Utility of exercise testing to assess athletes for post COVID-19 myocarditis

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ABSTRACT

Purpose: This study assessed a functional protocol to identify myocarditis or myocardial involvement in competitive athletes following SARS-CoV2 infection.

Methods: We prospectively evaluated competitive athletes (n = 174) for myocarditis or myocardial involvement using the Multidisciplinary Inquiry of Athletes in Miami (MIAMI) protocol, a median of 18.5 (IQR 16–25) days following diagnosis of COVID-19 infection. The protocol included biomarker analysis, ECG, cardiopulmonary stress echocardiography testing with global longitudinal strain (GLS), and targeted cardiac MRI for athletes with abnormal findings. Patients were followed for median of 148 days.

Results: We evaluated 52 females and 122 males, with median age 21 (IQR: 19, 22) years. Five (2.9%) had evidence of myocardial involvement, including definite or probable myocarditis (n = 3). Of the 5 athletes with myocarditis or myocardial involvement had clinically significant abnormalities during stress testing including ventricular ectopy, wall motion abnormalities and/or elevated VE/VCO2, while the other two athletes had resting ECG abnormalities. VO2max, left ventricular ejection fraction and GLS were similar between those with or without myocardial involvement. No adverse events were reported in the 169 athletes cleared to exercise at a median follow-up of 148 (IQR108,211) days. Patients who were initially restricted from exercise had no adverse sequelae and were cleared to resume training between 3 and 12 months post diagnosis.

Conclusions: Screening protocols that include exercise testing may enhance the sensitivity of detecting COVID-19 related myocardial involvement following recovery from SARS-CoV2 infection.

1. Introduction

Myocardial involvement has been identified in 20–35% of patients hospitalized with SARS-CoV-2 infection [1–5]. Individuals with myocarditis may incur risk of serious clinical events in the acute and possibly convalescent phase, that can be exacerbated by exercise [6].

Abbreviations: CPET, cardiopulmonary exercise test; ECG, electrocardiogram; ECHO, echocardiogram; EF, ejection fraction; GLS, global longitudinal strain; LGE, late gadolinium enhancement; LV, left ventricular; MIAMI, Multidisciplinary Inquiry of Athletes in Miami In COVID-19 recovery; MRI, magnetic resonance imaging.

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The first report to detail cardiac injury in the convalescent phase of COVID-19 included identified cardiac MRI abnormalities identified in 78% of the 100 patients evaluated a median of 71 days after COVID-19 diagnosis [7]. Subsequent reports [8-14] have revealed much lower incidence rates among athletes, raising a serious diagnostic conundrum and management dilemma for this population.

Initial reports using cardiac MRI in athletes recovered from COVID-19 have shown incidence of myocarditis ranging from 2 to 15% [8,9,12,13], while screening test limited to troponin testing, ECG and resting echocardiography (ECHO) identified an incidence of myopericarditis <1% [11,12]. It is important to establish the presence of post-COVID19 cardiac injury or myocardial involvement, as current guidelines [6] state that athletes with myocarditis and/or pericarditis should be restricted from exercise for at least 3 months. Initial consensus recommendations proposed algorithms to allow athletes to return to training and competition [15,16] which did not include functional testing.

It is impractical to screen all athletes post COVID-19 infection with an MRI. We hypothesized that a comprehensive screening protocol incorporating exercise stress testing and performing only targeted cardiac MRIs, may detect myocardial involvement while allowing most athletes to safely return to training and competition. We therefore developed the Multidisciplinary Inquiry of Athletes in Miami In COVID-19 recovery (MIAMI) protocol to screen professional and college athletes recovered from COVID-19 with a medical examination, biomarker analysis, ECG, cardiopulmonary exercise test (CPET) with resting and peak exercise echocardiogram with global longitudinal strain (GLS), and cardiac MRIs, the latter limited to those with initial abnormal findings. We hypothesized that exercise stress testing would enhance the diagnostic yield of a screening protocol to detect myocardial involvement following infection with the SARS-CoV2 infection. We report our acute findings and long-term follow-up on athletes diagnosed with myocarditis or myocardial involvement who were restricted from exercise.

2. Methods

This protocol was approved by the University of Miami Miller School of Medicine Institutional Review Board. We included the first 174 athletes recovered from an initial episode of COVID-19 who underwent the MIAMI protocol. The first 24 of these athletes were included in the ORRCA registry [12].

