Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Severity does not impact on exercise capacity in COVID-19 survivors

Rocco Francesco Rinaldo a,⁎, Michele Mondoni a, Elena Maria Parazzini a, Andrea Baccelli b, Federica Pitari b, Elena Brambilla b, Simone Luraschi b, Maurizio Balbi b, Marco Guazzi c, Fabiano Di Marco d, Stefano Centanni a

a Respiratory Unit, ASST Santi Paolo e Carlo, San Paolo Hospital, Department of Health Sciences, University of Milan, Milan, Italy
b Cardiology Unit, ASST Santi Paolo e Carlo, San Paolo Hospital, Department of Health Sciences, University of Milan, Milan, Italy
c Respiratory Unit, ASST Papa Giovanni XXIII Hospital, Department of Health Sciences, University of Milan, Bergamo, Italy
d Radiology Unit, ASST Papa Giovanni XXIII Hospital, Department of Health Sciences, University of Milan, Bergamo, Italy

⁎ Corresponding author. San Paolo Hospital, Via Antonio di Rudinì 8, 20142, Milano, Italy.
E-mail addresses: rocco.rinaldo@unimi.it (R.F. Rinaldo), michele.mondoni@asst-santipaolocarlo.it (M. Mondoni), elena.parazzini@asst-santipaolocarlo.it (E.M. Parazzini), andrea.baccelli@unimi.it (A. Baccelli), federica.pitari@unimi.it (F. Pitari), eletta.brambilla1@unimi.it (E. Brambilla), simone.luraschi@unimi.it (S. Luraschi), balbi.m@libero.it (M. Balbi), marco.guazzi@unimi.it (M. Guazzi), fabiano.dimarco@unimi.it (F. Di Marco), stefano.centanni@unimi.it (S. Centanni).

https://doi.org/10.1016/j.rmed.2021.106577
Received 15 June 2021; Received in revised form 11 August 2021; Accepted 12 August 2021
Available online 14 August 2021
0954-6111/© 2021 Elsevier Ltd. All rights reserved.

1. Introduction

The heterogeneity of COVID-19 clinical manifestations became evident since its appearance in December 2019 [1]. However, the impact of the severity of the acute phase of the disease on potential long-term sequelae is still unclear, particularly regarding exercise response [2]. The aim of our study was therefore to compare cardiopulmonary exercise testing (CPET) outcomes in patients with different acute disease severity, in the mid-term after COVID-19 resolution.

2. Methods

The present study is a post-hoc analysis of the data collected in our cohort observational prospective study aimed at evaluating the mechanisms of residual reduced exercise capacity in COVID-19 survivors (Milan Area 1 Ethics Committee - 2020/ST/407) [3]. Consecutive patients admitted during the first wave of COVID-19 [4], between February–April 2020, at the Respiratory Unit at San Paolo Hospital (Milan, Italy), who attended post-COVID-19 respiratory clinic were invited to undergo CPET in May–August 2020. Inclusion criteria were: 1) age ≥18 years, 2) previous molecular diagnosis of SARS-CoV-2 infection. Exclusion criteria were the absence of a signed informed consent, acute respiratory exacerbation in the previous 4 weeks and the presence of medical conditions contraindicating CPET.

Clinical data of the patients were reviewed during the clinical visit. Severity of the disease was defined on WHO guidance [5]: 1) mild...
(symptomatic patients with no evidence of pneumonia); 2) moderate (pneumonia and an oxygen saturation measured by pulse oximetry, SpO2 >90% in room air); 3) severe (pneumonia and SpO2 <90% in room air); 4) critical (Acute Respiratory Distress Syndrome, ARDS, with an arterial oxygen partial pressure to fractional inspired oxygen - P/F ratio - <300 mmHg during the application of Continuous Positive Airway Pressure, CPAP, with at least 5 cmH2O of Positive End-Expiratory Pressure, PEEP, in case of bilateral pneumonia). Dyspnoea was quantified according to the Italian version of the modified Medical Research Council dyspnoea during daily life scale (mMRC) [6,7].

