

# Exercise-induced cardiac troponin T release in veteran athletes recovered from COVID-19

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Coronavirus disease 2019 (COVID-19) can cause myocardial injury as evidenced by increased resting cardiac troponin (cTn) concentrations.<sup>1</sup> Stressing the heart with exercise potentially increases sensitivity of detecting myocardial injury, as evidenced by exercise-induced cTn elevations.<sup>2</sup> Hence, exercise might reveal myocardial vulnerability, which could remain unrecognized under resting conditions. Therefore, we assessed exercise-induced high-sensitivity cardiac troponin T (hs-cTnT) release in middle-aged athletes recovered from COVID-19 and compared their response to matched controls. We hypothesized that athletes who recovered from COVID-19 would have greater exercise-induced cTn release compared to controls.

We recruited 32 male recreational endurance athletes aged 56 (interquartile range: 54–58) years from an ongoing cohort study<sup>3</sup> and via a newsletter from a local mass-participation running event. Eligible participants were contacted via e-mail and/or phone and invited to participate in this laboratory study. Participants were allocated to a COVID-19 group ( $n = 16$ ) or control group ( $n = 16$ ) and matched for age, sex, and cardiovascular risk factors (i.e. hypertension, hypercholesterolaemia, diabetes mellitus, family history of cardiovascular disease, and smoking status) at a group level. All COVID-19 participants had a positive polymerase chain reaction (PCR) test of a nasopharyngeal sample for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) within 6 months prior to study participation. Serology testing was not performed for the controls, but they had no signs or symptoms of COVID-19 nor a lifetime positive PCR prior to study participation. Participants performed a standardized yet personalized exercise test on a stationary bike (Lode Excalibur Sport, Groningen, Netherlands), consisting of a 30-min warm up with a gradually increasing workload, until they reached a stable heart rate at 70% of their

expected maximum heart rate. Maximal heart rate was obtained from training data, a previously performed exercise test or estimated based on age ( $208 - 0.7 \times \text{Age}$ ).<sup>4</sup> When 70% of maximum heart rate was reached, the workload was kept stable until 30 min of warming up had passed. Thereafter, workload increased by 5% at every 3 min until volitional exhaustion was reached, defining the end of the exercise test. During and following the exercise test, physiological measurements (i.e. heart rate, blood pressure, peripheral oxygen saturation, electrocardiography, perceived exercise intensity, lactate) were obtained. Blood samples were collected at the following 7 time points: baseline (before exercise), after the first 30 min of exercise and at 0, 30, 60, 120, and 180 min after exercise cessation. High-sensitivity cardiac troponin T concentrations were measured (Cobas 6000 analyzer, Troponin T Gen 5 STAT, Roche Diagnostics). An overview of the study protocol is presented in [Supplementary material online, Figure S1](#). The Medical Research Ethical Committee region Arnhem-Nijmegen approved this study (NL74326.091.20) and all participants provided written informed consent. Due to the skewed nature of hs-cTnT concentrations, data were logarithmically transformed prior to analyses. Data are presented as mean  $\pm$  standard deviation, median (interquartile range), or frequency (%). A mixed model analysis using random intercepts was performed to compare time-dependent changes in outcome measures between groups. All statistical tests were two-sided and  $P$ -values below 0.05 were considered as statistically significant.

Participant characteristics were comparable between groups ([Table 1](#)). Median time since COVID-19 diagnosis was 175 (166–183) days. One month after the onset of COVID-19 infection, 7 athletes (43.8%) did not exercise at all and 9 athletes (56.3%) exercised less

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**Table 1** Baseline characteristics and exercise test performance, total and split for different study groups

