. Idiopathic giant cell myocarditis (GCM) is a rare and usually rapidly progressive form of autoimmune myocarditis generally found in younger men and women.[25] Although GCM may respond to immunosuppressive therapy with early diagnosis and treatment, the disease is often fatal secondary to life-threatening arrhythmias or cardiogenic shock.[25] A more chronic form of autoimmune myocarditis is idiopathic granulomatous myocarditis or sarcoid myocarditis. The incidence of cardiac involvement with pulmonary or systemic sarcoidosis is reported around 5%; however, this number is likely an underestimate of cases with histologic cardiac involvement.[26] Morbidity and mortality from sarcoid myocarditis are common and result from bradyarrhythmias or tachyarrhythmias and SCD.[27]

Inherited cardiomyopathies can lead to the development of myocarditis as evident in both premortem and postmortem studies.[28,29] Therefore, family screening may be beneficial for the early recognition and delivery of preventative therapies and/or treatments to this patient population, and exercise restrictions may be warranted owing to the genetic propensity for phenotypic expression with exposure to exercise. Arrhythmogenic right ventricular cardiomyopathy (ARVC) causes mutations in genes encoding desmosomal proteins and is most often acquired in an autosomal dominant pattern, which can lead to ventricular arrhythmias, ventricular dysfunction, and SCD.[30,31] In addition, initially introduced in 2008 by Sen-Chowdhry and

colleagues,[32–34] there is growing evidence of arrhythmogenic left ventricular cardiomyopathy (ALVC) linked to gene mutations, which encode desmoplakin and Filamin C. The result is cardiomyocyte loss and repair with replacement by fibrofatty tissue, similar to what causes the arrhythmogenic milieu implicated in ARVC.[34,35] Fabry disease is an X-linked disease caused by deleterious mutations in the GLA (α-galactosidase A) gene and has a prevalence of about 1:117,000 in the general population.[36] Fabry myocarditis results from glycosphingolipid accumulation in cardiac myocytes, which generates a proinflammatory response from cardiomyocyte necrosis and fibrosis.[37]

Pathogenesis

The pathogenesis of viral myocarditis in mouse models and clinically can be divided into 3 phases: an early phase of viral entry into cells and activation of the innate immune response (develops in minutes to hours and is upregulated in the heart from day 3–5), activation of the adaptive immune response leading to acute myocarditis (which typically occurs in the first 7–14 days after infection), and a chronic phase that can last from months (in animal models and humans) to years (in humans), where remodeling and fibrosis progress to dilated cardiomyopathy (DCM) and chronic heart failure.[38–41] SARS-CoV-2 largely follows the same pattern, although the spike protein itself can persist in cells studied in vitro and cause myocyte dysfunction. The long-term clinical impact of these findings is under investigation.[42] GCM generally has an accelerated disease course with quick progression to heart failure and intractable ventricular arrhythmias. In comparison, inherited cardiomyopathies, such as Fabry disease and ARVC, are slowly progressive over time with symptoms developing after myocardial tissue is replaced by fibrosis or fibrofatty scar, respectively, similar to the progression to DCM after myocarditis.[15,38] The clinical presentation of arrhythmia varies greatly during myocarditis. During the acute phase of illness, arrhythmia is thought to be secondary to multiple factors, including the following: (1) direct cytotoxic effects leading to electrical instability from membrane dysfunction; (2) ischemia from macrovascular or microvascular and endothelial dysfunction; (3) gap junction dysfunction; and (4) abnormal calcium handling particularly with arrhythmogenic cardiomyopathies.[13] In contrast, arrhythmia presenting in the chronic DCM phase of disease is likely secondary to fibrosis and scar.[13]

