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LETTER TO THE EDITOR

Intermittent versus equivalent constant-load cycle training in COVID-19 patients

Dear Editor,

While the need to implement evidence-based training following COVID-19 is imperative, no consensus exists as to how such programmes should be designed.¹⁻³ Between 20 July 2020 and 30 April 2021, we assessed tolerability and safety of high-intensity constant-load exercise (CLE) and high-intensity intermittent exercise (IE) in 14 patients presenting pneumonia and acute respiratory failure (ARF) (mean age: 63±13 years) with ongoing symptomatic COVID-19 from 4 to 12 weeks following the infection. Anthropometric data, body mass index (BMI), and the number of comorbidities were recorded. Patients undertook spirometry (FEV₁, FVC, FEV₁/FVC, transfer factor for Carbon Monoxide (DLCO), blood gases in room air (PaO₂, PaCO₂, pH), functional status (the Short Physical Performance Battery-SPPB test and the 6-minute walking distance [6MWD: in meters and as a percentage of predicted]), an incremental cardiopulmonary exercise test (CPET) [assessing oxygen uptake (VO₂), carbon dioxide output (VCO₂), oxygen uptake at the anaerobic threshold (AT), respiratory exchange ratio (RER), minute ventilation (V_E), tidal volume (V_T) and respiratory rate] using a portable metabolimeter; transcutaneous carbon dioxide tension (TcCO₂) was also recorded continuously. In this cross-over study (Ethics Committee approval on 30 June 2020, Protocol No. 2449CE), training exercise intensity was balanced to provide the same average work rate for IE and CLE modalities. CLE was set at 70% of peak work rate (WR_{peak}) and IE consisted of one minute of exercise at 100% WR_{peak}, alternated with one minute at 40% WR_{peak}, to the limit of tolerance (T_{lim}). Dyspnea and leg muscle discomfort (1-10 Borg scale), heart rate and safety were assessed. Of the 220 consecutively admitted patients at the Respiratory Rehabilitative Unit - ICS Maugeri of Lumezzane (BS) - as inpatient and outpatient between 20 July 2020 and 30 April 2021, 14 patients were eligible for the study. We excluded from this study 63 patients presenting symptoms for less than four weeks following infection, 35 patients with more than 12 weeks following infection, 44 clinically unstable patients, 20 patients with severe orthopedic diseases, 15 patients with cognitive impairment, 29 patients with previous severe

heart disease (congestive heart disease, severe aortic stenosis, atrial fibrillation). We did not successfully exclude patients for technical reasons or missing data.

Table 1 shows the study population and cardiorespiratory function at peak exercise; two patients presented mitral valve insufficiency and one chronic atrial fibrillation, while two patients suffered from mild COPD. At study entry, patients showed breathlessness (71.4%), fatigue (64.3%), cough (14.4%), palpitations (21.4%) and pain (35.7%), respectively. Patients presented the following lung function data: FEV₁ % predicted (prd): 83.2±15.7, FVC, % prd: 79.1±15.8., FEV₁/FVC: 84.1±8.5, DLCO % prd: 56.7±26.6, PaO₂: 73.7±11.8 mmHg, PaCO₂: 36.9±3.01 mmHg. We reported no adverse events for either of the two modalities. We detected no ECG abnormalities during or after IE or CLE. At peak exercise, WR_{peak} and VO_{2peak} were reduced below normal predicted levels. Premature metabolic acidosis was evident by the low fraction of predicted normal VO₂ when the anaerobic threshold (AT) was detected (AT at 48±9% VO₂ prd). Overall, respiratory reserve was not exhausted in patients with COVID-19. Ventilatory equivalents for VO₂ (V_E/VO₂) and VCO₂ (V_E/VCO₂), and transcutaneous carbon dioxide tension (TcCO₂) were compatible with exercise hyperventilation (Table 1). A recent study in survivors from COVID-19 pneumonia has suggested that exercise hyperventilation after COVID-19 is frequent and principally due to enhanced chemoreflex sensitivity rather than increased V_D/V_T.⁴ We observed a mild reduction in arterial oxygen saturation (SpO₂). Arterial blood pressure was normal, whereas the mean heart rate reached approximately 80% of predicted normal value. Sensations of breathlessness and leg discomfort were indicative of severe symptoms. The predominant symptom for stopping exercise was breathlessness (6/14), leg discomfort (2/14) or both dyspnoea and leg discomfort (6/14). Exercise endurance time was not different between IE compared to CLE (p = 0.1594, Table 2). The average cycling work rate did not differ between IE and CLE. The same was also the case for VO₂ and for both ventilatory equivalents (Table 2). At the limit of cycling tolerance, none of the ventilatory or cardiovascular responses differed between IE and CLE (Table 2) and there was no difference in the intensity of breathlessness or leg discomfort between the two modalities. The ventilatory reserve, reflected by the ratio of V_E/maximal voluntary ventilation (V_E/MVV), did not differ between IE and CLE. During CLE and IE 36% and

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Table 1 Demographic, anthropometric and clinical characteristics.

