

## ORIGINAL ARTICLE

# Cardio-pulmonary function among children with mild or asymptomatic COVID-19 infection needing certification for return-to-play

Daniela Chicco,<sup>1</sup> Francesco Rispoli,<sup>2</sup> Laura De Nardi <sup>2</sup>, Sara Romano,<sup>2</sup> Michele Mazzolai <sup>2</sup>, Marco Bobbo,<sup>1</sup> Irena Tavcar,<sup>3</sup> Gilberto Cattarini,<sup>4</sup> Laura Badina,<sup>1</sup> Egidio Barbi <sup>1,2</sup> and Massimo Maschio<sup>1</sup>

<sup>1</sup>Department of Pediatrics, Institute for Maternal and Child Health IRCCS “Burlo Garofolo”, <sup>2</sup>Department of Medicine, Surgery and Health Sciences, University of Trieste, <sup>3</sup>Cardiovascular Department, Sport Medicine Unit, Maggiore Hospital of Trieste, A.S.U.G.I., Trieste and <sup>4</sup>Cardiovascular Department, Sport Medicine Unit, Gorizia-Monfalcone Hospital, A.S.U.G.I., Gorizia, Italy

**Aim:** To explore the cardio-pulmonary function of children returning to play sports after mild or asymptomatic SARS-CoV-2 infection.

**Methods:** This is a consecutive case series conducted at the Institute for Maternal and Child Health, Trieste, Italy. Paediatric patients who accessed the Institute for cardiologic and pneumological evaluation before the return-to-play competitive sports were recruited, according to the Italian Sports Medical Federation recommendations. Echocardiogram, electrocardiogram, treadmill ECG test and pulmonary function tests were performed.

**Results:** One hundred and thirty-two patients (aged 8–17 years old, mean age  $12.8 \pm 2.5$ ) were recruited. Among these, 127 children were considered for the final analysis (49.6% females). Out of 127, 84 (66.1%) had a mild symptomatic form of SARS-CoV-2 infection, while 43 (33.9%) were asymptomatic. The main referred symptoms were fever ( $n = 37$ , 44%), asthenia ( $n = 14$ , 16.7%), rhinitis ( $n = 16$ , 19%), ageusia ( $n = 19$ , 22.6%), anosmia ( $n = 24$ , 28.6%), sore throat ( $n = 3$ , 3.6%), cough ( $n = 9$ , 10.7%), arthralgia-myalgia ( $n = 11$ , 13.1%), headache ( $n = 23$ , 27.4%) and gastrointestinal symptoms ( $n = 7$ , 8.3%). No child presented evidence of cardio-pulmonary function impairment after an average time of 77.3 days (SD 35) from SARS-CoV-2 swab positivity and a median of 68 days (IQR 52, IQR 92.5).

**Conclusion:** This preliminary study suggests that, in the absence of specific symptoms, the diagnostic yield of cardio-pulmonary tests before returning to play sports may be very low.

**Key words:** adolescent; COVID-19; return-to-play; sport.

## What is already known on this topic

- 1 Several guidelines and consensus documents have been created to regulate a safe return-to-play for athletes with a history of COVID-19 infection.
- 2 Adult evidence of cardiac and pulmonary disease persistence after moderate or severe COVID-19 infection led to the prudent need of multiple medical tests before sport readmission.
- 3 Few data are available in literature on children and young athletes needing return-to-play sport.

## What this paper adds

- 1 This study explores the impact of mild or asymptomatic SARS-CoV-2 infection on the pulmonary and cardiac function of paediatric patients needing certification for return-to-play.
- 2 It shows that occult cardio-pulmonary involvement is unlikely to occur in such population.
- 3 The results of this study could be interesting for sport health professionals in order to better analyse the cost-effectiveness of such an amount of required medical tests for children, families and the National Health System overall.

