Supplemental material

Detailed CMR acquisition protocol

Cardiac magnetic resonance (CMR) was performed using preferentially 1.5 Tesla- scanners, a dedicated body coil for cardiac measurements, and electrocardiographic gating.

The standardised protocol consisted of:
(1) standard cardiac localizers
(2) modified Dixon sequence (lumbar spine)
(3) balanced turbo field echo cine imaging of long-axis views (two-, three-, and four-chamber left ventricle views, right ventricle outflow tract, pulmonary artery; field of view (FOV): 400 mm x 400 mm; voxel size: 2,1 x 2,1 x 6 mm; echo time (TE): 1,19 ms; repetition time (TR): 40,65 ms; flip angle: 70°)
(4) native T1 shortened modified look locker inversion recovery sequence (ShMOLLI) mapping on short-axis view in three slices (FOV: 400 mm x 400 mm; voxel size: 1,6 x 1,6 x 8 mm; 12 mm gap; TE: 1,09 ms; TR: 298,6ms; flip angle: 35°). Same position as slices of 2D balanced turbo field echo cine imaging SA.
(5) intravenous gadolinium (Dotarem®,Guerbet, Roissy, France) body weight dependent bolus injection (0.2 ml/Kg)
(6) 2D balanced turbo field echo cine imaging stack of 9-17 contiguous short-axis slices, covering both ventricles from apex to base, using balanced turbo field echo cine imaging (FOV: 400 mm x 400 mm; voxel size: 1,6 x 1,6 x 8 mm; 8 mm gap; TE: 1,16 ms; TR: 41,4 ms; flip angle: 70°)
(7) late gadolinium enhancement (LGE) 'overview' images (phase-sensitive inversion recovery sequence; PSIR) in two-, three-, four-chamber and short-axis views (identical to cine imaging localization and voxel size; TE: 1,03 ms; TR: 700 ms; flip angle: 40°), after a minimum of 8 minutes of intravenous Gadolinium injection. Same position as balanced turbo field echo cine imaging SA, 2,3 and 4 CH.
(8) LGE 'high-resolution' PSIR images (identical to LGE overview location; voxel size 1,6 x 1,6 x 8 mm; TE: 1,55 ms; TR: 750; flip angle: 20°)
(9) Post-contrast (15 minutes after Gadolinium injection) T1 ShMOLLI mapping (identical to native settings positions not parameters)
(10) three-dimensional whole heart dataset using respiratory navigator gating and electrocardiograph triggered isotropic 1.5 mm in diastole.

Cross-sectional cardiovascular assessment

Supplemental Table 1 presents the missing data from cross-sectional cardiovascular assessments, including laboratory measurements and ECGs. In the cross-sectional analyses, we were unable to conduct functional and volumetric CMR analyses of the right ventricle in one athlete due to the unavailability of contrast-enhanced images. Additionally, late gadolinium enhancement analysis was not performed in one athlete for the same reason. Furthermore, a total of 21 athletes did not undergo CMR at the Amsterdam UMC, and 26 athletes had their CMR conducted using a 3 Tesla MRI scanner.

Supplemental Table 1. Missing data of cross-sectional assessment of ECG, and laboratory findings in elite athletes exposed to SARS-CoV-2 versus non-exposed elite athletes.

		Total n=259			P-value
	SARS-CoV-2 infected elite athletes n=123	**Missing, n (%)**	**Elite athlete controls n=136**	**Missing, n (%)**	
Elevated Troponin T (>14 ng/L) , n (%)	9 (7.3)	7 (6)	6 (4.4)	7 (5)	0.456
Elevated NT-proBNP (>130 ng/L)	2 (1.6)	9 (7)	3 (2.2)	4 (3)	1.000
Elevated CKMB (>5.2 ug/L)	14 (11.4)	25 (20)	21 (15.4)	37 (27)	0.278
Elevated CRP (>5 mg/L)	2 (1.6)	27 (22)	4 (2.9)	33 (24)	0.743
Elevated leukocytes (>10.5 x10^9/L)	4 (3.3)	5 (4)	3 (2.2)	5 (4)	0.888
Heart rate (bpm), median (IQR)	57.0 (51.0 to 65.8)	5 (4)	52.0 (46.0 to 57.0)	1 (1)	**<0.001**
ECG assessment (according to 2017 international athlete ECG criteria)		5 (4)		1 (1)	0.357
Normal	101 (82.1)		118 (86.8)		
Borderline	11 (8.9)		14 (10.3)		
Abnormal	6 (4.9)		3 (2.2)		

Borderline findings of ECG assessment

In elite athletes exposed to SARS-CoV-2, according to consensus document certain borderline ECG findings did not warrant additional examinations. This included left atrial enlargement (LAE) in five athletes, right atrial enlargement (RAE) in two athletes, right axis deviation (RAD) in one athlete, and complete right bundle branch block (RBBB) in one athlete. However, according to consensus document two athletes exposed to SARS-CoV-2 warrant additional examinations based on their borderline ECG findings, which included both LAE and RAE in one athlete, and RAD combined with RBBB in another athlete.

For the athlete controls who were not exposed to SARS-CoV-2, there were also borderline ECG findings that did not warrant additional examinations according to consensus document. These findings included LAE in six athletes, RAE in three athletes, and complete RBBB in two athletes. However, three athlete controls required further evaluation based on their borderline ECG findings, which included both LAE and RAE in two athletes, and prolonged QTc with biphasic T waves in lead V3 and V4 in one athlete.

