Time to negative conversion and cardiopulmonary performance in athletes with COVID-19

To the Editor:

Asymptomatic athletes positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, may start training during self-isolation after three days of physical training abstinence and in all individuals with prior coronavirus disease 2019 (COVID-19) a graded return to play regimen is recommended to ensure the monitoring of new onset cardiorespiratory symptoms [1]. Registries evaluating the involvement of cardiac abnormalities following SARS-CoV-2 infection in professional and collegiate athletes report rare adverse events [2]. However, the clinical implications of COVID-19 among athletes are still unknown.

SARS-CoV-2 is a single stranded RNA virus and reverse transcription (RT)-PCR screening test of respiratory specimens mainly obtained from nasal-pharynx swabs is still the gold standard for the diagnosis of COVID-19 infection and useful for the pandemic prevention and control. Negative conversion of SARS-CoV-2 RNA and clinical presentation of COVID-19 disease are essential for both hospitalised or patients in self-isolation. Older age, comorbidities, severity of COVID-19 disease and corticosteroid treatment has been associated with a longer time to negative conversion of SARS-CoV-2 infection [3]. Longer SARS-CoV-2 time to negative conversion may be explained by virus mutation, immune tolerance or impairment of immune system, however the relationship between a longer time to negative SARS-CoV-2 conversion and cardiopulmonary performance has not been evaluated. In this study, we aimed to explore if a prolonged RT-PCR time to negative conversion of SARS-CoV-2 is associated with impairment of cardiorespiratory performance in competitive athletes.

Forty-three competitive national football and basketball athletes with COVID-19 were included in this study. Competitive athletes train regularly for >10 h per week and participate in official sports competition [4]. The study protocol was approved by the Institutional Review Board of the Department of Medicine and Health Sciences University of Molise. All participants agreed to have their anonymised data used for research and gave written consent.

In all participants SARS-CoV-2 infection and negativisation were confirmed by RT-PCR swabs. The standard for negative conversion were two negative RT-PCR swabs in 24 h minimum sampling intervals. Time to negative conversion was calculated in days from the first positive to the first negative RT-PCR nasal-pharynx swab. Once negative for SARS-CoV-2 infection spirometry and cardiopulmonary exercise test (CPET) were performed in the same day, in accordance to recommended standards [5, 6]. The median age of participants was 23 years interquartile range (IQR): 18–27, 86% males. None of the participants was hospitalised. The median negative conversion time of SARS-CoV-2 was 21 days (IQR: 14–24). Fifty one percent of athletes presented persisting symptoms such as: myalgia, fatigue, cough or shortness of breath. For the purposes of this study the participants were divided in two groups according to the median conversion time: $\leqslant$21 days and >21 days. Compared with the participants with shorter time to negative conversion, those with longer time to conversion had a lower forced vital capacity (FVC): 4.8 l IQR: (4.2–5.4) *versus* 5.5 l IQR: (4.9–6.3) p=0.002; FVC % predicted 93.5% IQR: (88–100.5) *versus* 98% IQR: (94–108) p=0.005; and lower FEV_1: 4.2 l IQR (3.7–4.5) *versus* 4.6 l (4–5.2) p=0.024. Participants with longer time to negative conversion did not differ regarding peak oxygen uptake ($V'O_2$) ml·kg^{-1}·min^{-1} and peak $V'O_2$ expressed as percentage of predicted $V'O_2$. In addition, peak heart rate (HR), oxygen pulse, peak respiratory exchange ratio and tidal volume expressed as percentage of peak $V'O_2$ registered during exercise

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Athletes with longer time to negative conversion for COVID-19 do not present reduction of exercise capacity. However, respiratory and ventilatory parameters are modified. https://bit.ly/3TMdrFL