There is currently no clear understanding of why viruses such as coxsackievirus (CVB), influenza, HIV, poliovirus, hepatitis C virus, or SARS-CoV-2 would target the heart or the mechanism for how these relatively mild viral cardiac infections lead to sex differences in heart failure. CVB3 has been shown to require mitochondria for viral replication,[43] and many of the viruses that cause myocarditis target mitochondria as part of their replicative cycle.[44–47] The abundant mitochondria required to meet the heart's high energetic demands provide an explanation for why such disparate types of viruses, that have no obvious cardiac tropism, would target the heart. Exercise typically improves cardiac function even after diseases such as ischemia[48,49]; however, during viral myocarditis, strenuous exercise increases the risk of SCD leading to the current guidelines recommending that patients abstain from exercise for 3 to 6 months after diagnosis.[12] Surprisingly, basic research animal studies conducted to understand the mechanisms that may account for SCD with myocarditis after exercise is around 30 years old.[50–53] These studies demonstrated increased mortality, viral titers, autoantibodies, and inflammation in animals with viral myocarditis after exercise.[50–53] More recently, exercise has been found to cause mitochondrial fission mediated by Drp1, while Drp1/fission is required for CVB3 replication.[54] In addition, b-adrenergic receptor activation also leads to mitochondrial fission of cardiac myocytes in culture,[54] providing a further possible mechanism for heart failure. Research is needed in this area, and the authors' laboratory (Fairweather) is examining the potential role of these pathways in increasing heart failure during viral myocarditis.[55]

Clinical Presentation

The clinical presentation of myocarditis is heterogeneous but generally includes cardiac symptoms, including chest pain, dyspnea, palpitations, heart failure, syncope, and rarely, SCD.[56] Exertional symptoms include exercise intolerance/fatigue, palpitations/tachycardia, or presyncope with return to exercise.[57] The disease can present at any age, but it is most frequently diagnosed in young adults.[56] When considering the diagnosis in the older adult population, it is imperative to rule out other causes of symptoms, such as coronary artery disease and/or anomalous coronary arteries with invasive coronary angiography or cardiac computed tomography angiography.

In general, myocarditis is considered acute when symptoms develop within 3 months and chronic when symptoms develop after 3 months

of illness. There should be a high index of suspicion for viral myocarditis with the development of cardiac symptoms coinciding 1 to 4 weeks after viral illness. Following a new or recent diagnosis of SARS-CoV-2, development of cardiopulmonary symptoms at any time, particularly when returning to sports participation, should prompt further evaluation for myocardial involvement.[57] Although rare (0.5%–3.0%), cardiopulmonary symptoms of chest pain or dyspnea is considered an independent predictor of SARS-CoV-2 cardiac involvement in young healthy athletes.[22,23,58]

Diagnosis

Initial tests for clinically suspicious myocarditis should include the following: (1) a complete blood count, basic metabolic panel, cTn, C-reactive protein, and natriuretic peptide if heart failure is uncertain; (2) an ECG; and (3) an echocardiogram. If there is a clinical concern for arrhythmia, an ambulatory ECG monitor should be obtained. Elevated troponin, ECG abnormalities (diffuse T-wave inversions, ST-segment elevation without reciprocal ST-segment depression, prolongation of the QRS duration, arrhythmia, and/or heart block), and/or new echocardiographic abnormalities (ventricular dysfunction in a noncoronary distribution) should trigger additional studies, including CMR and/or EMB if clinically warranted. Application of the previously mentioned LLC when interpreting CMR may aid in the diagnosis of myocarditis. However, the gold standard for diagnosis is histopathologic evidence on EMB using Dallas or immunocytochemical criteria.[59] It should be noted that cardiac necrosis that is part of the Dallas criteria is not necessary for the development of myocarditis, fibrosis, or progression to DCM in translational animal models of myocarditis.[39,41] Although not routinely performed, EMB should be considered when all other causes of heart failure have been excluded, and there remains a likelihood that EMB will yield a diagnosis that will change prognosis or management.[60]

If sarcoid myocarditis is suspected, fluorodeoxyglucose-PET may be obtained for both the diagnosis and the monitoring response to therapy.[13] If GCM is suspected, EMB is the only test to provide a definitive diagnosis. For the inherited cardiomyopathies, the 2010 Task Force Criteria facilitate the diagnosis of ARVC by a point system for specific major and minor criteria, including the presence of structural abnormalities, histopathologic findings, repolarization abnormalities, depolarization abnormalities, arrhythmia, and family history.[31] However, these same criteria can lead to the misdiagnosis of left ventricular arrhythmogenic cardiomyopathy. Therefore, genetic testing for mutations in the genes encoding desmoplakin, filamin C, and desmin may provide the most accurate means for the diagnosis of arrhythmogenic cardiomyopathies.[61] If Fabry disease is suspected, measurement of alpha-Gal A activity in men or gene analysis of the GLA gene may confirm diagnosis.[36]

