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LETTER

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Cardiopulmonary exercise testing in children six months after COVID-19

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1 | INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has spread worldwide since March 2020, causing the coronavirus disease 2019 (COVID-19), mainly a respiratory disease, that can present in the pediatric age with protean clinical manifestations.

After each pandemic peak, clinicians reported a growing number of patients with persistent symptoms after the SARS-CoV-2 infection. This syndrome has been named "long-COVID," characterized by a broad range of manifestations that impair everyday life. Initially described only in adults, reports about a minor pediatrics form of the syndrome slowly increased, despite the prevalence and severity of long-COVID in children are not well defined.[1]

In adults, both spirometry and cardiopulmonary exercise testing (CPET) alterations are reported in COVID-19 survivors 3 months after SARS-CoV-2 infection,[2,3] whereas there are no data about the decline of physical performance or lung function in pediatric COVID-19 survivors. Thus, we evaluated the pulmonary and cardiac functional capacity of children that experienced moderate or severe COVID-19 by performing CPET 6 months after SARS-CoV-2 infection.

2 | METHODS

2.1 | Patients

From March 2020 to October 2021, 251 children were admitted to our department for a positive SARS-CoV-2 molecular test or positive serology. Exclusion criteria were: admission for other diseases with an incidental diagnosis of COVID-19 or mild COVID-19, Multisystem Inflammatory Syndrome, presence of previous severe pulmonary diseases or other chronic conditions, absence of adequate physical characteristics (height ≥ 125 cm, weight ≥ 25 kg, minimum age 8 years) to successfully perform the CPET on the cycle ergometer. After all, 13 children were enrolled in the CPET study protocol.

2.2 | Protocol

All patients underwent a maximal incremental exercise test conducted on an electronically-braked cycle ergometer (Ebike V2, GE Fairfield for subjects of >135 cm; Excalibur, Lode, BV, NL for subjects of <135 cm) using a metabolic cart (VyntusTm CPX, CareFusion Australia Pty Ltd, Becton-Dickinson Company) with a continuous acquisition of flows, volumes, and respiratory gases, integrated with an ECG monitoring system (GE Cardiosoft, GE Healthcare) as previously detailed[4] and according to international guidelines.[5] Ventilation, oxygen uptake ($V'O_2$, expressed in $mL/min^{-1}/kg^{-1}$), respiratory exchange ratio (RER), and transcutaneous oxygen saturation were collected for further analysis. The cardiac frequency at peak exercise (HRmax) and 1 min after peak-exercise were used for heart rate recovery (HRR-1) computation, where HRR-1 is HRmax – HR at 1 min after peak exercise.

Written consent to participate in the study was obtained from at least one parent. Patients' data were deidentified. The study protocol was approved by the Ethics Committee of the Città della Salute e della Scienza di Torino.

TABLE 1 Clinical features, pulmonary function tests, and cardiopulmonary exercise testing (CPET) at 6 months postdischarge follow-up.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13
Illness severity	severe	moderate	moderate	moderate	moderate	moderate	moderate	moderate	moderate	moderate	moderate	moderate	moderate
Gender	M	M	M	M	F	M	F	F	M	M	M	M	M
Age	13.3	15.4	8.1	13.3	11.8	10.9	10.5	12.2	9.3	15.1	15.1	14.6	11.1
BMI	36	22	15	18	21	18	13	22	17	23	23	16	19
FEV1% pred	95.5%	96.0%	97.8%	92.8%	92.6%	99.1%	99.4%	99.4%	103.9%	104.6%	124.8%	80.92%	80.08%
FVC % pred	97.4%	100.6%	82.2%	83.4%	88.9%	95.3%	87.6%	96.2%	89.6%	95.1%	109.5%	67.83%	105.2%
Peak $V'O_2$% pred	100%	101%	117%	85%	81%	89%	96%	98%	111%	72%	88%	90%	84%
$V'O_2$AT % pred	33.3%	51%	56%	55%	57%	51%	52%	56%	82%	43%	63%	53%	44%
Breathing reserve	23%	35%	21%	35%	38%	34%	54%	37%	24%	39%	41%	33%	41%
$V'O_2$/HR % pred	90%	124.9%	138.9%	75.6%	105.6%	92.7%	78.4%	101.8%	138.5%	83.4%	98%	66.8%	116.8%
WR % pred	96.8%	98%	116%	99%	84%	87%	92%	102%	98%	80%	88%	94%	84%
RER	1.02	1.07	1.00	1.18	1.01	1.03	0.88	1.10	1.01	1.17	1.06	1.08	0.83
HRR-1 (beat/min)	24	25	16	30	42	47	65	17	39	35	34	19	52

Abbreviations: FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HRR-1, heart rate recovery at 1 min after peak exercise; Peak $V'O_2$, peak oxygen uptake; $V'O_2$AT, oxygen uptake at the anaerobic threshold; $V'O_2$/HR, oxygen pulse; RER, respiratory exchange ratio; WR, work rate.