| Measures | |
|---|-------------|
| Patients, n | 14 |
| Age, years | 63.1±12.9 |
| BMI, kg/m ² | 28.0±5.2 |
| Male, n (%) | 11 (78.6%) |
| Comorbidities | |
| None, n (%) | 9 (64.3%) |
| Cardiac, n (%) | 3 (20.0%) |
| Respiratory, n (%) | 2 (14.3%) |
| Diabetes, n (%) | 1 (7.1%) |
| Hypertension, n (%) | 9 (65.0%) |
| Days since acute hospitalisation, n | 54.6± 22.0 |
| Functional status | |
| SPPB, score | 9.9±1.9 |
| 6MWD, m | 411.4±111.6 |
| 6MWD, % of predicted | 77.3±17.9 |
| Physiological responses at the limit of tolerance during the CPET | |
| WRpeak, Watts | 87.1±31.5 |
| WRpeak, % predicted | 59.4±22.1 |
| VO ₂ peak, ml/kg/min | 12.7±4.6 |
| VO ₂ peak, % of predicted | 57.6±16.2 |
| VCO ₂ peak, ml/kg/min | 13.0±4.8 |
| VO ₂ -AT, ml/kg/min | 10.6±3.2 |
| VO ₂ -AT, % VO ₂ peak predicted | 48.2±9.4 |
| V _E /VO ₂ peak | 50.4±10.4 |
| V _E /VCO ₂ peak | 40.6±9.2 |
| RER peak | 1.1±0.1 |
| TcCO ₂ peak, mmHg | 37.4±5.3 |
| V _E peak, l/min | 46.8±20.7 |
| V _E /MVV, % | 42.5±17.1 |
| SBPpeak, mmHg | 171.8±26.4 |
| DBPpeak, mmHg | 96.6±14.2 |
| SpO ₂ peak, % | 92.5±3.3 |
| HRpeak, beats/min | 124.3±2.3 |
| HRpeak, % of predicted | 79.0±10.4 |
| Borg dyspnea at peak exercise, score | 7.4±2.3 |
| Borg Leg discomfort at peak exercise, score | 5.8±3.1 |

Legend: Results are expressed as mean± Standard Deviation; BMI, body mass index; SPPB, Short Physical Performance Battery; 6MWD, six minute walking distance; CPET, cardiopulmonary exercise test; WRpeak, maximum load in watts at peak exercise; VO₂, oxygen uptake; V_E, ventilation; SpO₂, peripheral oxygen saturation; TcCO₂, transcutaneous carbon dioxide tension; VO₂-AT, oxygen uptake at the anaerobic threshold; RER, respiratory exchange ratio; V_E/VO₂; ventilatory equivalent for VO₂, V_E/VCO₂, ventilatory equivalent for VCO₂; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR, heart rate.

21% of patients, respectively, ended the test with a HR greater than 80% of maximal predicted. Forty-three percent of patients ended CLE and 50% ended IE with a decrease in SpO₂ greater than 4%, compatible with exercise-induced arterial oxygen desaturation. The fraction of patients who

reasoned dyspnoea as the limiting factor was identical between IE and CLE corresponding to 57%. The fraction of patients who stopped exercise because of leg discomfort was relatively low for IE (n=2, 14%) and for CLE (n=3; 21%). Both dyspnoea and leg discomfort as the limiting factors were reported by n=4 for IE (29%) and n=3 for CLE (22%). At exercise iso-time and the limit of tolerance during IE and CLE protocols, V_E, SPO₂ and VO₂ did not differ (Table 2). Moreover, symptoms for breathlessness, leg discomfort, heart rate or blood pressure measurements were not different during IE and CLE protocols.

The lack of adverse events occurring during exercise modalities was in line with previous studies on COVID-19 survivors.⁵ Moreover, several studies on other 'high risk' patients' groups (e.g., such as ischemic heart disease and heart failure) showed that high-intensity exercise is considered safe.^{6,7} Recent studies in COVID-19 survivors^{4,8} have attributed early metabolic acidosis to myopathic changes occurring for medications administered during the hospital stay (e.g., steroids) as well as because of the potential direct or indirect myopathic damage from COVID-19 rather than muscle disuse.⁷ Hence, several opinion papers and guidelines favour low-intensity exercise with gradual increases in intensity, mostly due to safety concerns.^{2,3} Early experiences of rehabilitation in post-COVID-19⁵ individuals show that low-to-moderate intensity of exercise in this population is safe and effective in improving exercise tolerance and peripheral muscle strength. Accordingly, our study was designed to investigate the safety and tolerability of high-intensity (continuous or interval) exercise in this population.

Individuals with ongoing symptomatic COVID-19 could successfully and safely undertake high-intensity exercise performed continuously or intermittently. These findings are relevant both for a better understanding of consequences of COVID-19 on exercise tolerance. They also provide a clearer suggestion to survivors on how they should undertake regular exercise when expecting to resume their previous lifestyle.

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Author contributions

MP (Guarantor) had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. MV, IV, MP and MVE contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. BS, LB contributed to data collection and interpretation. All Authors reviewed the manuscript.