An internal panel of physician-experts in sudden cardiac death prediction and prevention, cardiomyopathy/myocarditis, exercise physiology, sports medicine and cardiac imaging developed the protocol and collectively reviewed all results in athletes for whom clearance to return to training and competition after recovery from COVID-19 was being sought. The MIAMI protocol consisted of a medical history and physical examination, biomarkers (troponin T, CRP, NT-proBNP), complete blood count and ECG. Troponin T ≥ 0.6 ng/ml, high sensitivity CRP ≥ 0.5 mg/dl and NT proBNP ≥ 125 pg/ml were defined as abnormal based on our laboratory standards. In cases of borderline or abnormal ECGs, we compared with the baseline ECG performed prior to SARS-CoV2 infection. As infection with SARS-CoV2 was a novel disease, and it was unknown to what extent athletes might have subclinical myocardial abnormalities during the convalescent phase, we incorporated a comprehensive stress echocardiogram with CPET and we measured rest and peak global longitudinal strain (GLS) averages to determine if these additional parameters from stress testing would aid in identifying athletes with subclinical cardiac injury or myocarditis. The GLS measurements, specifically were included to assess cardiac myocyte deformity to identify subtle functional abnormalities. We defined GLS less negative than −16% as abnormal [17]. CPET was also utilized to measure VO2max. Each athlete was considered in the context of what would be expected in an athletic heart [18,19]. Targeted cardiac MRI was obtained if initial tests were abnormal.

We defined a clinically relevant ECG abnormalities as the presence of any premature ventricular complex, ST segment and/or T wave changes, or intraventricular conduction delay. Changes in ECGs expected in athletes such as left ventricular hypertrophy, sinus bradycardia, first or 2nd degree Type I AV block were not included. Premature atrial complexes were also not considered relevant to a diagnosis of COVID-19 associated myocardial injury.

2.1. Metabolic stress test protocol

CPET with echocardiogram was performed on a treadmill (General Electric T2100-ST2) following the RAMP protocol. After written informed consent was obtained, patients underwent symptom-limited treadmill testing. The individualized RAMP protocol was designed based on age, gender, and weight. Predicted values of VO2max (ml/min) were calculated using the formulas:

$$[50.72 − (0.372 \times \text{age})] \times \text{weight} \times 1.1$$ for men

$$[22.78 − (0.17 \times \text{age})] \times (\text{weight} + 43) \times 1.1$$ for women.

The maximum treadmill incline was based on maximum effort (respiratory exchange ratio ≥ 1.1) and VO2max [20]. Resting heart rate, peak heart rate, systolic blood pressure, diastolic blood pressure, and peak pressure-rate double product were calculated for each test. Exercise duration, absolute measured VO2max, anaerobic threshold VO2 and VE/VO2 slope were recorded based on American College of Sports Medicine equations for the RAMP protocol [21]. Ventricular ectopy during the CPET was defined as multiple (2 or more ventricular ectopic complexes during exercise and/or recovery).

2.2. Echocardiography

Transthoracic echocardiography (ECHO) was performed using a commercially available ultrasound system (PHILIPS EPIQ CVx3D), including baseline and post-exercise GLS following American Society of Echocardiography guidelines [22].

Digital loops that included three successive cardiac cycles from the apical four, two and long-axis views were acquired to assess GLS. Tracking quality was assessed by the operator and scored by the software with automated function in the region of interest adjusted by correcting the endocardial border or width if deemed necessary.

2.3. Cardiac MRI

Imaging was performed on a 3.0-T scanner (Skyra; Siemens) equipped with phased-array receiver coils. After performing multiplanar localizers, cine images were performed using a steady-state free precession sequence (25 frames/cardiac cycle) in a short axis stack covering the LV from base to apex and in standard 2-, 3-, and 4-chamber long axis views. Quantitative ventricular volumes, function, and mass were measured (Argus, Siemens). Precontrast T1 and T2 mapping of the myocardium was performed at three short-axis slice positions using a modified look-locker inversion recovery (MOLLI) technique (T1 mapping) and a balanced steady-state free precession (bSSFP) sequence (T2 mapping) (MyoMaps, Siemens). Regions of interest were measured in the septum and interlateral wall. Results were compared with scanner-specific values to determine variations from normal. Ten minutes after intravenous administration of 0.2 mMol/kg gadobenate dimeglumine (Multihance, BraccoCorp), images were acquired in identical slice positions as the cine views using a segmented phase sensitive inversion recovery spoiled gradient recalled echo sequence. To null the signal of the normal myocardium, an individually adjusted inversion time in the range of 250–300 ms was used as determined by a TI-scout scan. If present, late gadolinium enhancement (LGE) was characterized by myocardial segment location and extent of myocardial involvement.
2.4. Diagnosis of potential COVID-19 myocardial involvement

The multidisciplinary panel adjudicated each athlete based on the findings from the MIAMI Protocol. The panel also considered findings in the context of criteria for athletes’ heart [9,23]. Borderline increases in RV or LV volumes, decreases in RV or LV ejection fraction and isolated RV septal insertion late gadolinium enhancement (LGE) were considered associated with physiologic adaptation to chronic exercise rather than COVID-19 related injury. All athletes with abnormalities on initial testing underwent cardiac MRI which was used for final adjudication and confirmation of cardiac injury. Athletes with evidence of myocarditis or other myocardial involvement in the convalescent phase of COVID-19 infection were not cleared to return to exercise and competition.