test were not different in participants with shorter or longer time to negative SARS-CoV-2 conversion. Ventilatory equivalent for carbon dioxide ($V'_E \cdot V'_{CO_2}{}^{-1}$) slope increased significantly in athletes with longer time to negative conversion: 29.6 IQR (27.7–32.3) *versus* 27.3 IQR (25.5–29.6) p=0.034. (table 1). To identify whether longer time to negative conversion was independently associated with a higher $V'_E \cdot V'_{CO_2}{}^{-1}$ slope a multivariate analysis was performed. In this model time to negative conversion was adjusted for confounders which influence $V'_E \cdot V'_{CO_2}{}^{-1}$ slope as age and sex, FVC, forces expiratory volume in 1 s (FEV$_1$), smoking status and asthma. In addition, persisting symptoms at the time of the enrolment were also considered. As resulted from the analysis $V'_E \cdot V'_{CO_2}{}^{-1}$ slope was significantly associated with time to negative SARS-CoV-2 conversion in our population. Coefficient β: 0.16; R2 0.0.45 95% confidence interval (CI) 0.006–0.318; p=0.042, and longer time to negative conversion was associated with higher $V'_E \cdot V'_{CO_2}{}^{-1}$ slope values. Relationship between FVC, FEV$_1$, and time to negative conversion was also investigated with multivariable regression analysis. Time to negative conversion resulted inversely and independent associated with FVC: Coefficient β: −0.04 95% p=0.016. Between FEV$_1$ and time to negative conversion did not result significant association: Coefficient β: −0.02 95% CI −0.04–0.006 p=0.141.

Respiratory function in athletes following COVID-19 diseases has been evaluated by different studies. In a previous study we reported a reduction of FEV$_1$% in post-COVID-19 athletes compared to healthy controls [7]. Similar results were also described by another study, where abnormal spirometry was present in 42% of post-COVID-19 athletes with abnormal FEV$_1$ and FEV$_1$/FVC [8]. Lower levels of cluster of differentiation (CD)3$^+$CD4$^+$ lymphocytes have been associated to impairment of immune system and

TABLE 1 Characteristics of overall population and stratified by time to negative conversion of severe acute respiratory syndrome related coronavirus 2 (SARS-CoV-2) RNA infection

Characteristics of population	All population (N=43)	Time to negative conversion[#] ⩽21 days (N=23)	Time to negative conversion>21 days (N=20)	p-value
Age years, median (IQR)	23 (18–27)	24 (20–28)	21.5 (18–25)	0.24
Males, n (%)	37 (86)	20 (86.9)	17 (85)	0.853
BMI kg·m^{-2}, median (IQR)	23.5 (22.7–24.6)	23.8 (22.8–24.9)	22.9 (22.2–24.2)	0.062
Persisting symptoms, n (%)	22 (51.2)	12 (52.2)	10 (50)	0.887
Time to negative SARS-CoV-2 conversion, median (IQR)	21 (14–24)	14 (12–19)	24 (22–28)	⩽0.0001
Time to spirometry and CPET[¶], median (IQR)	3 (1–6)	4 (2–7)	2 (1–5)	0.152
FVC$_1$, median (IQR)	5.3 (4.4–5.7)	5.5 (4.9–6.3)	4.8 (4.2–5.4)	0.002
FVC % pred, median (IQR)	97 (91–103)	98 (94–108)	93.5 (88–100.5)	0.005
FEV$_1$, median (IQR)	4.3 (3.9–4.8)	4.6 (4–5.2)	4.2 (3.7–4.5)	0.024
Resting HR, median (IQR)	62 (56–67)	63 (59–71)	59.5 (50–67)	0.164
Resting SBP mmHg, median (IQR)	120 (110–120)	120 (110–120)	120 (100–120)	0.128
Resting DBP mmHg, median (IQR)	70 (70–80)	80 (70–80)	70 (65–80)	0.612
Resting V'_{O_2} ml·kg^{-1}·min^{-1}, median (IQR)	4.3 (3.6–4.7)	4.1 (3.6–4.5)	4.5 (3.6–5.4)	0.082
Peak HR, median (IQR)	172 (167–179)	173 (167–179)	171.5 (166.5–178)	0.698
Peak SBP mmHg, median (IQR)	175 (170–180)	170 (170–180)	180 (170–180)	0.552
Peak V'_{O_2} ml·kg^{-1}·min^{-1}, median (IQR)	47.2 (38.3–50.9)	46.5 (38.3–50.9)	47.8 (39.1–50.6)	0.713
Peak V'_{O_2}% pred, median (IQR)	108 (91–116)	106 (87–111.6)	108.5 (96–115)	0.659
Oxygen pulse ml·kg^{-1}·min^{-1}·beat^{-1}, median (IQR)	21.8 (17.5–24.8)	22.8 (17.5–25.2)	20.5 (18–23.9)	0.363
Peak V'_E l·min^{-1}, median (IQR)	104.8 (92.4–127.6)	103.5 (91.8–130.4)	105.35 (97.35–123–05)	0.665
Peak RER, median (IQR)	1.1 (1.05–1.14)	1.1 (1.05–1.17)	1.1 (1.04–1.13)	0.386
V'_E/V'_{CO_2} slope, median (IQR)	28.4 (26.1–30.3)	27.3 (25.5–29.6)	29.6 (27.7–32.3)	0.034
1st VT % V'_{O_2} pred, median (IQR)	73.9 (70.9–79.3)	73.7 (71.5–81.4)	74.2 (70.4–78.6)	0.918
RER at 1st VT	0.96 (0.9–1.01)	0.96 (0.92–1.01)	0.92 (0.86–1)	0.406
Breathing reserve %, median (IQR)	38.4 (31–44.4)	38.4 (32.3–47.2)	37.9 (30.4–43.2)	0.365
Peak S_{pO_2}%, median (IQR)	96 (95–97)	96 (95–97)	96 (95–97.5)	0.18