Management

Most cases of myocarditis resolve in the first 2 to 4 weeks. However, approximately 25% of cases develop persistent symptoms, and 12% to 25% decompensate acutely and require advanced therapies.[56] Recent translational studies suggest benefits of a tailored therapy approach for specific causes of myocarditis in conjunction with guideline-directed medical care.[62] There should also be a low threshold for repeat testing with imaging or arrhythmia monitoring in patients with ongoing or worsening symptoms and/or for disease surveillance. Reliance on normalization of cardiac and inflammatory biomarkers to predict resolution of LGE on initial CMR should be correlated with caution, as 1 study reported an improvement in biomarkers and LGE on follow-up imaging, whereas a significant minority (21%) had worsening LGE despite normalization of cardiac biomarkers.[63] These data suggest that repeat CMR to assess the change in LGE may have unique prognostic value in the risk assessment of myocarditis.[63]

Mild to severe cases of myocarditis should initially be managed in a hospital setting, preferably one capable of providing advanced heart failure therapies. Treatment of heart failure is managed with standard therapies, including diuretics, ACE inhibitors, and beta-blockers. In patients with heart failure symptoms refractory to medical therapy or with hemodynamically significant arrhythmia, mechanical circulatory support may be used during the acute phase of illness or as a bridge to transplant. Arrhythmia is common and may respond to medications like class III antiarrhythmics. An implantable cardioverter-defibrillator (ICD) or pacemaker may be indicated in cases of sustained or symptomatic ventricular arrhythmia or high-grade conduction abnormalities, respectively. Temporary implanted devices are frequently used in the acute setting and transitioned to permanent devices if survival after the acute phase is expected to be greater than 1 year.[64]

The use of antiviral therapies for treatment of viral myocarditis is not yet established based on randomized clinical trial data.[25] Immunosuppressive

agents may be considered in cases of fulminant myocarditis with biopsy evidence of severe inflammatory infiltrates.[65] However, the effect of such therapy in SARS-CoV-2 remains unknown. Firm evidence for the use of immunosuppressive therapies for the treatment of myocarditis is limited to use with GCM and sarcoid myocarditis. Treatment of GCM with immunosuppressive therapies includes steroids, cyclosporine, and sometimes azathioprine.[25] Treatment of sarcoid myocarditis is similar with first-line therapy-inducing steroids and second-line therapy with methotrexate.

Treatment of the inherited cardiomyopathies relies largely on supportive measures. Although less is known about the development of ALVC from desmoplakin mutations, emerging evidence suggests there is a greater propensity toward the development of myocarditis when compared with ARVC.[34] In general, therapies include medical management of heart failure symptoms, amiodarone, and beta-blocker use for arrhythmia, ICD for SCD prevention, and ultimately heart transplantation for the most refractory cases. In addition, restriction from sports participation is recommended for healthy gene carriers and individuals affected by the disease owing to the high risk of disease progression with exposure to exercise.[30,66] For Fabry disease, early diagnosis and consideration for enzyme replacement therapy (ERT) may prevent development of myocarditis. Although response to ERT after the development of Fabry myocarditis remains controversial, most experts agree ERT early in the disease course may prevent disease progression.[37,67]

Return to Play

The Task Force 3 criteria for return to sports following an acute clinical syndrome consistent with myocarditis recommend repeat evaluation no sooner than 3 to 6 months following the initial illness. At that time, athletes should undergo repeat testing with a resting echocardiogram, 24-hour Holter monitor, and exercise ECG. It is reasonable to RTP with normalization of systolic function, cardiac biomarker, and absence of arrhythmia on exercise ECG and/or Holter monitoring.[66] When doubt exists regarding resolution of inflammation based on cardiac testing or if symptoms persist or develop after RTP, there should be a low threshold for repeat CMR testing.[63,68] For patients with confirmed COVID-19 myocarditis, RTP following 3 months of exercise abstinence was deemed safe in a study with a 12-month follow-up period.[69]

It is important to address RTP strategies in the era of COVID-19 owing to the potential, albeit low likelihood of developing viral myocarditis.[22,23,58] Initial RTP strategies were more conservative and recommended a 10-day self-isolation with abstinence from exercise owing to concerns of clinical deterioration. However, follow-up studies demonstrating a lack of myocardial involvement in mild COVID-19 cases resulted in a recent update to the RTP guidelines by the American College of Cardiology Expert Consensus Decision Pathway.[17] New RTP recommendations include the following: (1) asymptomatic cases are recommended to abstain from exercise for 3 days to ensure symptoms do not develop; (2) mild or moderate cases with mild to moderate noncardiopulmonary symptoms are recommended to abstain from exercise until symptom resolution. No additional cardiac tests are required before RTP in these 2 clinical scenarios, but it is recommended that RTP begin with a graded regimen.