The diagnosis of acute and/or fulminant myocarditis is a more straightforward diagnosis. The diagnosis of subclinical myocarditis that may or may not be resolving is a more difficult clinical diagnosis. The Lake Louise criteria [24,25] were developed for the diagnosis of acute myocarditis in patients hospitalized with recent symptom onset, rather than in the convalescent phase of a viral infection. Nevertheless, we used these criteria to categorize the patterns of cardiac injury noted in this study. We defined myocarditis as definite if there were abnormalities in both T1 and T2 along with other clinical findings. Probable myocarditis was diagnosed if T1 or T2 were increased and there were other structural and/or clinical abnormalities (pericardial effusion, hypokinesis). Otherwise we defined myocardial involvement, likely related to the recent SARS CoV-2 infection, if there was a constellation of abnormal clinical findings (abnormal T1 or T2, pericardial effusion, inflammatory biomarker elevation, abnormal ECG and/or echocardiogram). The diagnosis of myocardial involvement was sufficient to restrict the athlete given that SARS CoV2 was a novel pathogen whose long-term sequelae had not been defined. These athletes with myocardial involvement or myocarditis were referred to our myocarditis expert (JMH). Changes in ECG/ECHO/MRI that were consistent with athletes

2.5. Statistics

Data are summarized as mean ± SD or median (IQR). A Fishers exact test was used to compare categorical variables. t-Tests were used to compare normally distributed continuous data. The Wilcoxon test was used to test differences between non-normally distributed continuous data. A p-value < 0.05 was considered significant.

3. Results

The study population (n = 174) included 23 professional athletes and 151 Division 1 collegiate athletes, comprised of 54 women and 122 men (Table 1). Median age was 21 years (IQR: 19.22; range 17–35, Table 1). There were 36 baseball players, 72 football players, 11 basketball players, and 55 athletes who competed in other sports. Medical history included hypertension in 2 athletes and their echocardiograms showed normal chamber size and wall thickness. Some athletes also had a history of asthma (n = 10), remote syncope (n = 1, previously evaluated and deemed benign), anemia (n = 3), or Factor V Leiden deficiency (n = 1).

3.1. COVID-19 illness and recovery

Athletes were routinely screened a few times each week based on NCAA or major league baseball protocols. A total of 26 (14.9%) of the 174 athletes were asymptomatic, while the remainder initially had COVID-19-associated symptoms (Table 1). No athlete was hospitalized, or received specific treatment for COVID-19, and no athlete had acute biomarker testing or Echocardiogram during the acute phase of COVID-

| Table 1 | Clinical results from 174 athletes who underwent MIAMI protocol. |
|---------|------------------------------------------------------------------|
|         | Baseline (n = 174) | Exercise (n = 172) | Recovery (n = 172) |
| Median age (IQR) | 21 (19,22) | Male/female | 122/54 |
| Sport | Baseball | 36 | Football | 72 |
|       | Basketball | 11 | Volleyball | 7 |
|       | Soccer | 10 | Crew | 14 |
|       | Tennis | 9 | Track and field | 7 |
|       | Swimming/diving | 8 | Past medical history | |
| Hypertension | 2 | Asthma | 10 |
| Anemia | 3 | Diabetes Type I | 1 |
| COVID 19 symptoms | | | |
| Cough | 67 | Shortness of breath | 28 |
| Chest pain | 15 | Anemia | 88 |
| Fever | 55 | Palpitations | 9 |
| Dizziness/ | 84 | light headedness | |
| Sore throat | 28 | Asymptomatic | 26 |
| Hospitalized with COVID 19 | 0 | Abnormal CRP reference | 7 |
| Abnormal troponin | (reference: 0–0.06 ng/ml) | 0 |
| ECG abnormalities | | |
| NSIVCD | 4 | PAC | 5 |
| 2nd degree Type I AV block | 3 | Incomplete RBBB | 5 |
| Ventricular ectopy | 2 | T wave abnormality | 6 |
| Median peak heart rate (IQR) | 171 (164,184) | Left ventricular ejection fraction | 57.6 ± 4.5% (range 49–69%) |
| Median VO2max ± SD ml/Kg/min | 37.7 ± 8.0 | Mean GCS ± SD | −25.7 ± 3.5% |
| Probable myocarditis | 3 | Significant PFO | 1 |
| Significant VSD | 1 | Mitral Valve prolapse | 1 |
| Right atrial myxoma | 1 |

LVId in - diastolic left ventricular internal dimension, NSIVCD - nonspecific intraventricular conduction delay, PAC - premature atrial complex, PFO - patent foramen ovale, RBBB - right bundle branch block, RV - right ventricular, SD - standard deviation, VSD - ventricular septal defect; *P < 0.001 for comparison of GCS at rest and at peak exercise.