In December 2019, a severe acute respiratory syndrome known as SARS-CoV-2 disease broke out in Wuhan and by March 2020 the World Health Organisation (WHO) designated it as COVID-

19 pandemic.<sup>1</sup> It affected every aspect of life including sport and at first people were obliged to stop playing physical activities. Successively several guidelines and consensus documents have been developed in order to regulate a safe return-to-play (RTP) for athletes.<sup>2–5</sup> This conservative approach derives from several studies in adults demonstrating cardiac and pulmonary disease persistence, especially after moderate or severe COVID-19 infection.<sup>6–8</sup> Moreover, signs of cardiac involvement were detectable after months on MRI even in patients who had an asymptomatic or mildly symptomatic course.<sup>9,10</sup> All these elements, along with

**Correspondence:** Dr Laura De Nardi, University of Trieste – Via dell’Istria 65/1 – 34137, Trieste, Italy. Fax: +39040 378 5111; email: laura.denardi1993@gmail.com

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the concerning about the known association between occult myocarditis and sudden cardiac death during physical exercise,<sup>11</sup> led athletes to the need of undergoing several cardio-pulmonary tests before getting permission to return to competitive activities. Such approach, based on a cardiovascular risk stratification, has been endorsed by the Italian Sports Medical Federation (FMSI) protocol, in agreement with the American College of Cardiology's Sports and Exercise Cardiology Section guidelines, which also address children.<sup>2–5,12</sup>

However, paediatric literature on the topic is poor and guidelines are not uniform, varying from the need of minimal to more invasive medical tests. Echocardiogram, electrocardiogram (ECG), pulmonary function test, ergometric test and Holter-ECG are usually performed, depending on the clinical history of SARS-CoV-2, but in some cases computed tomography (CT) and cardio-pulmonary ergometric test can be required.

This study aims to explore the cardio-respiratory function of a paediatric cohort of athletes with a history of mild or asymptomatic SARS-CoV-2 undergoing through the FMSI protocol evaluation before RTP.

## Methods

This is a consecutive case series conducted between 1 December, 2020, to the 30 April, 2021, at the Institute for Maternal and Child Health 'Burlo Garofolo' of Trieste, Italy. Eligible patients were young athletes between 8 and 17 years performing sport at a competitive level, who experienced a history of mild symptomatic or asymptomatic SARS-CoV2 infection. According to the FMSI protocol in force in Italy at the time of data collection, such athletes required cardiological and pneumological evaluation before RTP comprehensive of ECG, echocardiogram, pulmonary function test and ergometric test. Inclusion criteria encompassed having a history of laboratory confirmed asymptomatic or mild symptomatic SARS-CoV-2 infection provided by a positive real-time-PCR test on a nasal swab specimen. Severity of SARS-CoV-2 infection was classified according to the National Institutes of Health (NIH) guidelines.<sup>13</sup> Patients with a laboratory-confirmed diagnosis of SARS-CoV-2 who were completely asymptomatic were categorised as 'asymptomatic infection', while those with mild symptoms (fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhoea, loss of taste and smell) and a laboratory-confirmed diagnosis, in the absence of dyspnea or radiological chest abnormalities, were included among 'mild symptomatic infection'. Exclusion criteria included having experienced a Multi-System Inflammatory Syndrome (MIS-C),<sup>14</sup> a moderate or severe SARS-CoV2 infection<sup>13</sup> and having a preexisting heart or lung disease. Controlled asthma was not considered an exclusion criterion.

For each enrolled patient, demographic variables (age, gender, weight and height), symptoms of SARS-CoV2 infection and clinical data from the cardiological and pneumological evaluations before RTP were collected. After obtaining the informed consent to take part in the study, data were collected from patient's clinical records and stored in an anonymised Microsoft Office Excel file. The Local Ethical Committee approved the study. Ethics Committee and approval number: IRB, RC 14/20.