3 | RESULTS

The 13 patients studied had a median age of 12.1 years (range 8–15.4 years), 10 males and three females. During COVID-19, seven patients required oxygen therapy, six with low flow with a nasal cannula, and one with high flow with a Venturi mask. The mean length of hospital stay was 5.5 days, median of 5 days (range 2–13 days). The 69% of patients had pathologic findings at x-ray or ultrasound chest examination. Two patients were affected by mild asthma, and one by obesity (BMI 36). Despite five children (38.4%) reporting easy fatigue during daily activities, when performing CPET, only one interrupted the test due to muscle exhaustion.

All CPET parameters fell within the normal range, with the exception of one child who performed a submaximal test (Table 1).

4 | DISCUSSION

The main finding of the present study is that cardiopulmonary function was normal 6 months after moderate/severe SARS-CoV-2 infection in children, allowing a normal exercise capacity in all subjects except one in whom functional parameters indicated normal cardiopulmonary function but submaximal exercise. These results confirm and extend previous reports of apparent resolution of COVID-19 in pediatric patients and provide robust data to support the hypothesis that, differently from adults, COVID-19 in children did not significantly produce permanent damage. This is reasonable from a pathophysiological point of view because SARS-CoV-2-related endothelitis found in long-term pathological lung alterations in adults, is rarely reported in children.

Exercise limitation could occur not only because of pulmonary gas exchange or ventilatory limitations that can be assessed with pulmonary function testing at rest but also can depend on extra-pulmonary (e.g., cardiovascular) documented in adults with CPET.[2] This was not the case in our study since O_2 pulse at peak exercise, an index of cardiac output, was in-range in almost all children, except for the one who performed a submaximal exercise in whom O_2 pulse was anyway proportionate to its peak VO_2.

Our finding of normal cardiopulmonary function and exercise capacity conflicts with two previous papers about adults after SARS-CoV-2 infection.[2,3] All our children had a normal exercise capacity; the different ages of the patients studied, and the assessment timing can explain this discrepancy in favour of younger patients.

A second major finding of the present study is that, notwithstanding in-range peak oxygen consumption, peak exercise capacity, and peak O_2 pulse at 6 months after SARS-CoV-2 infection, 38.4% of the children studied still complained of easy fatigue during daily activities. Since CPET variables are better tailored to investigate cardiac and pulmonary causes of exercise impairment, they might prove less sensitive or inadequate to discover more peripheral causes, such as oxygen delivery to skeletal muscles or muscle impairment.

Endurance tests measure the ability to sustain a submaximal exercise capacity, which could characteristically change without a significant variation in maximal exercise capacity. O'Donnell et al.[6] also reported exercise endurance's reliability as reproducible and responsive to change. These tests could be more sensitive in assessing the residual exercise fatigability found in children.

An alternative hypothesis may be that the long in-home period and the social pressure (e.g., social media reporting the devastating impact of COVID in adults) lead to de-conditioning and to a psychological impairment with more perceptive fatigue despite a completely normal CPET. In this context, differently from adults, children are even more vulnerable to psychological distress.

Whatever the possible explanation of the residual exercise-related symptoms after healing from SARS-CoV-2 infection, the evidence disclosed by normal CPET in children remains relevant. In fact, it excludes a poorer prognosis and permanent handicaps and suggests a possible role of exercise re-training in this cohort of patients.

The major limitations of our study are the small size of the cohort and the absence of the patient's baseline pulmonary function tests before SARS-CoV-2 infection. However, post-COVID CPET in the normal range makes the latter less significant since, in this condition, changes from the pre-COVID assessment are not expected. Furthermore, to the best of our knowledge, this is the first preliminary study investigating CPET in pediatric patients after COVID-19. Thus, patient recruitment is still ongoing to expand the sample analyzed.

5 | CONCLUSION

In conclusion, this preliminary physiological study suggests that long-lasting cardiopulmonary impairment affecting exercise capacity is not present in children not affected by the pediatric multisystem inflammatory syndrome who recovered from mild to moderate SARS-CoV-2 infection, which required hospitalization. Under these conditions, CPET remains a tool of paramount importance in the differential diagnosis in the assessment of residual tiredness and fatigue perceived by children, but further functional investigations and medical assessment are warranted.

AUTHOR CONTRIBUTIONS

Marco Denina and Lorenzo Appendini gave a substantial contribution to conception and design, drafted the article, reviewed, and critically revised the manuscript; Lorenzo Appendini performed CPET. Marco Denina made the statistical analysis; Lucia Ronco, Elisa Funiciello, and Silvia Garazzino contributed to conception and design, collected data, and revised the manuscript. Elisabetta Bignamini critically revised the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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