Two athletes were unable to exercise due to orthopedic injury (n = 1) and possible right atrial myxoma (n = 1).

19. Anosmia was the most common symptom.

All athletes had recovered prior to testing, although non-limiting nonspecific symptoms persisted in 11 (Supplemental Table 1). By design, subjects underwent our evaluation a minimum of 14 days following their positive COVID-19 test (one was tested at 11 days). Athletes were evaluated a median of 18.5 (IQR: 16, 25) days after a
positive test. Based on the MIAMI protocol, 26 (14.9%), underwent cardiac MRI (Fig. 1).

Five of the 174 athletes (2.9%) exhibited evidence of cardiac involvement (Fig. 1; Table 2) including definite or probable myocarditis (n = 2), or potential myocardial involvement (n = 3). These 5 individuals were not cleared to return to training or competition. Three of the 5 athletes with cardiac involvement (60%) had persistent nonspecific cardiopulmonary symptoms (Supplemental Table 1). These nonspecific symptoms included fatigue, cough, lightheadedness and shortness of breath. This proportion was greater than among those without cardiac involvement (10/169 [5.9%], p = 0.003). The remaining 169 (97.1%) athletes were cleared to return to sport participation (Table 2).

| Table 2 | Comparison of athletes with and without diagnosis of myocarditis/myocardial involvement. |
|---------|------------------------------------------------------------------------------------------------|
|         | Myocardial involvement | No myocardial involvement | P value |
| N       | 5                      | 169                       |         |
| Median age (median,IQR) | 20 (19,20)             | 21 (19,2)                 | 0.18    |
| Sex (M/F) | 2/3                   | 120/49                    | 0.16    |
| Elevated CRP | 2                     | 5                         | 0.013   |
| Time to test (days) (median, IQR) | 32 (24,38)             | 18 (16,25)                | 0.11    |
| Persisting symptoms | 3                     | 10                        | 0.003   |
| QRS ≥ 120 msec | 2                     | 3                         | 0.006   |
| Peak VO2 (mL/Kg/min) | 42.0 ± 11.3            | 37.6 ± 7.9                | 0.47    |
| LV GLS | −25.3 ± 2.5           | −25.7 ± 3.5               | 0.77    |
| Change in GLS | −1.6 ± 3.2            | −3.3 ± 3.4                | 0.34    |
| Peak HR (complex/min) | 181 ± 4               | 171 ± 16                  | 0.095   |
| LVEF (%) | 56 ± 3                | 58 ± 4                    | 0.38    |
| Ventricular ectopy (≥2 PVCs) during stress test | 2                     | 7                         | 0.023   |
| Abnormal resting ECG (T wave inversion, IVCD or PVC) | 3                     | 9                         | 0.002   |
| Abnormal resting ECHO- (pericardial effusion, LV dysfunction, abnormally low GLS) | 1                     | 2                         | 0.084   |
| Abnormal stress test results (ECHO, or ECG relevant abnormalities) | 3                     | 8                         | 0.002   |
| Any relevant abnormality in ECG, ECHO or stress test | 5                     | 18                        | <0.001  |

The Wilcoxon test was used to compare continuous variables and Fisher’s Exact Test compared categorical variables. GLS - global longitudinal strain, LV left ventricular, LVEF - left ventricular ejection fraction, PVC - premature ventricular complex. Abnormal resting ECHO did not include incidental findings (bicuspid Aortic valve, Patent foramen ovale, atrial septal defect, small atrial myxoma).

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Fig. 1. This figure demonstrates the results of the MIAMI protocol in 147 consecutive competitive athletes.
3.2. Biomarkers and electrocardiogram

All 174 athletes had undetectable troponin (<0.01 ng/ml). One athlete had a borderline elevated NT-proBNP level (0–125 pg/ml), and, 7 had elevated CRP (0.6–2.3 mg/dl; normal range 0–0.5 mg/dl), Two of 5 (40%) subjects diagnosed with myocardial involvement had elevated CRP compared with 5 (3.0%) of 169 subjects without myocarditis. A total of 30 athletes (17.2%) had abnormalities on ECGs, and 25 had at least one relevant abnormality on ECG, echocardiogram or stress testing, together with other clinical features led to a targeted CMR and a diagnosis of myocardial involvement. The median age, mean VO2max, left ventricular ejection fraction, left ventricular GLS, timing of undergoing MIAMI protocol after COVID19 diagnosis were not different between those with or without myocarditis or myocardial involvement (Table 2).