The cardiological evaluation consisted of ECG, echocardiogram and a treadmill ECG test (effort test). Basal ECG was evaluated to

detect the presence of any arrhythmia, conduction disturbance and anomalies of ventricular repolarization. Treadmill ECG test was performed following the Bruce protocol to exclude the occurrence of desaturations or arrhythmias.<sup>15</sup> Echocardiographic examination was performed by a paediatric cardiologist using the cardiac ultrasound device Vivid E95 (E95, GE Health Care Milwaukee, WI, USA). Left ventricular (LV) end-diastolic volume (EDV) and LV ejection fraction (EF) were obtained from the apical four-chamber view through the two-dimensional echocardiography mode. The two-dimensional and echo colour-Doppler modalities also studied for the presence of pericardial effusion, valvopathy and myocardial wall motion assessment. Pulsed-wave Doppler was performed at the apical four-chamber view to assess mitral inflow velocity in the early phase (*E*-wave). Pulsed tissue Doppler imaging was conducted at the apical four-chamber view, positioning the sample volume at the septal and lateral insertion of the mitral leaflets, to obtain the early diastolic annular velocity (*e'*). The *E/e'* ratio was then obtained and used to assess the intra-cardiac filling pressure.

The pneumological evaluation was performed using a spirometer (MIR Spirolab, MIR-Medical International Research USA, New Berlin, WI, USA) capable of measuring the maximum volume ventilation (MVV). The spirometric pulmonary function parameters included in the study are the Forced Expiratory Volume in the first second (FEV1), Forced Vital Capacity (FVC), Peak Expiratory Flow (PEF), Forced Expiratory Flow (FEF25–75%) and MVV. Spirometric parameters were reported as absolute and percentage of the theoretical values for age, weight and height.<sup>16</sup> Parametric data indexed for age, sex and height were used when available.

According to the RTP FMSI protocol, the cardiological and pneumological evaluations were performed after at least 30 days of complete recovery from symptoms or after 30 days from the swab positivity.

## Statistical analysis

Continuous data were presented as means (SDs) or medians (IQRs), they were compared with Student's *t*-test or Mann–Whitney–Wilcoxon test for statistical analysis, after testing for normality of distributions using Shapiro–Wilk test. Categorical variables were expressed as numbers (%) and compared by the  $\chi^2$  test or Fisher's exact test. All analyses used two-sided tests, and *P*-values < 0.05 were considered statistically significant. Statistical analysis was performed using SPSS software version 26.0 (IBM).

## Results

One hundred and thirty-two patients were recruited. All patients accepted to be enrolled in the study. Among these, five patients were excluded for the evidence of a preexisting lung or hearth condition (four patients for a history of not controlled asthma and one for congenital vascular ring). Demographic data, results and timing of cardio-pulmonary function tests are summarised in Table 1. Basal ECG and echocardiography were normal in all patients. No ischemia, arrhythmias or conduction and repolarization abnormalities were detected among the tested subjects. Stress-test ECG showed rare, isolated ventricular premature beats (VPB) and supraventricular premature beats (SVPB) in six (6.5%) cases. In one case, these findings could be explained

**Table 1** Demographic, cardio-pulmonary function and clinical data

Demographic data		(Total <i>n</i> = 127)		
Females, <i>n</i> (%)	63 (49.6)			
Males, <i>n</i> (%)	64 (50.4)			
	<b>Mean</b>		<b>SD/IQR</b>	
Age (years)	12.8		2.5	
Weight (kg)	51.8		13.7	
Height (cm)	160		15.4	
(% of the theoretical)				
Spirometric parameters	<i>n</i>	Mean	SD	
FVC (%)	115	99.3	14.4	
FEV1 (%)	115	99.8	12.6	
PEF (%)	74	94.6	15.4	
FEF25–75% (%)	69	99.7	23.8	
FEV1/FVC ratio (%)	115	101	8	
MVV (%)	110	94.7	15.8	
Echocardiographic parameters				
	<i>n</i>	Median	Q1 – Q3	
EF (%)	112	65	62–68	
LVEDV (mL/m <sup>2</sup> )	109	53	45–63	
<i>E/e'</i>	39	7	6–8	
GLS (%)	9	–21	–21,3 to –19,5	
Symptoms (for mild symptomatic group)				
	<i>n</i>	%		
All	84	66.1		
Rhinitis	16	19		
Fever	37	44		
Sore throat	3	3.6		
Cough	9	10.7		
Asthenia	14	16.7		
Anosmia	24	28.6		
Ageusia	19	22.6		
Headache	23	27.4		
Gastrointestinal	7	8.3		
Palpitations	0	0		
Chest pain	0	0		
Arthralgia-Myalgia	11	13.1		
Timing of performed investigation				
	Average days	SD	Median	Q1–Q3
After swab positivity	77.3	35	68	52–92.5