Symptom-limited, incremental, exercise testing was performed a week from the clinical visit (Vmax Spectra Cardiopulmonary Exercise Testing System, SensorMedics, Yorba Linda, USA) using individualized ramp protocols on an electronically braked cycle ergometer. Gas exchange variables were acquired breath-by-breath; measured and computed variables were collected [8,9]. We obtained an arterial blood sample for blood gas analysis (BGA) and lactates at the peak of the exercise [10]. A reduced exercise capacity was defined by a peak oxygen consumption (VO2) <85% predicted. Ventilatory inefficiency was defined by a slope of the relation between ventilation and carbon dioxide output during exercise (VE/VCO2 slope) > 30 L/L.

Quantitative data are described with means and standard deviations (SD) or median and interquartile ranges (IQR) according to their distribution, and qualitative data with absolute frequencies and percentages. Anova and Kruskal Wallis tests were computed to assess statistical differences for normal or non-normal quantitative variables, respectively. Qualitative data were analysed with Pearson’s chi-squared test. A p-value <0.05 was considered statistically significant. Statistical tests were performed using the Statistical Package for Social Sciences (SPSS, Chicago IL, USA), version 23.0.

### 3. Results

We enrolled 75 patients, of whom 18 with mild-to-moderate disease, 18 with a severe disease, and 39 with a critical disease (Table 1). Mean time (SD) between hospital discharge and PFT/CPET was 97 (26) days. Patients with critical disease were older than those with mild-moderate disease. No significant differences were observed in terms of pulmonary function tests (PFT), though with some residual impairment, and mMRC score across the different severity groups. A higher share of critical vs mild-moderate illness patients presented abnormal CT findings at follow-up, although the magnitude of parenchymal involvement in these patients was not different compared to the other two groups. We did not find any statistical difference among groups in the distribution of comorbidities, with systemic hypertension and asthma being the most common cardio-respiratory chronic conditions (data not shown). No differences emerged in terms of peak exercise capacity, peak blood gas parameters or cardiovascular response to exercise. The number of patients presenting reduced exercise capacity was comparable among groups (p = 0.790), as those presenting a residual ventilatory inefficiency (p = 0.718). One patient in the critical group presented hyperventilation, with no evidence of DLCO and CT residual involvement, as in the emerging entity of Long COVID. Nevertheless, patients with severe disease showed a significantly higher mean value of VE/VCO2 slope in comparison with those with a mild-moderate disease (p-value = 0.028).