Overall, all 5 athletes with myocarditis or myocardial involvement had at least one relevant abnormality on ECG, echocardiogram or stress test compared with 18 of 169 athletes (P < 0.001).

3.3. Metabolic stress echocardiogram (Tables 2 & 3)

Two athletes were unable to exercise due to orthopedic injury (n = 1) and incidental finding of a right atrial myxoma (n = 1). All subjects had normal LV ejection fractions with minimum EF of 49% and mean EF of 57.4 ± 4.3%. Resting GLS was −25.7 ± 3.5% which increased to −28.8 ± 5.6% post-exercise (p < 0.001). Baseline LV end diastolic dimension was 5.2 ± 0.4 cm (range 4.2–6.1 cm). Incidental findings on echocardiography were noted in 5 athletes (Table 1).

During exercise, subjects achieved a median peak heart rate of 171 (IQR 164, 184). Mean VO2max was 37.7 ± 8.0 ml/Kg/min. The 5 athletes with myocardial involvement had a mean VO2max of 42.0 ± 11.3 (range: 21.5–55.3) ml/Kg/min, which was not different from the athletes without myocardial involvement (Table 2).

Ventricular ectopy was present during exercise testing in 2 (40%) of the 5 athletes (Fig. 2) with myocardial involvement vs 7 (4.1%) of the 167 athletes without myocardial involvement (p = 0.023). There were only two athletes with PVCs on resting ECG and one of them had PVCs reproduced during exercise. In one of the athletes, the exercise induced ventricular ectopy was the only abnormality on the MIAMI protocol and was the deciding factor to proceed with a CMR which confirmed the diagnosis of definite myocarditis (abnormal T1 and T2 imaging). PVCs were noted during exercise in 6 of the 9 athletes and during recovery in 8 of the 9 athletes.

Other notable findings included exercise induced wall motion abnormality in one and abnormal VE/VCO2 in another athlete. These findings, together with other clinical features led to a targeted CMR and a diagnosis of myocardial involvement. The median age, mean VO2max, left ventricular ejection fraction, left ventricular GLS, timing of undergoing MIAMI protocol after COVID19 diagnosis were not different between those with or without myocarditis or myocardial involvement (Table 2).

Overall, all 5 athletes with myocarditis or myocardial involvement had at least one relevant abnormality on ECG, echocardiogram or stress test compared with 18 of 169 athletes (P < 0.001).

3.4. Cardiac MRI

Twenty-eight of the 174 (16.1%) athletes underwent cardiac MRI for the following indications: pericardial effusion, exercise-induced wall motion abnormality, borderline QRS prolongation, decreased GLS, borderline or markedly diminished RV function, ventricular arrhythmias, abnormal high sensitivity CRP and/or low VO2max. Delayed enhancement was not available in 3 studies due to allergic reaction or subject movement. MRI demonstrated T1 and/or T2 elevations in 3 (10.7%) of the 28 patients (along with other clinical findings), consistent with myocarditis or myocardial involvement (Table 4). One athlete (#72) was diagnosed with myocardial involvement based on wall motion abnormality, pericardial effusion and depressed right ventricular ejection fraction. Another athlete (#10, Fig. 3) had delayed gadolinium enhancement along the subepicardial lateral wall from the base to the apex which was attributed to prior myopericarditis from his incident SARS-CoV2 infection. This athlete had no other history of significant viral illness or cardiac injury. Although he was thought not to have active inflammation based on T1 and T2 measurements, he was also restricted from exercise and competition. Athlete 111 had focal
elevations of T1 and T2 identified along with small area of delayed gadolinium enhancement and two morphologies of PVCs during her stress test. Interestingly one of the PVC morphologies had RBBB, superior axis, somewhat rightward oriented which may have correlated with an area of T2 elevation and focal delayed enhancement in the inferolateral LV wall.