PARTICIPANT CHARACTERISTICS	Total (n = 32)	COVID-19 group (n = 16)	Control group (n = 16)	P-value
Age, years	56 (54–58)	54 (53–61)	57 (55–58)	0.18
Height, cm	182 ± 6	182 ± 6	184 ± 6	0.19
Body mass, kg	88.3 ± 10.4	86.9 ± 10.7	89.8 ± 10.1	0.44
BMI, kg/m <sup>2</sup>	26.7 ± 3.0	26.7 ± 3.4	26.7 ± 2.5	0.97
Blood pressure				
Systolic, mmHg	140 ± 13	139 ± 14	140 ± 11	0.81
Diastolic, mmHg	88 ± 9	87 ± 7	88 ± 10	0.70
Resting heart rate, b.p.m.	62 ± 10	63 ± 7	60 ± 12	0.24
Expected maximal heart rate, b.p.m.	172 ± 11	174 ± 9	169 ± 11	0.15
Cardiovascular risk factors	10 (31.3)	5 (31.3)	5 (31.3)	1.00
Hypertension, n (%)	2 (6.3)	1 (6.3)	1 (6.3)	1.00
Hypercholesterolaemia, n (%)	8 (25.0)	4 (25)	4 (25)	1.00
Statin users, n (%)	5 (15.6)	1 (6.3)	4 (25)	0.33
Diabetes mellitus, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	<sup>a</sup>
Family history of CV disease, n (%)	2 (6.3)	1 (6.3)	1 (6.3)	1.00
Smoking				
Current or stopped <2 years ago, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	<sup>a</sup>
Baseline blood tests				
hs-cTnT, ng/L	6.8 (5.6–8.8)	6.6 (5.3–7.9)	7.5 (5.9–9.9)	0.15
>LoD (2.85 ng/L), n (%)	32 (100)	16 (100)	16 (100)	<sup>a</sup>
>URL (14 ng/L), n (%)	0 (0.0)	0 (0.0)	0 (0.0)	<sup>a</sup>
<b>EXERCISE TEST PERFORMANCE</b>				
Exercise duration, min	72.1 (63.5–84.1)	72.1 (63.4–77.7)	73.0 (64.7–91.3)	0.56
Peak HR, b.p.m.	167 ± 14	167 ± 13	167 ± 14	0.98
Exercise intensity, %HR <sub>max</sub>	97.1 ± 6.1	95.6 ± 6.4	98.7 ± 5.6	0.15
Maximal workload, W	207 ± 42	189 ± 39	224 ± 38	0.016
Maximal workload, W/kg	2.37 ± 0.54	2.22 ± 0.59	2.52 ± 0.45	0.13
Lactate 2 min post-exercise, mmol/L	10.1 ± 4.0	9.9 ± 2.8	10.3 ± 5.1	0.93
Maximal RPE	19 (18–20)	19 (17–20)	19 (19–20)	0.12

%Hrmax, percentage of expected maximal heart rate; BMI, body mass index; CV, cardiovascular; HR, heart rate; hs-cTnT, high-sensitive cardiac troponin T; LoD, limit of detection; Maximal W/kg, maximal workload per kilogram of body weight; RPE, rating of perceived exertion scale (6 = very, very light–20 = maximal exertion); URL, 99% upper reference limit.

<sup>a</sup>Statistics could not be computed because this condition was absent/prevalent in all participants.

due to persisting symptoms. The exercise test lasted 72.1 (63.5–84.1) min with a peak heart rate of 167 ± 14 b.p.m. (97.1 ± 6.1% of HR<sub>max</sub>), which did not differ between groups (Figure 1). Maximal workload was significantly lower for the COVID-19 vs. control group (189 ± 39 W vs. 224 ± 38 W,  $P = 0.016$ ).