BMI: body mass index; IQR: interquartile range; FVC: forced vital capacity; FEV$_1$: forced expiratory volume in 1 s; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; V'_{O_2}: oxygen uptake; V'_E: ventilation; S_{pO_2}: oxygen saturation; pred.: predicted; RER: respiratory exchange ratio; V'_{CO_2}: carbon dioxide uptake; 1st VT: first ventilatory threshold. [#]: Time to negative SARS-CoV-2 conversion: time from the first positive RT-PCR nasal-pharynx swab to the first- negative RT-PCR (reverse transcription polymerase chain reaction) naso-pharynx swab. [¶]: Time to spirometry and CPET: time from the negative RT-PCR naso-pharynx swab to spirometry and CPET evaluation.

delayed negative conversion of SARS-CoV-2 infection [9] and CD4$^+$ T-cells correlate with clinical characteristics and lung function of patients with chronic obstructive lung disease [10]. However, the specific mechanisms which link the immune response, lung function and SARS-CoV-2 infection need clarification and further studies are necessary.

In our study time to negative conversion did not influence peak V'_{O_2} and O_2 pulse, indicating no modification on exercise capacity and stroke volume. It should be mentioned that all participants of our study presented mild COVID-19 disease and hospitalisation was not necessary.

Both univariate and multivariate analysis in our study indicated a significant positive correlation between time to negative conversion and $V'_E \cdot V'_{CO_2}^{-1}$ slope. $V'_E \cdot V'_{CO_2}^{-1}$ slope over 30 are considered abnormal and this is attributed to increased VE to perfusion ratio, enhanced ventilatory reflex sensitivity or a combination of both mechanisms [11]. A previous study has described higher $V'_E \cdot V'_{CO_2}^{-1}$ slope in COVID-19 survivors with worse disease severity compared to mild to moderate: 27.1±2.6 *versus* 29.8 ±3.9 p=0.02 but without clinical significance [12]. In line this study, we also did not observe reduced exercise capacity. Airway obstruction, hyperventilation and reduced lung perfusion may be the main clinical conditions associated with high $V'_E \cdot V'_{CO_2}^{-1}$ slope [13–15]. In addition, reduced exercise capacity and impaired ventilatory efficiency were present in smokers without airflow obstruction [16]. Other components of respiratory performance during exercise as peak VE, breathing reserve and S_{pO_2} were not significantly different in participants with longer or shorter time to negative SARS-Cov-2 conversion, and oscillatory breathing pattern was not observed in none of the patients. However, participants with longer time to negative conversion presented lower spirometry parameters as FEV_1 and FVC and higher $V'_E \cdot V'_{CO_2}^{-1}$ slope compared to those with shorter time to negative conversion. MOULSEN *et al.* also reported that CPET identified abnormal spirometry in 42% of post-COVID-19 athletes [8]. Of interest another study, did not find association between persisting symptoms, perceived functional limitation and dysautonomia, but observed a significant association between dysautonomia and steeper $V'_E \cdot V'_{CO_2}^{-1}$ slope in post-COVID-19 patients [17], suggesting a central mechanism of ventilation impairment related to SARS-CoV-2 infection.

A limitation of our study is related to asymptomatic athletes which may have encountered SARS-CoV-2 infection before performing RT-PCR nasal-pharynx swabs. However, in all athletes participating in competitive sports, nasal-pharynx swabs were performed periodically every four days and before participating in a competition as indicated by national guidelines.

Competitive athletes with longer time to negative SARS-CoV-2 conversion do not present reduction in exercise capacity compared to athletes with shorter time to negative conversion. A longer time to negative conversion is independently associated to steeper $V'_E \cdot V'_{CO_2}^{-1}$ slope and lower FVC.

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