COVID-19 Myocardial Pathology Evaluation in AthleteS with Cardiac Magnetic Resonance (COMPETE CMR)

Running Title: Clark et al.; COMPETE CMR

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Myocarditis is a leading cause of sudden cardiac death among athletes and may occur without antecedent symptoms. COVID-19-related cardiac magnetic resonance (CMR) abnormalities have been described in 78% of mostly ambulatory adults,

creating concerns over COVID-19-related myocarditis in athletes. A report of 26 COVID-19+ collegiate athletes revealed late gadolinium enhancement (LGE) in 46%, with 4 (15%) meeting modified Lake Louise criteria for myocarditis. However, without an athletic comparator group it is difficult to discern whether LGE represents healing myocarditis or athletic remodeling, as inferoseptal RV insertion LGE is common among athletes. We report the findings of a larger CMR study to evaluate the incidence and extent of cardiovascular pathology among COVID-19+ collegiate athletes, with comparison to athletic and healthy control groups.

The data supporting the findings of this study are available from the corresponding author upon request. All COVID-19+ athletes underwent an institutionally-mandated cardiovascular screening protocol, including clinical examination, electrocardiography, troponin I, echocardiography with strain, and contrasted CMR with parametric mapping on a 1.5T Siemens Avanto Fit magnet (Siemens Healthcare Sector, Erlangen, Germany). These subjects were retrospectively enrolled. Athletic controls were retrospectively selected from collegiate and tactical athletes (military personnel) referred to our center for clinical CMR prior to the first reported case of COVID-19 in our region. All athletes in our study participated in ≥6 hours of intense physical exercise weekly. Healthy controls (N=27) similar in age to COVID-19+ athletes were derived from a cohort of 54 healthy subjects prospectively enrolled for non-contrasted CMR to derive normative T1 and T2 values for our laboratory. The study was approved by the institutional review board with a waiver of consent for retrospective enrollment.
Contrasted studies were performed using 0.15 mmol/kg of gadobutrol. Volumetric and parametric mapping analyses were performed using Qmass and Qmaps (MedisSuite, Leiden, The Netherlands). Punctate inferoseptal RV insertion LGE was not considered a pathologic exclusion criterion.4

Categorical variables were compared using the chi squared test and continuous variables were compared using the Wilcoxon rank sum. Statistical analysis was performed using STATA, version 15 (StatCorp LLC, College Station, TX) software.

Fifty-nine COVID-19+ athletes, 60 athletic controls, and 27 healthy controls were included in our analysis (Table). The COVID-19+ athletes represented 9 collegiate sports and were 63% female and 15% non-white, with a median age of 20 years. The median time from SARS-CoV-2 detection to CMR was 21.5 days (IQR 13, 37; range 10-162). COVID-19+ athletes experienced mild illness (N=46, 78%) or were asymptomatic (N=13, 22%).

Two asymptomatic COVID-19+ athletes (3%) met criteria for myocarditis2; one athlete had pericarditis. These athletes had normal electrocardiograms, troponin I, and echocardiograms with strain. Both athletes with myocarditis had normal LVEF by initial CMR; however, one athlete developed new LV dysfunction (LVEF 45%) on a follow-up echocardiogram performed for worsening dyspnea.

COVID-19+ athletes had increased volumes and mass when compared with healthy controls, consistent with athletic remodeling. Most standard CMR parameters were similar between COVID-19+ athletes and athletic controls. Focal LGE isolated to the inferoseptal RV insertion was present in 22% of COVID-19+ athletes, compared to an identical LGE pattern in 24% of athletic controls.
COVID-19+ athletes had elevated myocardial T2 relaxation times in all myocardial segments compared with healthy controls, however only the mid-septal T2 was significantly elevated compared with athletic controls. Similarly, mid-septal extracellular volume (ECV) was elevated in COVID-19+ athletes compared with athletic controls. Mild segmental increases in T1, T2, or ECV were found in 39% of COVID-19+ athletes, 13% of athletic controls, and 8% of healthy controls compared with our laboratory-specific normative values.