### Table 1

| Lung function, CT and CPET parameters according to disease severity. |
|--------------------------|-----------------|-----------------|-----------------|-----------------|
|                          | All patients   | Mild-moderate disease | Severe disease | Critical disease |
|                          | (n = 75)       | (n = 18)          | (n = 18)       | (n = 39)       |
| Male/Female n (percentage) | 43/32 (57/43) | 9/9 (50/)         | 7/11           | 27/12          |
| Age years                | 57 (12)        | 50 (9)  | 1  | 58 (13)        | 59 (11)  | 1  |
| BMI kg/m²                | 28.6           | 26.7 (5.3)       | 28.2           | 29.6           | 0.047 |
| Smoking status           | 48/8/19        | 14/2/2           | 12/0/6         | 22/5/2         | 0.272 |
| Cardoso smoker (%)       | 64/10/26       | 78/11/11         | 66/0/0         | 56/13/31       | 0.559 |
| mMRC at the time of CPET | 32/35/9        | 5/9/4/0/0        | 7/9/2/0        | 17/13/9/0/0    | 0.932 |
| Mean follow-up time days | 97 (26)        | 95 (29)          | 97 (29)        | 98 (26)        | 0.928 |
| FEV1 % predicted         | 104 (17)       | 104 (13)         | 104 (19)       | 105 (18)       | 0.989 |
| FVC %predicted           | 100 (16)       | 101 (14)         | 101 (16)       | 100 (16)       | 0.923 |
| DLCO % predicted         | 71 (14)        | 72 (13)          | 67 (12)        | 73 (15)        | 0.378 |
| KCO % predicted          | 84 (15)        | 82 (15)          | 81 (15)        | 86 (14)        | 0.469 |
| Alveolar Volume % predicted | 86 (14)    | 89 (17)          | 85 (14)        | 84 (13)        | 0.505 |
| CT abnormal/total n (%)  | 43/68 (63)     | 5/16 (31)  | 9/18          | 29/38          | 0.006 |
| CT- SS f                 | 17 (10)        | 16.2 (8.4)       | 13.9           | 18.7           | 0.437 |
| %V-RHR        | 15 (20–35)     | 15 (15–20)       | 15             | 20             | 0.342 |
| VO2 peak % predicted     | 83 (15)        | 83 (17)          | 82 (16)        | 84 (15)        | 0.895 |
| VO2 peak absolute ml/min/kg | 20.0       | 22.1 (6.3)       | 18.4           | 19.8           | 0.127 |
| VO2 peak <85% predicted  | 41 (54)        | 11 (61)          | 9 (50)         | 21 (51)        | 0.790 |
| Work peak % predicted    | 85 (19)        | 84 (14)          | 88 (29)        | 85 (15)        | 0.832 |
| Anaerobic Threshold %    | 54 (13)        | 52 (14)          | 56 (15)        | 55 (12)        | 0.550 |
| VO2 max predicted        | 10.4           | 10.3 (1.1)       | 10.3           | 10.4           | 0.955 |
| VO2/work slope ml/min/W  | 1.21           | 1.22 (0.99)      | 1.18           | 1.21           | 0.594 |
| Heart rate reserve %     | 13 (11)        | 12 (13)          | 16 (13)        | 12 (10)        | 0.495 |
| Oxygen pulse peak %      | 96 (21)        | 94 (31)          | 100 (22)       | 96 (14)        | 0.679 |
| Breathing reserve % VE/VCO2 slope | 28.4        | 27.1 (2.6)       | 29.8           | 28.3           | 0.028 |
| VE/VCO2 slope >30 n (%)  | 11 (14)        | 1 (5)            | 5 (27)         | 5 (13)         | 0.718 |
| Alveolar-arterial gradient for O2mmHg | 94 (11) | 99 (10)          | 95(11)         | 96 (10)        | 0.205 |

(continued on next page)
3

In this post-hoc analysis, a ventilatory and gas exchange response proﬁle in the limit of normal was conﬁrmed irrespective of the severity of the acute disease, with comparable reduced exercise capacity and some impairment at resting examinations [5,11]. This is in line with a phenotypical heterogeneity of the acute disease, due to a different degree of adaptation to the stress of the inﬂammation affecting cardio-respiratory efﬁciency [12], which can possibly be restored after recovery. Our data expand the ﬁnding of Dorelli et al. [13] who did not ﬁnd differences in the share of patients presenting residual ventilatory cardio-respiratory efﬁciency [12], which can possibly be restored after 5 months from the discharge, based on ICU vs non-ICU patients. Lastly, we interpreted the difference in peak VO\textsubscript{2} between mild-moderate and severe patients as an independent risk factor for the development of pulmonary ﬁbrosis and the related increase in VE/VCO\textsubscript{2} slope at CPET at 7 months follow-up [14].

Of note, Ong et al. [15] also outlined similar results from SARS survivors at 3 months from hospital discharge, with no signiﬁcant difference in peak VO\textsubscript{2} nor PFT between those who required intensive care and mechanical ventilation and those who did not. Our patients reported lower than expected levels of dyspnoea and fatigue, in keeping with deconditioning as the main mechanism of exercise intolerance in post-COVID-19 survivors at 3 months after discharge, including a ventilatory response still in the limit of normal. However, further studies are needed to clarify the role of residual impairment on a longer term.

4. Discussion

Table 1 (continued)

|               | All patients (n = 75) | Mild-moderate disease (n = 18) | Severe disease (n = 18) | Critical disease (n = 39) | p-value* |
|---------------|---------------------|-------------------------------|------------------------|--------------------------|----------|
| PaO\textsubscript{2} peak\textsuperscript{b} mmHg | 95 (9.3)            | 96 (9)                        | 93 (9)                 | 94 (9)                   | 0.230    |
| PaCO\textsubscript{2} peak\textsuperscript{b} mmHg | 32 (4.9)            | 37 (4)                        | 31 (5)                 | 31 (5)                   | 0.405    |
| Physiologic dead space fraction peak % | 19 (8)              | 18 (7)                        | 20 (7)                 | 20 (9)                   | 0.559    |
| Lactate peak\textsuperscript{b} mmol/L | 7.5 (2.2)           | 8.2 (2.8)                     | 6.6 (2.4)              | 7.2 (2.6)                | 0.267    |
| BORG scale of dyspnoea peak | 4.0 (2.3)           | 3.5 (2.4)                     | 3.9 (2.0)              | 3.7 (0.7)                | 0.870    |
| BORG scale of perceived exertion peak | 5.3 (2.0)           | 5.4 (2.0)                     | 5.3 (2.2)              | 5.5 (2.0)                | 0.946    |