Table 4

| Subject  | Indication                                      | LVEF  | LVEDV ml/m² | RVEF  | RVEDV ml/m² | T1 a ms | T2 a ms | LGE Other findings                                                                 | Clinical diagnosis                                      |
|----------|-------------------------------------------------|-------|-------------|-------|-------------|---------|---------|------------------------------------------------------------------------------------|--------------------------------------------------------|
| 33-f     | Exercise-induced wall motion abnormality, Pericardial effusion and multiple exercise induced PVCs | 54    | 95          | 49    | 109         | 1292    | 41      | None                                                                               | T1 elevated, small pericardial effusion, mild inferior RV hypokinesis | Myocardial involvement, likely myocarditis based on clinical criteria |
| 39-f     | T wave abnormalities                             | 71    | 91          | NM    | NM          | 1153    | 48      | Focal                                                                               | Elevated T2, Focal LGE in RV-septal insertion site     | Potential myocardial involvement                        |
| 72-m     | IVCD, elevated CRP                               | 51    | 93          | 38    | 120         | 1141    | 39      | None                                                                               | Mild mid-inferior LV hypokinesis, small pericardial effusion, delayed hyperenhancement band in midseptum | Potential myocardial involvement                        |
| 105-m    | Abnormal EKG: IVCD, new T wave inversion in VI   | 52    | 106         | 42    | 140         | 1158    | 37      | Lateral wall subepicardial High signal in the subepicardium                        | Potential myocardial involvement                      |                                                                             |
| 111-f    | Multiple polymorphic PVCs and bigeminy in early recovery | 56    | 98.1        | NM    | NM          | 1297    | 42      | Focal                                                                               | Abnormal T1(septum) and abnormal T2(lateral wall-46msec) Small pericardial effusion; small focus LGE-inferolateral wall | Definite myocarditis                                    |

Normal ranges for site-specific T1 and T2 standardized for LV septum: values specific for the 3T Siemens Skyra (T1 1222 ± 46 ms, T2 41 ± 4 ms) or Vida (T1 1230 +/- 39 ms, T2 39 +/- 2 ms). Bold indicates abnormally elevated values. F – female, GLE – gadolinium late enhancement, GLS – global longitudinal strain, IVCD – intraventricular conduction delay, LVEDV – left ventricular end diastolic volume, LVEF – left ventricular ejection fraction, m – male, NM – not measured, RV – right ventricular, RVEDV – right ventricular ejection fraction, RVEF – right ventricular ejection fraction.

3.5. Follow-up

Five of 174 (2.9%) athletes in our cohort were not cleared to return to active sport participation due to initial diagnosis of myocardial involvement and/or myocarditis (Table 4). They were prescribed beta-adrenoreceptor blockers and ACE inhibitors as tolerated. None have had further clinical deterioration and were followed for a minimum of 6 and up to 14 months in our myocarditis clinic. One athlete (33f), diagnosed with likely myocarditis had persistent exertional chest pain with exertion during follow-up which gradually resolved. She had abnormal CMR, persistent chest pain, initial wall motion abnormalities, persistent pericardial effusion; these findings were consistent with myocarditis. In fact, CMR 11 months later showed subepicardial enhancement in the inferior and inferoseptal wall consistent with healed myocarditis, along with persisting small pericardial effusion. At 12 months post diagnosis, she has resumed exercise and has been gradually increasing effort. Athlete 39f, had resolving dyspnea attributed to both pulmonary and cardiac etiology. She resumed exercise at approximately 6 months post diagnosis. Repeat CMR showed resolution of T2 elevation. Athlete 72 m resumed light exercise at 3 months. Repeat CMR showed improvement of RVEF from 38 to 43%. Athlete 105 m had unchanged MRI 8 months...
later (Fig. 3) without any other CMR abnormalities. It was initially believed that the subepicardial delayed enhancement was due to a healed myocarditis, likely from COVID-19. As he had no other sequelae of myocarditis and had no other changes on CMR and no change in his CMR, he was cleared to exercise after the repeat CMR 8 months later. Athlete 1111 fulfilled CMR criteria for myocarditis. She had a CMR 7 months later showing resolution of the elevated T1 and T2. She had persistence of insertion point delayed enhancement felt not to be related to COVID-19. She also resumed exercise at 7 months.

The remaining 169 athletes were cleared to return to exercise training and competition and were followed for a median of 148 (IQR 108, 211) days. Following diagnosis of COVID-19 and clearance for return to physical activity, the athletes were monitored daily by the team athletic trainer. Any unusual symptoms (fever, shortness of breath, palpitations) were reported to the respective team physician who determined a management plan. This daily report was done for the first 7 days following return to physical activity and training. Beyond that any self-reported symptoms by the athlete were communicated from the athletic trainer to the team physician. There were no adverse cardiac events.