FEF25–75%, forced expiratory flow; FEV1, forced expiratory volume in the first second; FVC, forced volume capacity; GLS, global longitudinal strain; IQR, interquartile range; LVEDV, left ventricular end-diastolic volume; *E/e'*; MVV, maximum volume ventilation; PEF, peak expiratory flow; SD, standard deviation; SV, stroke volume.

by a concomitant thyroid disease. In the other cases, all premature beats were supraventricular and disappeared during the effort test with the onset of sinus tachycardia. For this reason, they were not considered signs of myocardial injury. Oxygen saturation monitoring was normal at rest, on effort and on recovery

**Table 2** Differences between mild symptomatic and asymptomatic groups

	Symptomatic	Asymptomatic	
Spirometric parameters (% of the theoretical)			
	Mean (SD)	Mean (SD)	<i>P</i> -value
FVC (%)	101.3 (15.5)	94.9 (13.6)	0.03
FEV1 (%)	101 (13.7)	96.4 (11.2)	0.07
FEF25–75% (%)	95.6 (21.4)	105 (28.9)	0.13
PEF (%)	96.1 (16.6)	89.3 (13.1)	0.08
FEV1/FVC ratio (%)	100.7 (8.1)	101.1 (9.1)	0.83
MVV (%)	97.6 (16.9)	89 (11.6)	0.01
Echocardiographic parameters			
	Median (IQR)	Median (Q1–Q3)	
EF (%)	65 (62–68)	65 (62–67)	0.27
LVEDV (mL/m <sup>2</sup> )	54 (46–68.5)	51 (45–58)	0.17
<i>E/e'</i>	7 (7–8)	6.5 (6–7)	0.14
GLS (%)	–20.9 (–21.3; –19.2)	–21 (–21.4; –20.3)	0.91

FEF25–75%, forced expiratory flow; FEV1, forced expiratory volume in the first second; FVC, forced volume capacity; GLS, global longitudinal strain; IQR, interquartile range; LVEDV, left ventricular end-diastolic volume; *E/e'*; MVV, maximum volume ventilation; PEF, peak expiratory flow; SD, standard deviation; SV, stroke volume.

in all subjects (being always over 96% with no evidence of desaturation). All echocardiographic parameters were within normal range for age and concerning pulmonary function, FVC, FEV, FEV1/FVC were well above the 70% of the predicted values for each of the participants. Among a total of 127 patients, 84 (66.1%) had a mild symptomatic form of COVID-19 infection. Referred symptoms were fever (*n* = 37, 44%), asthenia (*n* = 14, 16.7%), rhinitis (*n* = 16, 19%), ageusia (*n* = 19, 22.6%), anosmia (*n* = 24, 28.6%), sore throat (*n* = 3, 3.6%), cough (*n* = 9, 10.7%), arthralgia-myalgia (*n* = 11, 13.1%), headache (*n* = 23, 27.4%) and gastrointestinal symptoms (*n* = 7, 8.3%). We also compared cardio-pulmonary function data of patients with an asymptomatic infection course with those who reported symptoms. No significant difference was found, except for the FVC and MVV values, which were slightly higher in symptomatic patients (Table 2). The average timing of investigations performed was 77.3 days (SD 35) after COVID-19 swab positivity, with a median of 68 days (IQ1 52, IQ3 92.5).