All quantitative data mean (SD), unless otherwise speciﬁed; ∞ median (IQR); in bold: p < 0.05; * p-value refers to mild/moderate, severe and critical disease; |p < 0.05 between mild/moderate and critical; |p < 0.05 between mild/moderate and severe; technically acceptable DLCO exam available respectively for 16 mild-moderate, 16 severe and 36 critical patients; CT imaging available for 16 mild-moderate, 17 severe and 36 critical patients; 8 BGA data available for 17 mild-moderate, 15 severe and 37 critical patients; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; KCO: carbon monoxide transfer coefficient; CT-SS: CT severity score; %SV-RPE: visual percentage of residual parenchymal involvement; nMRC: modiﬁed medical research council scale for dyspnoea; VO\textsubscript{2}: oxygen consumption; VCO\textsubscript{2}: carbon dioxide output; VE: ventilation; PaCO\textsubscript{2}: partial arterial pressure for carbon dioxide; PaO\textsubscript{2}: partial arterial pressure for carbon dioxide.

4. Discussion

In this post-hoc analysis, a ventilatory and gas exchange response proﬁle in the limit of normal was conﬁrmed irrespective of the severity of the acute disease, with comparable reduced exercise capacity and some impairment at resting examinations [5,11]. This is in line with a phenotypical heterogeneity of the acute disease, due to a different degree of adaptation to the stress of the inﬂammation affecting cardio-respiratory efﬁciency [12], which can possibly be restored after recovery. Our data expand the ﬁnding of Dorelli et al. [13] who did not ﬁnd differences in the share of patients presenting residual ventilatory cardio-respiratory efﬁciency at CPET 5 months from the discharge, based on ICU vs medical ward stay. Similarly, Liu et al. showed that severity of the acute disease did not emerge as an independent risk factor for the development of pulmonary ﬁbrosis and the related increase in VE/VCO\textsubscript{2} slope at CPET at 7 months follow-up [14].

Of note, Ong et al. [15] also outlined similar results from SARS survivors at 3 months from hospital discharge, with no signiﬁcant difference in peak VO\textsubscript{2} nor PFT between those who required intensive care and mechanical ventilation and those who did not. Our patients reported lower than expected levels of dyspnoea and fatigue, in keeping with deconditioning as the main mechanism of exercise intolerance in post-COVID-19 survivors at 3 months after discharge, including a ventilatory response still in the limit of normal. However, further studies are needed to clarify the role of residual impairment on a longer term.

5. Conclusions

Disease severity does not impact on exercise capacity in COVID-19 survivors at 3 months after discharge, including a ventilatory response still in the limit of normal. However, further studies are needed to clarify the role of residual impairment on a longer term.

Support statement

This work was funded by Università degli Studi di Milano in the context of the Registry for COVID19 Emergency (RECOVER) electronic database. Funding information for this article has been deposited with the Crossref Funder Registry.

CRediT authorship contribution statement

Rocco Francesco Rinaldo: Conceptualization, Data curation, Formal analysis, Project administration, Methodology, Investigation, Writing – original draft, Writing – review & editing. Michele Mondoni: Conceptualization, Data curation, Project administration, Investigation, Writing – review & editing. Elena Maria Parazzini: Conceptualization, Investigation, Writing – review & editing. Andrea Baccelli: Conceptualization, Data curation, Investigation, Writing – review & editing. Federica Pitari: Data curation, Investigation, Writing – review & editing. Elena Brambilla: Data curation, Investigation, Writing – review & editing. Simone Luraschi: Data curation, Investigation, Writing – review & editing. Maurizio Balbi: Data curation, Investigation, Methodology, Writing – review & editing. Marco Guazzi: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. Fabiano Di Marco: Conceptualization, Methodology, Formal analysis, Supervision, Writing – original draft, Writing – review & editing. Stefano Centanni: Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