Table 2 Responses at the limit of tolerance (Tlim) to constant-load exercise (CLE) and interval exercise (IE) protocols.

| | Tlim_CLE | Tlim_IE | P |
|--|------------|------------|--------|
| Cycling responses | | | |
| Work rate, Watts | 59.6±23.4 | 60.0±23.2 | 0.4845 |
| Endurance time, min | 12.7±8.5 | 14.7±9.0 | 0.1594 |
| Cadence, rpm | 60.2±7.1 | 59.1±7.0 | 0.9150 |
| Total work, kJ | 45.9±31.2 | 54.3±40.2 | 0.1580 |
| Metabolic and ventilatory responses | | | |
| VO ₂ , ml/kg/min | 12.3±3.8 | 11.9±3.2 | 0.6494 |
| VO ₂ , % VO ₂ peak | 94.6±18.9 | 95.6±24.3 | 0.8676 |
| RER | 0.9±0.1 | 0.9±0.1 | 0.4513 |
| V _E , L/min | 46.9±22.3 | 44.3±16.8 | 0.5767 |
| V _E /MVV, % | 41.4±2.9 | 41.5±19.3 | 0.9927 |
| VE/VO ₂ | 47.6±8.0 | 47.1±10.2 | 0.8157 |
| V _E /VCO ₂ | 52.0±9.6 | 50.6±10.6 | 0.2317 |
| Ti, sec | 0.7±0.1 | 0.7±0.2 | 0.6128 |
| Ti/Ttot | 0.4±0.0 | 0.4±0.0 | 0.8041 |
| Bf, breaths/min | 35.9±6.4 | 36.1±7.1 | 0.8970 |
| SpO ₂ , % | 92.9±3.6 | 92.3±3.4 | 0.1788 |
| TcCO ₂ , mmHg | 33.4±4.0 | 32.5±4.5 | 0.2289 |
| Cardiovascular and symptoms responses | | | |
| Mean BP, mmHg | 119.9±18.7 | 113.1±8.2 | 0.1494 |
| HR, beats/min | 117.1±17.2 | 114.6±13.4 | 0.4712 |
| HR, % of predicted | 74.7±8.6 | 73.4±8.2 | 0.5681 |
| Borg dyspnea, score | 6.6±2.6 | 6.4±2.8 | 0.3456 |
| Borg leg discomfort, score | 5.0±3.0 | 4.3±3.3 | 0.2206 |

Legend: Results are expressed as mean± Standard Deviation; VO₂, oxygen uptake; V_E, minute ventilation; arterial oxygen saturation; TcCO₂, transcutaneous carbon dioxide; CPET, cardiopulmonary exercise test; RER, respiratory exchange ratio; V_E/VO₂, ventilatory equivalent for VO₂; V_E/VCO₂, ventilatory equivalent for VCO₂; BP, blood pressure; HR, heart rate.

Declaration of competing interest

The authors declare no conflict of interest related to this manuscript.

References

- Sivan M, Taylor S. NICE guideline on long covid. *BMJ (Clin Res Ed)*. 2020;371:m4938. <https://doi.org/10.1136/bmj.m4938>.
- Vitacca M, Carone M, Clini EM, et al. Joint statement on the role of respiratory rehabilitation in the COVID-19 crisis: the Italian position paper. *Respiration*. 2020;99:493–9. <https://doi.org/10.1159/000508399>.
- Barker-Davies RM, O'Sullivan O, Senaratne KPP, et al. The Stanford hall consensus statement for post-COVID-19 rehabilitation. *Br J Sports Med*. 2020;54:949–59. <https://doi.org/10.1136/bjsports-2020-102596>.
- Baratto C, Caravita S, Faini A, et al. Impact of COVID-19 on exercise pathophysiology: a combined cardiopulmonary and echocardiographic exercise study. *J Appl Physiol (1985)*. 2021;130:1470–8. <https://doi.org/10.1152/jappphysiol.00710.2020>.
- Daynes E, Gerlis C, Chaplin E, Gardiner N, Singh SJ. Early experiences of rehabilitation for individuals post-COVID to improve fatigue, breathlessness exercise capacity and cognition - a cohort study. *Chron Respir Dis*. 2021;18:14799731211015691. <https://doi.org/10.1177/14799731211015691>.
- Hermann M, Pekacka-Egls AM, Witassek F, Baumgaertner R, Schoendorf S, Spielmanns M. Feasibility and efficacy of cardiopulmonary rehabilitation after COVID-19. *Am J Phys Med Rehabil*. 2020;99:865–9. <https://doi.org/10.1097/PHM.0000000000001549>.
- Batacan RB Jr, Duncan MJ, Dalbo VJ, Tucker PS, Fenning AS. Effects of high-intensity interval training on cardiometabolic health: a systematic review and meta-analysis of intervention studies. *Br J Sports Med*. 2017;51:494–503. <https://doi.org/10.1136/bjsports-2015-095841>.
- Skjørtén I, Ankerstjerne OAW, Trebinjac D, et al. Cardiopulmonary exercise capacity and limitations 3 months after COVID-19 hospitalisation. *Eur Respir J*. 2021;58:2100996. <https://doi.org/10.1183/13993003.00996-2021>.

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