4. Discussion

To our knowledge, this is the first single center study assessing athletes who recovered from COVID-19, incorporating a functional test-stress echocardiogram with CPET, with cardiac MRI performed based only on specific indications, and providing follow-up data of a median of 148 days for athletes found to have myocardial involvement including potential or definite myocarditis following COVID-19 infection. To our knowledge, this is also the first study to provide detailed follow-up of athletes restricted from competition due to concern for COVID-19 related myocarditis or myocardial involvement. The main finding is that the MIAMI protocol was critical in making a final diagnosis of myocardial involvement including myocarditis. The finding of stress test associated ventricular ectopy was associated with diagnosis of myocarditis in 2 (40%) of the 5 athletes with myocardial involvement. The combination of resting ECG, resting ECHO and stress ECHO was 100% sensitive at identifying the athletes ultimately adjudicated to have myocardial involvement. Importantly, there was no difference in VO2max, EF, or resting or exercise GLS, between patients with or without a diagnosis of myocardial involvement. Persistent cardiopulmonary symptoms, QRS ≥ 120 msec, and elevated CRP were also associated with myocardial involvement in a retrospective analysis.

There are several relevant findings in our study. Most importantly, there was a small but clinically relevant incidence of post-COVID19 myocardial involvement of 2.9% and, specifically, of myocarditis of 1.1%, detected a median of 18.5 days after a positive COVID-19 PCR test among highly trained athletes, even in the presence of normal resting left ventricular function, normal GLS and normal or even elite VO2max. In prior studies that examined only resting ECG, ECHO and troponin level, the incidence of myocarditis was <1% [11] while in studies that incorporated routine CMR, the incidence of myocarditis was 2–3% [9,12,13]. Our data are consistent with these larger multicenter studies.

The data also suggest that athletes can be safely cleared to return to training/competition following MIAMI protocol evaluation, with MRIs limited to those with specific indications. In addition, athletes with myocardial involvement or myocarditis detected in the convalescent phase of COVID-19 infection require close cardiovascular follow-up since abnormalities there appears to be a heterogenous pattern of cardiac injury with varied recovery patterns. Indeed, all athletes were returned to exercise from 3 to 12 months post diagnosis. Given the novelty of the SARS-CoV-2 infection, and the limited information on its natural history, as well as the potential risk of moderate to high intensity exertion in the setting of cardiac injury and/or potential myocarditis, uniform protocols for the identification of post-COVID19 cardiac injury are important for determining athlete safety.

As noted above, it is important to identify overt and/or subclinical cardiac injury in athletes recovering or recovered from COVID-19, even in the absence of LV dysfunction, due to the potential risk for life-threatening arrhythmias that can be triggered by exercise [6,16]. To date, no studies have specifically evaluated arrhythmias during follow-up of patients with myocarditis whose ventricular function has recovered, but some reports suggest residual arrhythmia risk. Autopsy series of patients with sudden cardiac death (SCD) have found myocarditis as a potential explanation in a low but significant number of cases, even in the setting of a grossly normal appearing heart [26–28].

Cardiac MRI LGE and T1 and T2 mapping are increasingly used for characterization of local or diffuse myocardial tissue abnormalities, such as inflammation, edema, and fibrosis. MRI evidence of myocarditis includes the presence of myocardial edema (T2 mapping or T2 weighted images) and/or nonischemic myocardial injury (T1 mapping, extracellular volume increase, or LGE) [24]. According to the Lake Louise criteria [24], acute myocarditis is based on at least one T2-based criterion, namely global or regional increase of myocardial T2 relaxation time or an increased signal intensity in T2-weighted CMR images. If there is also at least one T1-based criterion (increased myocardial T1, extracellular volume, or late gadolinium enhancement), there is enhanced specificity for a diagnosis of myocarditis. However, the authors also noted that having only one (i.e., T2-based or T1-based) marker may still support a diagnosis of myocarditis in an appropriate clinical context.
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scenario. Supportive diagnostic criteria include pericarditis (effusion, enhancement) and LV dysfunction. It is important to note that the Lake Louise criteria were based on MRI evaluation of patients hospitalized with acute onset of symptoms, typically with elevated troponin. The diagnostic accuracy is reported to be as high as 90% [24]. However, in the MyoRacer Trial, the AUC for the Lake Louise criteria for biopsy proven myocarditis in patients evaluated within 2 weeks of symptom onset was 0.56 [29]. The AUC dropped to 0.53 for those evaluated more than 3 weeks after symptom onset. The current cohort does not include subjects who required hospitalization, reflecting a milder expression of disease, and median time from viral diagnosis to testing was 18.5 days. These critical differences must be considered in the clinical evaluation and diagnosis of post-COVID-19 myocardial involvement and/or myocarditis.