## Discussion

This study shows that no child of our cohort of athletes with a history of asymptomatic or mild symptomatic SARS-CoV2 infection presented any limitation in terms of pulmonary or cardiovascular function.

COVID-19 pandemic entailed numerous consequences on sport activities like postponements and suspensions of sporting events to minimise the spreading of the virus. Without enough literature evidence on the cardio-pulmonary risk of early sport

readmission, the suspicion of cardiorespiratory sequelae after SARS-CoV-2 infection produced careful health recommendations to support a safe RTP.<sup>17</sup> The concern about possible development of cardio-respiratory impairment after COVID-19 infection derives from some adult literature reporting a high prevalence of cardiac and lung injury in patients hospitalised with severe infection.<sup>6–8,17</sup> Few data are available regarding the extent of occult myocardial injury after asymptomatic or mildly symptomatic cases of COVID-19 infection.<sup>9,10,18,19</sup> Moreover, the difficulty to distinguish COVID-19-associated cardiac injury from cardiac adaptation among athletes led the current international guidelines to recommend a conservative RTP approach for competitive athletes, entailing several medical tests based on a cardiac disease risk stratification.<sup>3,20</sup> Remarkably, specific paediatric indications for RTP have been developed only by the American College of Cardiology's Sports and Exercise.<sup>21</sup> Although highlighting the lower burden of disease risk in children when compared with adult population, these guidelines argue the limited sensitivity of isolated ECG screening for the detection of myocarditis (47%) and underline the importance of a screening algorithm stratified on the clinical severity of infection.<sup>11</sup> It is well known that children have different infection rates, symptoms and mortality compared to adults.<sup>22</sup> Moreover, they develop a relatively mild disease with rates of 83% of mild to moderate infection, 13–26% asymptomatic, and only 3% presenting with severe illness.<sup>22,23</sup> Critical illness mainly includes an adult-like severe pneumonia requiring oxygen or mechanical ventilation and the Multisystem Inflammatory Syndrome associated with COVID-19.<sup>14,22,23</sup> Besides these last two conditions where cardiac and lung damage is well reported and regular follow-up with heart magnetic resonance and pulmonary function tests is mandatory, multisystem complications are not highlighted in children with mild and asymptomatic disease. Furthermore, in mild and asymptomatic infections, full recovery is reported to occur within a few weeks of acute disease onset<sup>24</sup> and the risk of myocarditis seems to be very low for such group of children. This is probably due to the fact that SARS-CoV-2 infection acts differently in children, mimicking other common viruses such as rhinovirus, other coronavirus or influenza virus.<sup>24</sup>

This study shows that none of the analysed athletes developed cardiac or pulmonary sequelae after a short-term follow-up. As a matter of fact, this preliminary evidence suggests a very limited risk of cardiac and pulmonary consequences after asymptomatic and mild COVID-19 paediatric infection. Although guided by a precautionary attitude, the weight of all the investigations required to readmit children to sport should not be under-estimated. In fact, the impact on children and families and the economic burden for the National Health System of a 'mass testing', poorly justified by evidence, should be considered. If further confirmed, these data should challenge the real need to perform different clinical tests to let thousands of young athletes return-to-play after asymptomatic and mild symptomatic SARS-CoV-2 infection.

Limits of this study include the small number of children enrolled at a single centre and the absence of a longitudinal follow-up. Furthermore, the diagnosis of myocarditis should not be definitively ruled out without cardiac MRI and troponin levels. Nevertheless these tests have not been included in FMSI protocol, considering their high impact on resources and the low expected diagnostic yield, particularly in asymptomatic children with mild COVID-19 infection. The point of strength is the sound methodology of patients' testing.

## Conclusion

This study shows that occult cardio-pulmonary involvement of children after mild symptomatic and asymptomatic SARS-CoV2 infection is unlikely to occur. In absence of specific symptoms, the diagnostic yield of cardio-pulmonary test before returning to play may be very low. Further data on a larger cohort of patients are needed to confirm such results.

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Matisse Fish by Cody Tracy (age 8) from Operation Art 2021