Case Discussion on 'Return-to-Play' for the Athlete Following COVID-19 Infection

NATHANIEL MOULSON, MD; MEAGAN WASFY, MD, MPH

KEYWORDS: COVID-19, SARS-CoV-2, myocarditis, athletes, return-to-play

INTRODUCTION

Myocarditis, or inflammatory disease of the myocardium, is a well described etiology of sports-related sudden cardiac death.[1] Viral illness is amongst the most common causes for myocarditis.[2] Shortly after the emergence of coronavirus disease 2019 (COVID-19) as a global pandemic, reports of associated myocarditis led to concern regarding how to appropriately evaluate athletes who had COVID-19 prior to return to their sport. This concern arose given the potential risk of arrhythmia and cardiac arrest, potentiated by exercise, in those who have had recent myocarditis. Resultant expert consensus guidelines have addressed the clinical dilemma of athlete evaluation prior to returning to sport following COVID-19 infection and have evolved over the past year in order to address new data. Herein we describe an illustrative case of a young (<35 years of age) college athlete presenting for assessment prior to returning to competitive athletics after COVID-19 illness. A similar framework may be utilized for the assessment of pediatric and masters (>35 years of age) populations consisting of both competitive and recreational athletes as outlined by the American College of Cardiology's (ACC) Sports and Exercise Cardiology Section guidelines.[3]

CASE PRESENTATION: PART 1

A 21-year-old Caucasian male college student contracted COVID-19 upon return to campus to resume in person classes and training. He is a member of his school's lacrosse team and immediately self-quarantined upon diagnosis. He has no relevant medical history, is on no regular medications, and has not previously undergone cardiac screening or evaluation. His initial symptoms included profound fatigue, subjective fever, headache, loss of taste and smell, and shortness of breath occurring with minimal exertion. He did not require medical assessment or hospitalization. While many of his symptoms resolved over the course of 72 hours, the fatigue and shortness of breath persisted for the remainder of his 14-day quarantine period. He felt back to normal by the conclusion of his quarantine, though had not completed any exercise over this span. About 10 days after the conclusion of his quarantine, he attempted a short distance run. During this run, he experienced shortness of breath with minimal exertion forcing him to cease exercise. He was referred by his school for outpatient cardiology evaluation prior to being permitted to return to organized team training.

'RETURN-TO-PLAY' ASSESSMENT POST-COVID-19

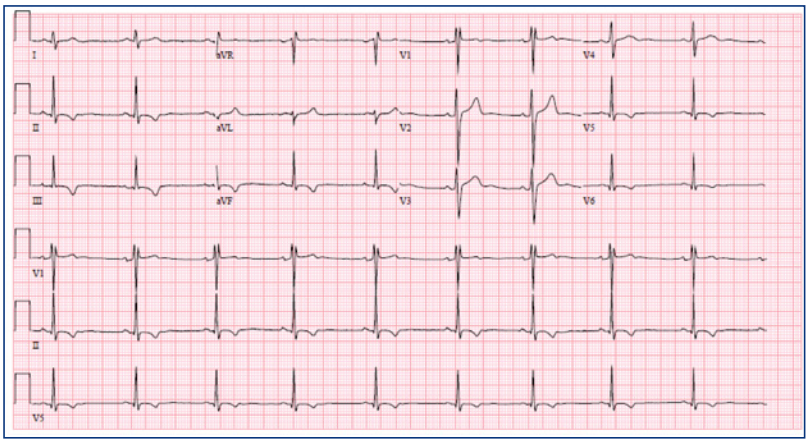
Among patients hospitalized with severe COVID-19, a high prevalence of 'cardiac injury,' defined as a cardiac specific troponin level exceeding the 99th percentile, was observed early in the pandemic.[4] In the critically ill population, this cardiac injury may be due to several different mechanisms, one of which is inflammatory heart disease (myocarditis, pericarditis) secondary to a systemic inflammatory response and/or direct viral invasion.[5] The concern that COVID-19 viral myocarditis may occur in young athletes suffering from non-severe infection resulted in a series of clinical practice recommendations aimed at identifying those at risk prior to return to sport and exercise.[6,7] The first set of U.S. recommendations were published in the spring of 2020, based largely on expert consensus. These recommendations were updated in the fall of 2020[3] to account for limited athlete-specific research data and growing clinical experience. The guidelines recommend that all athletes should avoid exercise during the acute infectious period. After quarantine, the recommended approach to post-COVID-19 cardiac screening is symptom-driven and stepwise. On the basis of experience suggesting the risk of COVID-19 related inflammatory heart disease is very low in this group, athletes with asymptomatic or mildly symptomatic initial infection do not need to undergo cardiac investigations prior to return to sport. In those suffering from moderate or greater severity infection, or those who develop cardiopulmonary symptoms on return to sport, cardiac diagnostic testing is warranted as detailed further below. Moderate symptoms are defined as persistent fever, chills, myalgias, lethargy, or any cardiopulmonary symptoms, which include chest pain or tightness, dyspnea, syncope, or palpitations. The presence of a 'multisystem inflammatory syndrome' in pediatric populations should also be considered in those with moderate or greater disease severity. This symptom-driven stepwise approach is supported by recent large cohort studies of both collegiate and professional athletes.[8,9]

CASE PRESENTATION: PART 2

The patient's initial symptom burden would most appropriately be classified as 'moderate.' Additionally, he experienced the cardiopulmonary symptom of dyspnea on attempted return to exercise after initial symptoms had resolved. The presence of both a moderate initial symptom burden and cardiopulmonary symptoms on return to exercise warranted further testing to both rule out cardiac involvement secondary to COVID-19 and assess for other clinically important causative etiologies. He underwent initial testing, with a 12-lead electrocardiogram (ECG), high-sensitivity cardiac troponin level, and a transthoracic echocardiogram, as recommended by the expert consensus statement.[3] His high-sensitivity cardiac troponin-T level was found to be mildly elevated at *18 ng/L* (0-14 ng/L) and his 12-lead electrocardiogram demonstrated *abnormal T-wave inversions in the inferolateral leads* (**Figure 1**). Notably, no exercise was performed within 24-hours of his blood draw and no prior 12-lead ECG existed. His echocardiogram demonstrated biventricular size at the upper limit of normal, and mild biatrial dilatation. His biventricular function was normal, and there was no evidence of wall motion abnormalities, pericardial effusion, or valvular disease.

Figure 1. 12-lead Electrocardiogram

Sinus bradycardia with RSR' pattern in V1 (QRS <100ms). Abnormal finding of T-wave inversion in the inferolateral leads.



INITIAL CARDIAC EVALUATION

In athletes for whom cardiac screening is warranted after COVID-19, 'triad' testing, which refers to the combination of a 12-lead ECG, cardiac troponin, and transthoracic echocardiogram, should be considered as the initial strategy to identify COVID-19 inflammatory heart disease.[3] Cardiac magnetic resonance imaging (CMR) should be reserved for athletes who have abnormal triad testing results that are concerning for COVID-19 inflammatory heart disease and that are not otherwise readily explained. CMR may also be considered for patients where a high index of clinical suspicion remains for COVID-19 cardiac involvement on the basis of the clinical history despite normal triad testing. Contemporary CMR diagnostic criteria for myocarditis include the combination of myocardial edema, as determined by abnormal T2-weighted images or T2 parametric mapping, and a non-ischemic myocardial injury, as determined by abnormal T1 mapping or late gadolinium enhancement (LGE).[10]

Several specific sports leagues[11] have utilized screening algorithms that stipulate all athletes who have had COVID-19 should undergo a screening CMR regardless of presenting symptoms and triad testing results. This practice is driven by several small observational studies in both non-athletic and athletic populations with COVID-19 that demonstrated a high prevalence of CMR abnormalities. In non-athletes, cardiac abnormalities were seen in up to 78%, while abnormalities in athletes suggestive of either myocarditis or pericarditis ranged from 1.4–40%, often without abnormal triad testing results.[12-14] These studies were limited by the absence of standardized disease definitions and lack of adequate control group comparators. Many of the athletes with CMR abnormalities lacked the other clinical features of inflammatory heart disease that would usually be paired with the CMR imaging findings to make the diagnosis, which makes the significance of these results unclear. Subsequent multi-center studies of both collegiate and professional athletes, utilizing the symptom-driven, stepwise approach described above, have demonstrated substantially lower prevalence of inflammatory heart disease after COVID-19 (0.5–3%), and importantly no adverse clinical events in short-term follow-up.[8, 9] This relatively low prevalence and favorable short-term outcomes support the symptom-guided and stepwise testing strategy.

Another important consideration in screening for COVID-19 cardiac involvement in athletes is the impact of exercise on the heart. Exercise is a well-established non-pathologic cause of low-level cardiac troponin elevation in otherwise healthy athletes.[15] The timing of last intensive exercise bout in relation to blood draw should be sought for all abnormal results, and a repeat level drawn 24–48 hr. after last exercise should performed prior to considering an elevated troponin result abnormal. Testing is also impacted by exercise-induced cardiac remodeling, which consists of cardiac structural and functional adaptations to sustained and repeated bouts of vigorous activity results. Care must be taken not to mistake findings of physiologic adaptation on 12-lead ECG and cardiac imaging as evidence of cardiac involvement from SARS-CoV-2 or other cardiac pathology. Athlete specific criteria for 12-lead ECG and cardiac imaging interpretation should be followed, and pre-COVID-19 ECG and imaging results reviewed for comparison whenever available (**Table 1**).[16-18]

Table 1. Normal or Non-specific Cardiac Testing Findings in Athletes* versus Abnormalities Possibly Related to COVID-19 Infection

Cardiac Testing Modality	Normal or Non-specific findings in Athletes	Abnormalities Possibly Related to COVID-19 infection
Cardiac Troponin	1) Below the 99th percentile for specific assay (either conventional or high sensitivity) 2) Isolated troponin elevation within 24–48 hr of moderate-to-vigorous exercise and resolved on repeat testing	1) Troponin elevation >99th percentile with no other readily explainable cause
12-lead ECG [Adapted from the International Criteria for Electrocardiographic Interpretation in Athletes[17]]	*Normal Athlete ECG findings* 1) Increased QRS voltage for LVH or RVH 2) Incomplete RBBB 3) Early Repolarization 4) ST elevation followed by TWI V1-V4 in black athletes 5) TWI V1-V3 < age 16 years old 6) Sinus bradycardia or arrhythmia 7) 1st degree AV block 8) Mobitz Type 1 2nd AV block *Borderline ECG findings*^ 1) Left axis deviation 2) Left atrial enlargement 3) Right axis deviation 4) Right atrial enlargement 5) Complete RBBB	1) Abnormal TWI 2) Pathologic Q waves 3) Abnormal ST-depressions 4) ≥2 PVCs 5) Complete LBBB 6) QRS≥140ms 7) 3rd degree AV block 8) Atrial tachyarrhythmias 9) Ventricular tachyarrhythmias 10) Complete RBBB combined with axis deviation or atrial enlargement 11) Diffuse ST elevations or PR depressions
Transthoracic Echocardiogram [Adapted from the 1) 2020 Recommendations on the Use of Multimodality Cardiovascular Imaging in Young Competitive Athletes,[16] and 2) Screening Potential Cardiac Involvement in Competitive Athletes Recovering from COVID-19: An Expert Consensus Statement[18]]	1) Mild symmetric increased LV wall thickness (<13mm; <15mm in black male athletes) 2) Symmetric biventricular enlargement at or mildly above ULN 3) Mildly enlarged atrial size/volume 4) Low normal biventricular systolic function 5) Supra-normal diastolic function 6) Normal global longitudinal strain (-16–22%)	1) LVEF <50% 2) Regional wall motion abnormality 3) Small or greater pericardial effusion 4) Focal thickening suggestive of edema 5) Intracavitary thrombi 6) Diastolic dysfunction 7) Global longitudinal strain<-15% 8) Failure to augment low-normal LVEF with exercise
Cardiac Magnetic Resonance Imaging [Adapted from the 1) 2020 Recommendations on the Use of Multimodality Cardiovascular Imaging in Young Competitive Athlete,[16] 2) Updated Lake Louise Criteria for CMR imaging in Non-ischemic Myocardial Inflammation,[10] and 3) Screening Potential Cardiac Involvement in Competitive Athletes Recovering from COVID-19: An Expert Consensus Statement[18]]	1) Mild symmetric increased LV wall thickness (<13mm; <15mm in black male athletes) 2) Symmetric biventricular enlargement at or mildly above ULN 3) Mildly enlarged atrial size/volume 4) Normal/ low normal biventricular systolic function 5) Isolated LGE particularly if confined to the RV insertion points	1) LVEF <50% 2) Regional wall motion abnormality 3) Focal thickening suggestive of edema 4) Small or greater pericardial effusion 5) Non-ischemic Myocardial Injury (Abnormal T1, ECV, or LGE)^ 6) Hyperemia, capillary leak or myocardial edema (T2-mapping or T2W imaging abnormality)^ 7) Intracavitary thrombi

*Findings should be considered within the context of sport type and volume

^Borderline ECG abnormalities in isolation require no further evaluation

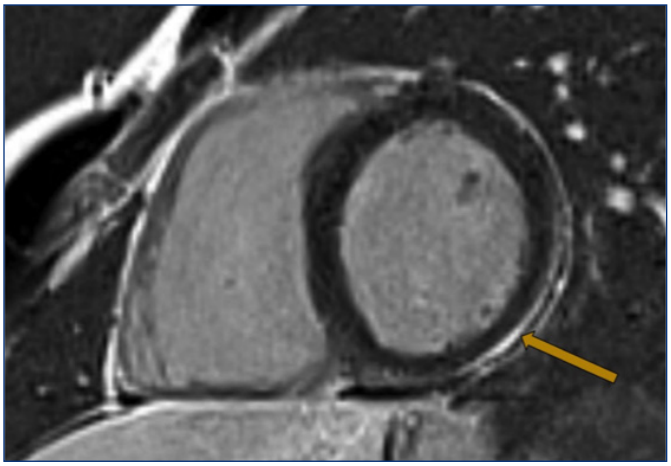
TWI = T wave inversions; LVH = Left ventricular hypertrophy; RVH = right ventricular hypertrophy; RBBB = right bundle branch block; LBBB = left bundle branch block; AV = atrioventricular; ULN = Upper Limit of Normal; RV = Right Ventricle; LGE = late gadolinium enhancement; ECV = extracellular volume; T2W = T2 weighted

CASE PRESENTATION: PART 3

The combination of clinical symptoms, troponin elevation, and abnormal T-wave inversions in the inferolateral leads elevated the pre-test probability of COVID-19 related myocarditis, and a CMR was performed. The CMR demonstrated normal biventricular size and function with no evidence of wall motion abnormalities or pericardial effusion. There was late gadolinium enhancement (LGE) within the subepicardial to mid-wall involving multiple left ventricular segments, and increased native T2 in a small focal area of the basal inferolateral septum (**Figure 2**). These imaging findings were consistent with a small area of myocardial edema (increased native T2) and corresponding injury (LGE) consistent with myocarditis.[10] His high-sensitivity troponin-T was undetectable on repeat testing 10 days later. Given the clinical presentation and diagnostic testing consistent with a diagnosis of myocarditis secondary to COVID-19, the patient was provided with the recommendation to avoid moderate to vigorous intensity physical activity for at least a 3-month period.[19] This recommendation is consistent with sports participation expert consensus guidelines for athletes with cardiovascular disease that pre-dated COVID-19 as discussed further below. In the absence of LV dysfunction or any high-risk arrhythmias on ambulatory ECG monitoring, no medical therapy was indicated.

Figure 2. Cardiac MRI with Gadolinium Contrast

Subepicardial to mid-wall late gadolinium enhancement involving the inferolateral wall of the left ventricular (Yellow arrow) with associated small area of increased native T2 (not shown).



MANAGEMENT CONSIDERATIONS

Patients with acute cardiac inflammation, either myocardial (myocarditis) or pericardial (pericarditis), should refrain from moderate-to-vigorous intensity physical activity until acute inflammation has resolved.[19] This acute inflammatory period represents one of increased arrhythmic risk particularly if placed under the physiologic stress of intensive exercise. In pericarditis, although the inflammation does not involve the myocardium, there is potential for a small degree of disease overlap in the form of myopericarditis. As such, the diagnosis of pericarditis results in similar exercise restriction recommendations as for myocarditis but for a shorter duration.[19] In pericarditis, if no evidence of myocardial inflammation is demonstrated and there is complete resolution of disease including symptoms, pericardial effusion, and serum markers of inflammation (i.e., CRP, ESR) with appropriate treatment, patients may resume exercise after two weeks. In contrast, the expert consensus recommendations for acute myocarditis suggest a period of 3–6 months of exercise avoidance to allow for resolution of myocardial inflammation[19] with the exact duration to be determined by disease severity and trajectory. This timeframe is based on expert opinion rather than any prospective data examining the appropriate duration of sports restriction. Return to sport may occur after this timeframe assuming symptoms have resolved, left ventricular systolic function has remained/returned to the normal range, serum markers of myocardial injury and inflammation have normalized (i.e. troponin), and there is no evidence of clinically relevant arrhythmia on exercise and ambulatory ECG monitoring.

This case represents a relatively straightforward clinical scenario in that the criteria for a clinical diagnosis of myocarditis were fulfilled, including the presence of suggestive symptoms, and cardiac testing was performed based on appropriate pre-test probability of disease. The clinical scenario becomes more challenging when cardiac testing abnormalities are present but do not formally fulfill diagnostic criteria for inflammatory heart disease, or testing is abnormal but there are no clinical symptoms. Examples of these scenarios include: 1) isolated troponin elevation and/or ECG abnormalities with a normal CMR, 2) isolated abnormal CMR findings (LGE, T1 or T2 mapping) that do not fulfill CMR criteria for myocarditis, 3) small pericardial effusions in the absence of symptoms. Expert consultation with a clinician, such as a sports cardiologist, is recommended in these situations to balance the need to identify clinically relevant disease with the importance of avoiding overdiagnosis and unwarranted restriction from sport.

This case also serves to highlight the uncertainty of current return-to-play recommendations regarding duration of sports restriction for mild presentations of myocarditis (i.e., cases in which there is no ventricular dysfunction or arrhythmia and a relatively small area of involvement on CMR). In athletes for whom restriction has been recommended, but where return to sport may be more pressing, such as in professional or high-level amateur athletics, re-imaging with CMR at the 3-month mark or potentially earlier, may be considered pending resource availability. If complete resolution of acute inflammation is demonstrated by biomarkers and imaging, and other appropriate risk stratification measures including exercise and ambulatory ECG monitoring are normal, an earlier return-to-sport may be considered in consultation with an experienced clinician.

CONCLUSION

The use of cardiac diagnostic testing to screen for cardiac involvement in athletes following COVID-19 infection should be performed by a symptom-guided and stepwise strategy. The interpretation of testing abnormalities should be considered within the context of exercise-induced cardiac remodeling and the pre-test probability of disease. Expert referral should be considered for challenging cases.

References

1. Eckart RE, Scoville SL, Campbell CL, Shry EA, Stajduhar KC, Potter RN, Pearse LA, Virmani R. Sudden death in young adults: a 25-year review of autopsies in military recruits. *Ann Intern Med*. 2004;141:829-34.
2. Tschope C, Ammirati E, Bozkurt B, Caforio ALP, Cooper LT, Felix SB, Hare JM, Heidecker B, Heymans S, Hubner N, Kelle S, Klingel K, Maatz H, Parwani AS, Spillmann F, Starling RC, Tsutsui H, Seferovic P, Van Linthout S. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. *Nat Rev Cardiol*. 2021;18:169-193.
3. Kim JH, Levine BD, Phelan D, Emery MS, Martinez MW, Chung EH, Thompson PD, Baggish AL. Coronavirus Disease 2019 and the Athletic Heart: Emerging Perspectives on Pathology, Risks, and Return to Play. *JAMA Cardiol. 2021;6(2):219-227*.
4. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, Jain SS, Burkhoff D, Kumaraiah D, Rabbani L, et al. COVID-19 and Cardiovascular Disease. *Circulation*. 2020;141:1648-1655.
5. Basso C, Leone O, Rizzo S, De Gaspari M, van der Wal AC, Aubry MC, Bois MC, Lin PT, Maleszewski JJ, Stone JR. Pathological features of COVID-19-associated myocardial injury: a multicentre cardiovascular pathology study. *Eur Heart J*. 2020;41:3827-3835.
6. American Medical Society for Sports Medicine and the American College of Cardiology. Cardiac Considerations for College Student-Athletes during the COVID-19 Pandemic. 2020.
7. Baggish A, Drezner JA, Kim J, Martinez M, Prutkin JM. Resurgence of sport in the wake of COVID-19: cardiac considerations in competitive athletes. *Br J Sports Med*. 2020;54:1130-1131.
8. Martinez MW, Tucker AM, Bloom OJ, Green G, DiFiori JP, Solomon G, Phelan D, Kim JH, Meeuwisse W, Sills AK, Rowe D, Bogoch, II, Smith PT, Baggish AL, Putukian M, Engel DJ. Prevalence of Inflammatory Heart Disease Among Professional Athletes With Prior COVID-19 Infection Who Received Systematic Return-to-Play Cardiac Screening. *JAMA Cardiol. Published online March 4, 2021*.
9. Moulson N, Petek BJ, Drezner JA, Harmon KG, Kliethermes SA, Patel MR, Baggish AL. SARS-CoV-2 Cardiac Involvement in Young Competitive Athletes. *Circulation*. 2021 Apr 17. doi: 10.1161/CIRCULATIONAHA.121.054824. Online ahead of print.
10. Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U, Kindermann I, Gutberlet M, Cooper LT, Liu P, Friedrich MG. Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation: Expert Recommendations. *J Am Coll Cardiol*. 2018;72:3158-3176.
11. Rink LD, Daniels CJ, Boersma D, Borchers J, Busch J, Kovan J, Kratochvil CJ, Rifat S, Rosenthal G, Chung EH. Competitive Sports, the Coronavirus Disease 2019 Pandemic, and Big Ten Athletics. *Circ Cardiovasc Qual Outcomes*. 2020;13:e007608.
12. Brito D, Meester S, Yanamala N, Patel HB, Balcik BJ, Casaclang-Verzosa G, Seetharam K, Riveros D, Beto RJ, Balla S, Monseau AJ, Sengupta PP. High Prevalence of Pericardial Involvement in College Student-Athletes Recovering From COVID-19. *JACC: Cardiovascular Imaging*. 2021 Mar;14(3):541-555.
13. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, Shchendrygina A, Escher F, Vasa-Nicotera M, Zeiher AM, Vehreschild M, Nagel E. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5:1265-1273.
14. Rajpal S, Tong MS, Borchers J, Zareba KM, Obarski TP, Simonetti OP, Daniels CJ. Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From COVID-19 Infection. *JAMA Cardiol*. 2021 Jan 1;6(1):116-118.
15. Shave R, Baggish A, George K, Wood M, Scharhag J, Whyte G, Gaze D, Thompson PD. Exercise-induced cardiac troponin elevation: evidence, mechanisms, and implications. *J Am Coll Cardiol*. 2010;56:169-76.
16. Baggish AL, Battle RW, Beaver TA, Border WL, Douglas PS, Kramer CM, Martinez MW, Mercandetti JH, Phelan D, Singh TK, Weiner RB, Williamson E. Recommendations on the Use of Multimodality Cardiovascular Imaging in Young Adult Competitive Athletes: A Report from the American Society of Echocardiography in Collaboration with the Society of Cardiovascular Computed Tomography and the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr*. 2020;33:523-549.
17. Drezner JA, Sharma S, Baggish A, Papadakis M, Wilson MG, Prutkin JM, Gerche A, Ackerman MJ, Borjesson M, Salerno JC, Asif IM, Owens DS, Chung EH, Emery MS, Froelicher VF, Heidbuchel H, Adamuz C, Asplund CA, Cohen G, Harmon KG, Marek JC, Molossi S, Niebauer J, Pelto HF, Perez MV, Riding NR, Saarel T, Schmied CM, Shipon DM, Stein R, Vetter VL, Pelliccia A, Corrado D. International criteria for electrocardiographic interpretation in athletes: Consensus statement. *Br J Sports Med*. 2017;51:704-731.
18. Phelan D, Kim JH, Elliott MD, Wasfy MM, Cremer P, Johri AM, Emery MS, Sengupta PP, Sharma S, Martinez MW, La Gerche A. Screening of Potential Cardiac Involvement in Competitive Athletes Recovering From COVID-19: An Expert Consensus Statement. *JACC Cardiovasc Imaging*. 2020;13:2635-2652.
19. Maron BJ, Udelson JE, Bonow RO, Nishimura RA, Ackerman MJ, Estes NAM, 3rd, Cooper LT, Jr., Link MS, Maron MS. Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities: Task Force 3: Hypertrophic Cardiomyopathy, Arrhythmogenic Right Ventricular Cardiomyopathy and Other Cardiomyopathies, and Myocarditis: A Scientific Statement From the American Heart Association and American College of Cardiology. J Am Coll Cardiol. 2015;66:2362-2371.

Acknowledgments

Dr. Moulson is supported by the University of British Columbia Clinician Investigator Program.

Authors

Nathaniel Moulson, MD, Massachusetts General Hospital, Division of Cardiology, Cardiovascular Performance Program.

Meagan Wasfy, MD, MPH, Massachusetts General Hospital, Division of Cardiology, Cardiovascular Performance Program.

Correspondence

Meagan Wasfy, MD, MPH
Massachusetts General Hospital
55 Fruit St, Yawkey 5E
Boston, MA 02114
617-643-7117
mwasfy@partners.org