Abnormal findings of ECG assessment

Abnormal ECG findings in elite athletes exposed to SARS-CoV-2 included prolonged QRS duration of 160ms combined with T-wave inversion (TWI) in lead I and aVL (n=1), left axis deviation (LAD) combined with 2 premature ventricular beats (PVBs) exhibiting right bundle branch block (RBBB) morphology (n=1), presence of 3 PVBs with left bundle branch block (LBBB) morphology (n=1), TWI in the inferior leads (lead II, III, and AVF) (n=1), TWI in lead V2 and V3 in a mature white athlete (n=1), and TWI in lead III and biphasic T-wave in lead aVF (n=1).

Among athlete controls not exposed to SARS-CoV-2, abnormal ECG findings included sinus rhythm combined with atrial tachycardia and a single premature atrial complex (n=1), J-point depression in lead III and aVF (n=1), and TWI in lead II, III, and V5 (n=1).

Prospective cardiovascular assessment

Population characteristics are presented in Supplemental Table 2. Within our prospective analyses, two athletes could not be included in the analysis of right ventricle functional and volumetric due to multiple CMR artefacts. In addition, one athlete had no T1-mapping images for native T1

assessment. In total 4 athletes were excluded from the ECG sub-analyses (no pre-SARS-CoV-2 ECG available). Additionally, from laboratory sub-analyses; HsTnT (n=2), NT-ProBNP (n=1), CKMB (n=13), and CRP (n=13) athletes were excluded as no pre-SARS-CoV-2 data was available.

Supplemental Table 2. Population characteristics of elite athletes with both pre- and post-SARS-CoV-2 cardiovascular assessment (prospective cardiovascular assessment).

	SARS-CoV-2 infected elite athletes n = 23
Age (years), mean (±SD)	26.8 (5.14)
Woman, n (%)	10 (43.5)
Ethnicity, n (%)	
Caucasian	21 (91.3)
African/Afro-Caribbean	1 (4.3)
West Asian (Arabic and Middle Eastern)	0 (0)
East Asian and South Asian	0 (0)
Latin America	1 (4.3)
Athletic discipline, n (%)	
Field hockey	1 (4.3)
Road cycling	3 (13.0)
Rowing	3 (13.0)
Football	2 (8.7)
Tennis	1 (4.3)
Track cycling	2 (8.7)
Water polo	6 (26.1)
Miscellaneous[a]	5 (21.7)
Professional athlete years, mean (±SD)	13.0 (5.0)
SARS-CoV-2 symptoms severity, n (%)	
Asymptomatic	0 (0)
Cardiovascular symptoms[b]	2 (9)
No cardiovascular symptoms	21 (91)

[a] *Miscellaneous: basketball (n=1), skateboarding (n=1), table tennis (n=1), and wheelchair basketball (n=2)*
[b] *Cardiovascular symptoms: chest pain (n=1, and both chest pain and palpitations (n=1)*

Case description of SARS-CoV-2 infected athletes with cardiac sequelae

Four (3%) male elite athletes, who engaged in mixed, high-intensity, competitive, acceleration-deceleration sports demonstrated pathological non-ischemic LGE patterns after confirmed SARS-CoV-2 infection. The LGE patterns showed distinct patterns of evolution over time and are shown in Figure 1.

Athlete A, with as main symptom cough (March 2020), initially demonstrated (CMR 5 months after infection) LV LGE of the basal to apical lateral myo- and pericardium, with normal native T1 relaxation time. However, CMR repeated at 8 and 18 months after infection demonstrated complete LGE resolution.

Athlete B had a fever and cough (March 2020), and initial CMR (5 months after infection) showed focal peri-/epicardial increased signal intensity at the inferolateral midventricular wall of the LV with pericardial effusion (PE) at the lateral wall; the LGE persisted without PE on repeated CMR 10 and 17 months after infection.

Athlete C had palpitations during a resting period after training 15 days after PCR- confirmed SARS-CoV-2 infection. The clinical course of this case has been extensively described elsewhere (1). Initial CMR demonstrated basolateral to midventricular posterior epicardial LGE with locally increased native T1 relaxation time (1232 ± 101ms). The athlete was diagnosed with focal COVID-19 myocarditis and was given a negative sports advice, which he adhered to. Repeated CMR nine months after infection showed resolution of all signs of ongoing myocardial inflammation but with persistent LGE.

Athlete D was referred for cardiovascular evaluation after demonstrating new inferolateral T wave inversions on ECG after a recent SARS-CoV-2 infection. Initial CMR 10 days after infection showed peri-/epicardial LGE at the inferolateral wall which persisted on CMR at 3 and 9 months. One month after the infection, there was a resolution of ECG abnormalities.

After a comprehensive multi-disciplinary evaluation (2), all four athletes made a complete return to elite competitive sports. Athletes A and B were not restricted from elite sports during follow-up (as there were no absolute contra-indications for sports in these athletes). Athletes C and D adhered to an extensive graduated return-to-play protocol before making a complete return to elite, competitive sports. All four athletes underwent intensive rhythm monitoring, including Holter monitoring during team-training sessions, which demonstrated no increases of PVCs over time and no complex ventricular tachycardias ((non-) sustained ventricular tachycardia).

References

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