Conflict of interest: Dr. Rinaldo has nothing to disclose. Conflict of interest: Dr. Mondoni has nothing to disclose. Conflict of interest: Dr. Parazzini has nothing to disclose. Conflict of interest: Dr Baccelli has nothing to disclose. Conflict of interest: Dr. Pitari has nothing to disclose. Conflict of interest: Dr. Brambilla has nothing to disclose. Conflict of interest: Dr. Luraschi has nothing to disclose. Conflict of interest: Dr. Balbi has nothing to disclose. Conflict of interest: Prof. Guazzi has nothing to disclose. Conflict of interest: Prof. Di Marco has nothing to disclose. Conflict of interest: Prof. Centanni has nothing to disclose.

Acknowledgements

The Authors wish to acknowledge Dr. Silvia Terraneo, Dr. Fausta Alfano, Dr. Matteo Davì, Dr. Sabrina De Pascalis, Dr. Alessandra Masseroni, Dr. Stefano Pavesi and Dr. Silvia Ruggeri and for their help in patient recruitment and data collection and their work in the post-COVID-19 outpatient service. Authors also wish to thank our outstanding CPET Laboratory nurses Mrs. Giulia Merli, Mrs. Claudia Migliacci and Mrs. Caterina Spannuolo.

References

[1] W. Guan, Z. Ni, Y. Hu, W. Liang, C. Ou, J. He, L. Liu, H. Shan, C. Lei, D.S.C. Hui, B. Du, L. Li, G. Zeng, K.-Y. Yuen, R. Chen, C. Tang, T. Wang, P. Chen, J. Xiang, S. Li, J. Wang, Z. Liang, Y. Peng, L. Wei, Y. Liu, P. Peng, J. Wang, J. Liu, Z. Chen, et al., Clinical characteristics of coronavirus disease 2019 in China, N. Engl. J. Med. 382 (2020) 1708–1720, https://doi.org/10.1056/NEJMoa2002052.
T.V. Lerum, T.M. Aaløkken, E. Brønstad, B. Aarli, E. Ikdahl, K.M.A. Lund, M.T. Durheim, J.R. Rodriguez, C. Meltzer, K. Stavem, O.H. Skjønsberg, H. Ashraf, G. Einvik, Dyspnoea, lung function and CT findings three months after hospital admission for COVID-19, Eur. Respir. J. 57 (2021) 2003448, https://doi.org/10.1183/13993003.03448-2020.

R.F. Rinaldo, M. Mondoni, E.M. Parazzini, F. Pitarì, E. Brambilla, S. Luraschi, M. Balbi, G.F. Sferrazza Papa, G. Sotgiu, M. Guazzi, F. Di Marco, S. Centanni, Deconditioning as main mechanism of impaired exercise response in COVID-19 survivors, Eur. Respir. J. 6 (2021) 2100870, https://doi.org/10.1183/13993003.00870-2021.

M. Mondoni, G.F.S. Papa, R. Rinaldo, F. Faverio, A. Marruchella, F. D’Arcangelo, A. Pesce, S. Pasini, S. Henchi, G. Cipolla, F. Tarantini, L. Giuliani, F. Di Marco, L. Saracino, T. Tomaselli, A. Corsico, S. Gasparini, M. Bonifazi, L. Zuccatosta, L. Saderi, G. Pellegrino, S. Centanni, P. Carlucci, G. Sotgiu, Utility and safety of bronchoscopy during the SARS-CoV-2 outbreak in Italy: a retrospective, multicentre study, Eur. Respir. J. 56 (2020) 2002767, https://doi.org/10.1183/13993003.02767-2020.

WHO, Clinical management of COVID-19: interim guidance, 25 January 2021, Date last accessed: 5 May 2021. [Internet]. 2021. Available from: https://apps.who.int/iris/handle/10665/338882.

R. Yang, X. Li, H. Liu, Y. Zhen, X. Zhang, Q. