EDITORIAL COMMENT

Subclinical COVID-19 Cardiac Imaging Findings

Resurgence of the Athletic "Grey-Zone"*

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Clinically relevant myocardial injury, defined by a cardiac specific troponin level exceeding the 99th percentile, is common among patients hospitalized with coronarvirus disease-2019 (COVID-19) infection (1). Although incompletely understood, COVID-19 infection appears to precipitate cardiovascular injury through multiple synergistic mechanisms including direct cytokine and catecholamine chemotoxicity, microvascular and endocardial thrombosis, lymphocytic and macrophagic infiltration, and myocarditis secondary to direct viral invasion (1). Although the exact pathophysiology remains murky, the prognostic implications are clear with COVID-19 cardiac injury now a well-established predictor of disease severity and mortality (2). These important lessons have emerged almost exclusively from the clinical care of moderate-to-severely ill COVID-19 patients, an older population with a significant burden of underlying pre-existing disease. At present, the prevalence, phenotypic characteristics, and clinical relevance of myocardial injury among the millions of people worldwide infected with COVID-19 with asymptomatic or mild infectious courses remains unknown. These fundamental uncertainties are particularly relevant to young competitive athletes returning to sport after COVID-19 infection because myocarditis is a well-recognized cause of sudden death during exercise (3). Concerns about athlete safety following COVID-19 infection emerged early during the viral pandemic as numerous sporting organizations sought to resume activity, leading to a series of clinical practice recommendations designed to detect at risk athletes (4). These recommendations, first based solely on expert opinion (5), but more recently driven by mounting clinical experience (6), call for symptom-driven application of multimodality testing including the use echocardiography and cardiac magnetic resonance (CMR). A consistent and prominent feature of these recommendations has been the call for the high-quality science that will be required to move from opinion to data-driven clinical care.

In this issue of *iJACC*, Brito et al. (7) describe West Virginia University's early experience with pre-participation cardiovascular screening during the COVID-19 pandemic. Among 160 student athletes returning to campus, 60 were found to have prior or active COVID-19 infection based on the results of PCR and/or IgG testing, among which 53 (37 symptomatic and 16 asymptomatic) completed further investigation to assess for myocardial and pericardial pathology. Their protocol included the universal use of 12-lead electrocardiogram, cardiac troponin testing, and echocardiography with speckle tracking strain imaging followed by the addition of CMR for all symptomatic athletes and asymptomatic athletes with abnormalities on 1 or more of the initial tests. The modified Lake Louise Criteria (8), a validated algorithm useful for confirming the presence of myocarditis among patients with intermediate or greater pre-test probability of disease based on clinical symptoms, were applied to CMR imaging data to detect myocardial inflammation. In addition, integration of echocardiographic and CMR data was used to define myocardial pathology as the presence of at least 1 of the following criteria: 1) left ventricular (LV) ejection fraction <50%; 2) presence of regional wall motion

abnormality; 3) global longitudinal strain value (GLS) <16%; and 4) native T1 time ≥990 ms, and pericardial pathology as the presence of late enhancement with pericardial effusion on CMR. Key results are summarized as follows. First, no athletes met the modified Lake Louise CMR criteria for myocarditis. Second, however, 27 of 48 athletes undergoing CMR were deemed to have abnormal results based on the presence of isolated pericardial involvement (13 of 27, 48%), isolated myocardial involvement (8 of 27, 30%), and combined myopericardial involvement (6 of 27, 22%). Factors accounting for cases of isolated myocardial involvement included LV ejection fraction <50% (n = 1), GLS <16% (n = 2), increased T1 time (n = 4), and 1 athlete with the combination of GLS <16%, myocardial enhancement, and increased T1 time. Among the 6 athletes with combined myopericardial pathology, myocardial abnormalities included GLS <16% (n = 2), increased T1 time (n = 3), and simultaneous GLS <16% and increased T1 time (n = 1). Third, echocardiographic data (no CMR athlete control data presented) revealed very few differences between COVID-19+ athletes and uninfected "control" athletes. Exceptions include comparatively lower LV early diastolic tissue velocities (yet within normal limits in both groups) and right ventricular fractional area change (absolutely and comparatively reduced) among COVID+ athletes. Finally, and perhaps of greatest clinical relevance, is the near complete absence of association between multimodality imaging evidence of pathology and COVID-19 symptoms with the exception of a higher incidence of pericardial involvement among athletes with a completely asymptomatic COVID-19 course.

The authors of this paper (7) are to be commended, both for the foresight to study this important issue early in the course of the COVID-19 pandemic and for their transparent reporting of a comprehensive dataset. Results from this effort will contribute to the ongoing dialogue about how to protect the health of competitive athletes infected with COVD-19 in several ways. First, West Virginia University's experience represents the first report of symptom-based, stepwise, multimodality imaging protocol to screen for COVID-19 cardiac sequalae and thereby demonstrates the feasibility of this approach, which is consistent with and therefore supportive of current recommendations (6). Second, the inclusion of GLS data derived from athletes with COVID-19, here used to support an interesting hierarchical cluster analysis, are the first available and will serve as an important future point of reference. Finally, the interesting, but clinically subtle, imaging abnormalities described in this athlete cohort support the notion that COVID-19 may

affect the cardiovascular system, specifically the pericardium, even among people with an asymptomatic or mild infectious course. However, the complete absence of overt myocarditis, the COVID-19-related cardiac pathology most likely to trigger sudden death or malignant arrhythmia during exercise, suggests that this concerning complication may be less common than previously reported among a small single-center cohort of collegiate athletes and among older nonathletic individuals recovering from infection (9,10).