It is also critical to consider that athletes’ hearts are subject to dynamic and static stress that can result in adaptive structural and functional remodeling. Depending on the type of training and patterns of exercise, athletes can develop LV hypertrophy, enlarged ventricular volumes, repolarization abnormalities, focal LGE abnormalities at septal insertion points, and other abnormalities [23]. Endurance training can lead to abnormal LGE and/or higher extracellular volume (T1 mapping) in up to 37% of athletes [30]. Other studies have confirmed right and left ventricular hypertrophy, and volume increases in young adult athletes engaged in endurance or combination endurance/strength training [31,32]. In our study, the CMR results were adjudicated and interpreted accordingly.

Larger multicenter registry studies have recently been published. In one study, 789 professional athletes underwent troponin testing, ECG and resting echocardiography following a positive COVID-19 test result [11]. Targeted Stress echocardiograms and/or CMR were then ordered. In this multicenter cohort, only 5 (0.6%) had evidence for myocardial inflammatory disease confirmed by CMR. In another multicenter study of 2820 collegiate athletes [12], with COVID-19, definite, probable or possible SARS-CoV2 myocardial involvement was identified in 0.7% of athletes. In a subgroup of 198 patients who received a primary screening CMR, there was a 3% incidence of cardiac injury or inflammation. Finally, in a study of 1597 collegiate athletes, all of whom received CMR, there were 37 athletes (2.3%) with clinical or subclinical myocarditis [13]. Interestingly, in this study 20 of the 37 athletes were asymptomatic and had normal troponin level, resting ECG and ECHO which were ‘not consistent with myocarditis.’ This supports the notion that a protocol that is limited to symptom evaluation, troponin level, resting ECG and resting ECHO may miss a significant number of athletes with subclinical myocarditis.

In this study, in the 5 athletes who were diagnosed with myocardial involvement and/or myocarditis, there was a variable pattern of presentation, including a constellation of acute myocarditis, pericarditis, late gadolinium enhancement, diminished RV function (even accounting for athletes’ heart), elevated biomarkers, specifically CRP, borderline QRS duration prolongation and/or ventricular ectopy during stress testing. In our cohort two athletes had definite or likely myocarditis. Both athletes had persisting cardiopulmonary symptoms and both athletes had ventricular ectopy during their exercise test. Both were cleared to exercise at 7 & 12 months. Of the other 3 athletes restricted from exercise due to myocardial involvement, there was no ventricular ectopy noted during exercise and one had persisting cardiopulmonary symptoms likely due to co-existing pulmonary complications from COVID-19. They were cleared to exercise between 3 & 8 months. We identified other factors that may predict myocardial involvement including elevated CRP, borderline QRS duration, abnormal ECG, abnormal echocardiogram.

The results from our study together with prior studies suggest that the incidence of clinically significant myocarditis is quite low. There has not been reports of increased rates of cardiac arrest among athletes. In fact, the ORCCA registry reported one cardiac arrest among 19,378 athletes that was likely not related to COVID-19. These data have led to revision of recommendations among an expert panel regarding return to play [33]. Specifically, screening cardiac testing is only recommended for athletes who have persisting cardiopulmonary symptoms. The results of our study are relevant and suggest that a functional protocol such as the MIAMI protocol may be applied to those athletes, competitive or recreational, who have persisting cardiopulmonary symptoms. In our study, 13 (7.5%) of the athletes had persisting symptoms (Supplemental Table 1). Of these 13 athletes, the MIAMI protocol identified 4 athletes with abnormal findings warranting CMR. Of these 4 athletes, 2 athletes had definite/likely myocarditis and 1 had myocardial involvement, and only 1 athlete was cleared to return to exercise after the CMR. As no data has yet been published after institution of the new screening protocol, the MIAMI protocol provides relevant guidance for screening.

5. Limitations

We did not perform cardiac MRI in all athletes which could have further validated a strategy of functional testing prior to CMR. While lack of a CMR may have led to an underdiagnosis of myocardial involvement, routine CMR could also provide inappropriately heightened sensitivity to this diagnosis in the setting of negative history, normal physical examination, normal rest ECG, normal biomarkers, normal resting echocardiogram, normal stress ECG and metabolic evaluation, and normal stress echocardiogram. The small sample size and small number of patients with diagnosis of myocardial involvement or probable/definite myocarditis also limit the ability to draw firm conclusions. High sensitivity Troponin was not used.

6. Conclusions

The addition of stress testing to a strategy of biomarker evaluation, resting ECG and ECHO was useful in identifying the small number of athletes following SARS-CoV2 infection who may have persistent inflammation or other cardiac involvement. In particular, the presence of cardiopulmonary symptoms and/or exercise-induced ventricular ectopy appears to be highly associated with myocarditis or myocardial involvement.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The University of Miami is an equity owner in Longeveron Inc., which has licensed intellectual property from the University of Miami.

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