The incidence of myocarditis in collegiate athletes after COVID-19 is modest (3%), but may be missed by conventional screening without CMR. Although the long-term significance of myocarditis detectable only by CMR remains unclear, one athlete with myocarditis did develop LV dysfunction on subsequent echocardiography. Future investigations are necessary to follow COVID-19+ athletes for long-term complications.

Our findings confirm that focal inferoseptal RV insertion LGE is common in athletes, may represent remodeling from athletic training, and should not be conflated with myocarditis. Disparities in volumetrics and LGE incidence between the COVID-19+ athletes and healthy controls were diminished when using athletic controls as the comparator. This highlights the importance of utilizing athletic controls when interpreting CMR findings in COVID-19+ athletes.5

There are limitations to our study. Athletic controls were preferentially matched by athletic training, not age or gender, which could contribute to differences between groups. Not all CMR were performed at a uniform time and myocardial strain was assessed only with echocardiography.
CMR with parametric mapping detects myocardial inflammation with high sensitivity. Clinical judgment remains imperative when contextualizing abnormal CMR findings in the adjudication of a safe return to athletic competition. Ongoing investigations of the short and long-term cardiovascular manifestations of COVID-19 are necessary to inform the optimal care of athletes recovering from infection.

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Conflict of Interest Disclosures
None

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### Table. Demographics, echocardiography, and cardiovascular magnetic resonance results.

| | COVID-19+ athletes (N=59)^† | Healthy controls (N=27)^# | Athletic controls (N=60)^‡ | P value^# | P value^‡ |
|---|---|---|---|---|---|
| Age, median (IQR), years | 20 (19, 21) | 30 (27, 34) | 25 (22, 27) | <0.001 | <0.001 |
| Height, cm | 173 (164, 188) | 173 (164, 183) | 175 (173, 185) | 0.50 | 0.17 |
| Weight, kg | 67 (59, 91) | 73 (66, 86) | 85 (72, 95) | 0.46 | 0.01 |
| Body surface area, kg/m² | 1.8 (1.6, 2.2) | 1.9 (1.7, 2.0) | 2.1 (1.9, 2.2) | 0.85 | 0.03 |
| Race: Non-White, N (%) | 6 (15%)^† | 3 (13%)^** | 3 (21%)^*** | 0.81 | 0.55 |
| Ethnicity: Non-Hispanic, N, (%) | 36 (95%)^# | 22 (88%)^## | 13 (87%)^### | 0.33 | 0.32 |
| Gender: Female, N, (%) | 37 (63%)^† | 10 (37%)^†† | 7 (12%)^††† | 0.04 | <0.001 |
| **Echocardiography** | | | | | |
| LVEF, % | 61 (57, 66) | NA | 60 (58, 61)^‡ | 0.24 | |
| GLS, % | -18.6 (-20.1, -17.4)^‡‡ | NA | NA | | |
| **CMR** | | | | | |
| **Volumetrics** | | | | | |
| LVEDV, mL | 160 (143, 213) | 164 (138, 210) | 195 (167, 235) | 0.61 | 0.02 |
| LVEDVi, mL/m² | 93 (84, 100) | 88 (78, 99) | 95 (86, 111) | 0.12 | 0.37 |
| LVESV, mL | 68 (58, 84) | 64 (55, 83) | 84 (66, 97) | 0.32 | 0.007 |
| LVESVi, mL/m² | 37 (34, 43) | 35 (31, 41) | 40 (35, 47) | 0.21 | 0.08 |
| LV mass, g | 112 (88, 147) | 71 (57, 96) | 117 (105, 143) | <0.001 | 0.26 |
| LV mass index, g/m² | 60 (52, 71) | 41 (32, 48) | 59 (53, 67) | <0.001 | 0.48 |
| RV mass, % | 53 (50, 56) | 58 (55, 60) | 53 (51, 57) | <0.001 | 0.53 |
| RVEDV, mL | 184 (153, 240) | 166 (136, 210) | 201 (170, 241) | 0.08 | 0.19 |
| RVEDVi, mL/m² | 100 (91, 115) | 89 (78, 104) | 99 (87, 117) | 0.004 | 0.61 |
| RVESV, mL | 86 (70, 117) | 67 (58, 86) | 94 (73, 116) | 0.002 | 0.46 |
| RVESVi, mL/m² | 48 (42, 55) | 36 (32, 45) | 45 (40, 55) | <0.001 | 0.53 |

**Parametric mapping and LGE**

| | | | | | |
|---|---|---|---|---|---|
| T1, median (IQR), ms | | | | | |
| Basal septum | 992 (970, 1007) | 988 (972, 1000) | 990 (973, 1003)^‡‡‡ | 0.44 | 0.64 |
| Basal lateral | 972 (952, 995) | 958 (945, 983) | 966 (954, 993)^‡‡¶ | 0.13 | 0.91 |
| Mid septum | 988 (973, 1013) | 979 (963, 1000) | 982 (960, 997) | 0.15 | 0.12 |
| Mid lateral | 984 (951, 996) | 965 (947, 975) | 965 (948, 987) | 0.06 | 0.07 |
| T2, ms | | | | | |
| Basal septum | 44.3 (42.8, 46.2) | 42.8 (41.7, 43.6) | 43.2 (42.4, 44.2)^## | 0.001 | 0.28 |
| Basal lateral | 45.4 (44.1, 46.6) | 44.2 (43.0, 44.6) | 44.2 (43.2, 45.3)^## | <0.001 | 0.25 |
| Mid septum | 46.8 (44.9, 48.4) | 44.7 (43.3, 46.1) | 44.9 (43.9, 46.4)^## | <0.001 | 0.02 |
| Mid lateral | 47.0 (44.9, 47.9) | 44.4 (42.6, 45.5) | 45.6 (44.0, 46.9)^## | <0.001 | 0.21 |
| ECV, % | | | | | |
| Basal septum | 24.6 (22.8, 25.9)^### | NA | 22.9 (20.8, 26.3)^## | 0.54 | |
| Basal lateral | 22.5 (20.7, 24.2)^### | NA | 23.9 (20.8, 25.8)^## | 0.42 | |
| Mid septum | 25.6 (23.9, 27.7)^### | NA | 22.7 (21.6, 24.3)^† | 0.006 | |
| Mid lateral | 23.9 (21.6, 25.6)^### | NA | 20.8 (19.9, 24.8)^† | 0.05 | |
| LGE (Any), N (%) | 16 (27%) | 0 | 10 (24%) | 0.56 | |
| Mid-inferior RV septal insertion site (without myocarditis) | 13 (22%) | 0 | 10 (24%) | 0.69 | |
| Meeting modified Lake Louise criteria | 2 (3%) | 0 | 0 | | |
| Other myocardial | 1 (2 %) | 0 | 0 |
|------------------|---------|---|---|
| Pericardial      | 1 (2 %) | 0 | 0 |

*N=41, **N=24, ***N=14, ****N=25, *****N=15, †N=59, ††N=27, †††N=60, †‡N=30, †‡‡N=49, †‡‡‡N=28, †§N=55, †‖N=4, †‖‖N=15, †‖‖‖N=57, †††N=11, ††††N=41 who received gadolinium, NA=not available. #Comparison of COVID-19+ athletes to healthy controls; ^comparison of COVID-19+ athletes to athletic controls.

4 ROIs in the left ventricle from short axis views were obtained for native T1, T2, and ECV. Healthy controls underwent CMR without contrast and therefore do not have ECV or LGE assessments.