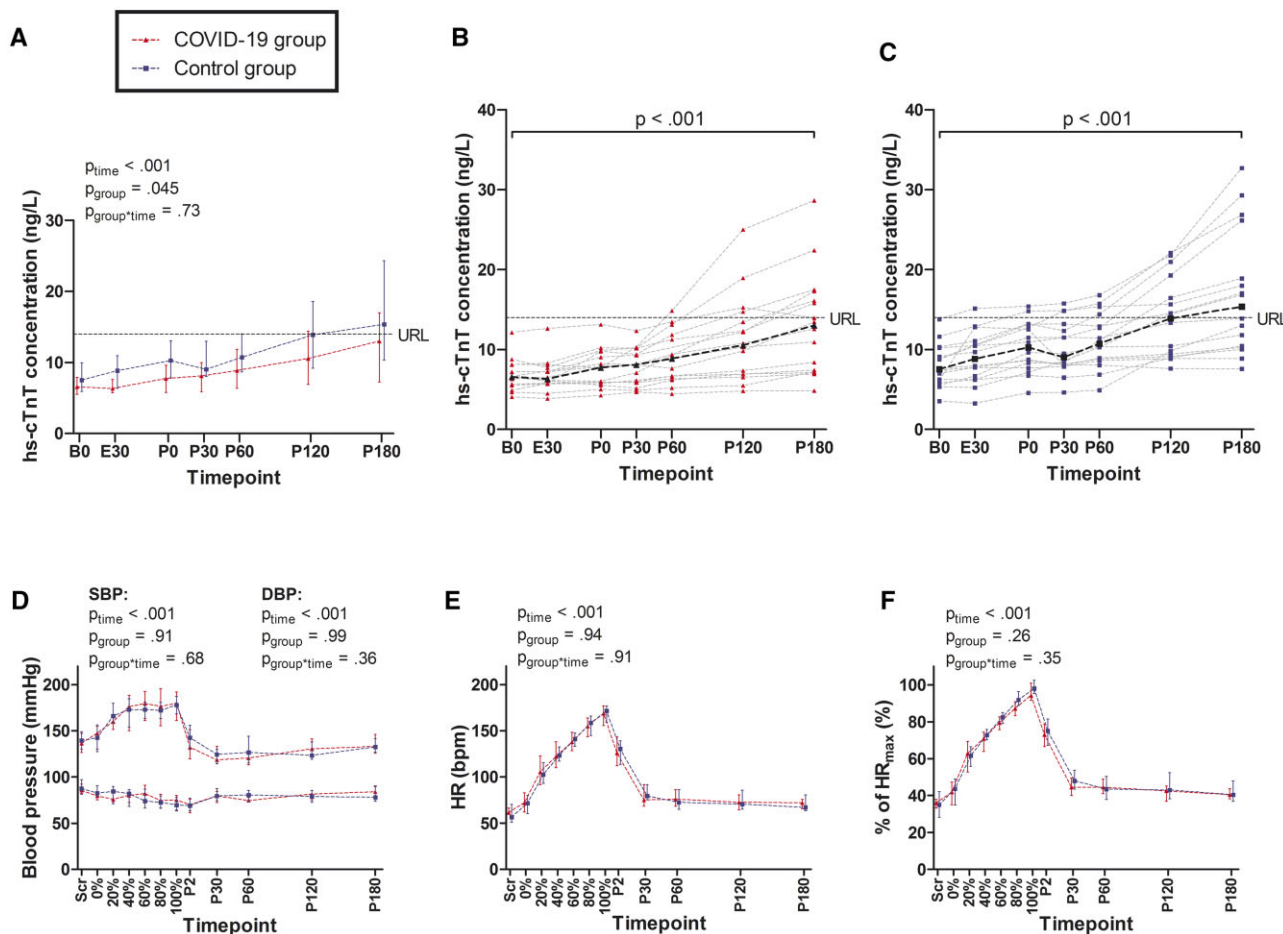
Baseline hs-cTnT concentrations did not differ between the COVID-19 [6.6 (5.3–7.9) ng/L] and control group [7.5 (5.9–9.9) ng/L,  $P = 0.15$ ]. High-sensitivity cardiac troponin T increased during and after exercise in the COVID-19 group [6.6 (5.3–7.9) ng/L to 13.0 (7.3–17.0) ng/L] and control group [7.5 (5.9–9.9) ng/L to 15.4 (10.3–24.3) ng/L,  $P < 0.001$ ], and hs-cTnT changes over time did not differ between groups ( $P = 0.73$ ). Peak hs-cTnT concentrations (at 180-min post-exercise) were slightly but significantly lower in the COVID-19 group compared to the control group ( $P = 0.045$ ).

To our knowledge, this is the first controlled study assessing exercise-induced hs-cTnT release in middle-aged athletes who recovered from COVID-19. The magnitude of exercise-induced cTn elevations, timing of peak concentrations and the prevalence of post-

exercise hs-cTnT concentrations above the upper reference limit align with findings from previous publications.<sup>2,5</sup> These observations show that the intensity and duration of our exercise protocol sufficiently stressed the heart to cause significant increases in hs-cTnT concentrations.

In contrast to our hypothesis, exercise-induced hs-cTnT release did not differ between groups and COVID-19 athletes even demonstrated lower peak hs-cTnT concentrations compared to controls ( $P = 0.045$ ). An explanation may be that exercise exposure was different between groups, which is known to impact exercise-induced cTn elevations.<sup>5</sup> Although, the absolute maximal workload was lower in the COVID-19 group compared to the controls, possibly due to COVID-19-related deconditioning, rating of perceived exertion scale, lactate concentration, exercise duration, and peak heart rate were comparable, which suggests that cardiac workload was similar across groups.