RTP recommendations differ for patients with cardiopulmonary symptoms and/or for patients diagnosed with severe COVID-19. These patients should undergo triad testing with ECG, cTn, echocardiogram, and cardiology consultation. If results of triad testing are normal, the athlete may RTP in a graded manner. If results to triad testing are abnormal or if symptoms develop after RTP, CMR and cardiology consultation is recommended. In patients with a prolonged COVID-19 course with symptoms beginning or lasting weeks to months after the initial infection, it is reasonable to perform triad testing and limit physical exercise. However, those with a prolonged course without cardiopulmonary symptoms are encouraged to resume a graded exercise regimen. In any of the above scenarios, if results to CMR testing reveal the presence of LGE, sports participation may be considered as part of shared decision making after cardiology consultation in the absence of systolic dysfunction, ventricular arrhythmia, and if cardiac biomarkers have normalized.[68]

Last, it should be noted that although CMR may be useful to guide diagnosis and prognosis, the routine use of CMR in the absence of concerning cardiopulmonary symptoms and/or abnormalities on prior cardiac tests is recommended against.[68] The application of CMR and the updated LLC to diagnose COVID-19 myocarditis in athletes with no symptoms of myocarditis and its use in RTP decision making require attention to detail. The use of CMR for myocarditis and outcome data involves symptomatic patients with inflammation largely limited to the heart. Most of the validation studies of myocarditis diagnosed on CMR have LGE, which has been validated more extensively than

mapping abnormalities in histologically proven viral myocarditis. In populations with low prevalence of myocarditis, including healthy athletes, T1 and T2 mapping will have a low positive-predictive value. In addition, studies have shown adverse prognostic significance for LGE in patients with myocarditis,[70] and there are no prognostic data for abnormalities on T1 or T2 mapping in the absence of LGE. Finally, there are few data regarding T1 and/or T2 mapping abnormalities in the absence of LGE, including whether its present in exercising athletes, transformation into cardiac damage (fibrosis/scar), and any prognostic implications. There is a need to improve interpretation methods for CMR to quantify cardiac involvement in myocarditis, particularly as they pertain to T1 and T2 measures, which can be variable.

As for RTP strategies for the inherited cardiomyopathies, athletes with a definite, borderline, or possible diagnosis of ARVC should not participate in most competitive sports, and the prophylactic placement of an ICD to permit participation in high-intensity sports is not recommended.[66] However, it may be considered reasonable for these athletes to participate in low-intensity sports.[66]

SUMMARY

Myocarditis is an inflammatory disease of the myocardium secondary to infectious or noninfectious causes. Although the disease is generally mild, the most feared consequences include heart failure, arrhythmia, and SCD. Early recognition is essential for optimal short- and long-term outcomes, and accurate diagnosis often relies heavily on cardiac imaging with CMR and appropriate application of the LLC for interpreting imaging abnormalities. Most therapies for myocarditis are considered supportive and focus on the treatment of heart failure and arrhythmia with directed medical therapy. Treatment with immunosuppressive agents is often reserved for specific cases, including GCM and sarcoid myocarditis. Management strategies also include abstinence from exercise in the short term with specific RTP recommendations instituted after 3 to 6 months following a comprehensive cardiovascular evaluation, which includes triad testing (echocardiogram, 24-hour Holter monitor, and exercise ECG). CMR as part of an RTP strategy is warranted if abnormalities are present on follow-up testing or if symptoms develop after reinstating an athlete. However, the routine use of CMR as part of an RTP strategy in asymptomatic athletes is generally recommended against.

CLINICS CARE POINTS

- Myocarditis is an inflammatory disease of the myocardium of infectious or noninfectious etiology
- Although mild in most cases, it is a recognized etiology for heart failure, rhythm disturbance and sudden death.
- Most require only abstinence from exercise with return to play strategies based on cardiac imaging, stress testing and ambulatory monitoring.
- CMR plays an integral role in diagnosis, risk stratification and prognosis but is not part of routine RTP strategies in those who are asymptomatic.

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