The strengths of this study are paralleled by several key limitations that underscore the need for future work and on-going clinical equipoise. The first consideration is the absence of an appropriate control population. Decades of work examining cardiac structure and function in competitive athletes has proven that differentiating benign adaptive findings from acquired pathology is of limited accuracy in the absence of a carefully selected control population (11). This reality remains of paramount importance during the COVID-19 pandemic. The application of a GLS lower limits of normal cutpoint of −16%, may be useful when evaluating grey zone LV hypertrophy or dilation (12). However, application of this parameter in isolation is of limited value as proven by a study showing that ∼10% of Olympic-level athletes demonstrate GLS values <16% (13). Similarly, myocardial architecture, including myocyte dimension and extracellular matrix properties, differ between athletes and more sedentary people, leading to potentially different reference values for sensitive markers of tissue morphology including CMR-derived relaxation times (14,15). Pending largescale normative datasets, the use of such indices should be applied with caution and their use as a sole determinant of pathology is difficult to justify. Second, we consider the pre-test probability of disease as it relates to the interpretation of imaging results. Well-established diagnostic and management protocols for pericarditis and myocarditis are predicated on scientific studies largely confined to patients presenting with the cardinal symptoms of these diseases (8,16). The diagnostic accuracy and clinical relevance of imaging findings derived from the screening setting of healthy people or those with viral infection of unclear downstream significance, particularly as they relate to key management decisions including medical therapy and exercise restriction, are completely unknown. The use of highly sensitive, but perhaps inadequately specific, modern imaging techniques among young, otherwise healthy athletes with low or uncertain pre-test probability has the potential to

do more harm than good due to unnecessary medication use, downstream testing, and athletic restriction.

The acquisition and dissemination of data describing the impact of COVID-19 on the cardiovascular system of previously healthy athletes represent a scientific priority. Initial case series reporting scientific observations, including the important study discussed in this editorial, represent a crucial first step of this process. But now, the time has come to move beyond this first step if we are to avoid opening a Pandora's box of "grey zone" imaging findings. Future studies should aim to unite phenotypic characterizations, ideally those derived from largescale, multicenter efforts, with definitive clinical outcomes. Future data derived from the screening of athletes for COVID-19 cardiovascular complications will only prove useful when their ability to define the risk of sudden death and other adverse outcomes is shown.

While we await this important next step, clinicians charged with the care of young competitive athletes are encouraged to make or refute potentially game changing diagnoses with care. This can only be accomplished by thoughtfully ordering and interpreting multimodality testing while relying on the most fundamental clinical tool at our disposal, the tried and true pre-test probability of disease.

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REFERENCES

1. Clerkin KJ, Fried JA, Raikhelkar J, et al. COVID-19 and cardiovascular disease. Circulation 2020; 141:1648–55.

2. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5:811–8.

3. Eckart RE, Scoville SL, Campbell CL, et al. Sudden death in young adults: a 25-year review of autopsies in military recruits. Ann Intern Med 2004;141:829–34.

4. 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;54:1130–1.

5. Phelan D, Kim JH, Chung EH. A game plan for the resumption of sport and exercise after coronavirus disease 2019 (COVID-19) infection. JAMA Cardiol 2020;5:1085–6.

6. Kim JH, Levine BD, Phelan D, et al. Coronavirus disease 2019 and the athletic heart: emerging perspectives on pathology, risks, and return to play. JAMA Cardiol 2020 Oct 26 [E-pub ahead of print].

7. Brito D, Meester S, Yanamala N, et al. High prevalence of pericardial involvement in college student athletes recovering from COVID-19. J Am Coll Cardiol Img 2021;14:541–55.

8. Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. J Am Coll Cardiol 2018;72:3158–76.

9. Rajpal S, Tong MS, Borchers J, et al. Cardiovascular magnetic resonance findings in competitive athletes recovering from COVID-19 infection. JAMA Cardiol 2021;6:116–8.

10. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5:1265–73.

11. Kim JH, Baggish AL. Differentiating exercise-induced cardiac adaptations from cardiac pathology: the "grey zone" of clinical uncertainty. Can J Cardiol 2016;32:429–37.

12. Baggish AL, Battle RW, Beaver TA, et al. 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;33:523–49.

13. Caselli S, Montesanti D, Autore C, et al. Patterns of left ventricular longitudinal strain and strain rate in Olympic athletes. J Am Soc Echocardiogr 2015;28:245–53.

14. Gormeli CA, Gormeli G, Yagmur J, et al. Assessment of myocardial changes in athletes with native T1 mapping and cardiac functional evaluation using 3 T MRI. Int J Cardiovasc Imaging 2016;32:975–81.

15. McDiarmid AK, Swoboda PP, Erhayiem B, et al. Athletic cardiac adaptation in males is a consequence of elevated myocyte mass. Circ Cardiovasc Imaging 2016;9:e003579.

16. Maron BJ, Zipes DP, Kovacs RJ. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: preamble, principles, and general considerations: a scientific statement from the American Heart Association and American College of Cardiology. J Am Coll Cardiol 2015;66:2343–9.

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