Second, cardiac involvement of COVID-19 may be less prominent than assumed. Rajpal et al.<sup>6</sup> found myocarditis in up to 15% of young



**Figure 1** Exercise-induced changes in hs-cTnT concentrations and physiological changes during exercise. No differences in changes in hs-cTnT concentrations were observed over time between the COVID-19 and control group ( $P = 0.73$ ), but average and peak hs-cTnT concentrations were significantly lower in the COVID-19 vs. control group ( $P = 0.045$ ) (A). Changes in individual hs-cTnT concentrations for the COVID-19 group (in red, B) and the control group (in blue, C) over time, with the group median in black. Time-dependent changes in blood pressure (D), heart rate (E), and percentage of maximal heart rate (F) for the COVID-19 group (in red) and control group (in blue). % of HR<sub>max</sub>, percentage of expected maximal heart rate; HR, heart rate; hs-cTnT, high-sensitivity cardiac troponin T; SBP/DBP, systolic/diastolic blood pressure, respectively; URL, 99% upper reference limit of 14.0 ng/L. hs-cTnT concentrations are presented at baseline (B0), after 30 min of warm up exercise (E30), and at  $t = 0$ ,  $t = 30$ ,  $t = 60$ ,  $t = 120$ , and  $t = 180$  min after exercise cessation (P0, P30, P60, P120, and P180, respectively). Physiological data are presented at screening (Scr), at 0%, 20%, 40%, 60%, 80%, and 100% completion of the exercise test, and at  $t = 2$ ,  $t = 30$ ,  $t = 60$ ,  $t = 120$ , and  $t = 180$  min after exercise cessation.

competitive athletes with COVID-19. However, previous studies did not include controls and were prone to several forms of bias, which may have led to overreporting of the prevalence of COVID-19-induced cardiac involvement.<sup>7</sup> Indeed, two large registries reported cTn elevations at rest and/or inflammatory heart disease in <1% of athletes.<sup>8,9</sup> Furthermore, a controlled cardiac magnetic resonance (CMR) study found definite signs of myocarditis in only 1.4% of athletes.<sup>10</sup> In addition, a recent systematic review concluded that athletes have an overall low risk (0–5%) of pericardial/myocardial involvement after recovery from COVID-19.<sup>11</sup> However, these studies<sup>8–11</sup> were conducted in young athletes (20–25 years), whereas it is known that COVID-19 is most severe at higher age. Findings from our study add to the current knowledge that even in middle-aged athletes hs-cTnT release was similar between athletes recovered from COVID-19 and

control subjects, both at rest and following an acute bout of vigorous-intensity endurance exercise.

Third, our participants were very fit and mostly had only mild to moderate symptoms. Only 1 out of 16 athletes (6.3%) required hospital admission due to COVID-19 symptoms and all were able to finish a 1–1.5 h exercise test. Possibly, more severely affected individuals might have shown more signs of cardiac involvement,<sup>12</sup> which could have led to exaggerated exercise-induced hs-cTnT elevations.

This study has several limitations. First, we did not measure hs-cTnT concentrations during COVID-19, which makes it harder to quantify the full magnitude of (potential) cardiac involvement at that time. Second, no cardiac imaging was available of (potential) COVID-19-induced myocardial injury. However, resting hs-cTnT concentrations significantly correlate with CMR findings<sup>13</sup> and troponin

elevations have been used to support CMR findings.<sup>9</sup> Since no abnormal hs-cTnT release was observed in our COVID-19 group, cardiac involvement at cardiac imaging seems rather unlikely. Third, our cohort is small and only consisted of male athletes. Nevertheless, this is the first controlled study to assess the impact of a prior COVID-19 infection on exercise-induced cTn release, whereas male sex is an independent predictor for worse outcomes of COVID-19.<sup>14</sup> Follow-up studies with a larger sample size and a more heterogeneous population (i.e. females, younger athletes, various ethnicities) are warranted to assess the extrapolation of our findings.

In conclusion, we found that middle-aged (>50 years) athletes who recovered from COVID-19 demonstrate similar exercise-induced hs-cTnT elevations following an endurance exercise test compared to non-COVID-19 controls. These findings may suggest that middle-aged athletes who recovered from COVID-19 do not demonstrate abnormal myocardial injury following a strenuous bout of exercise.

## Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

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## Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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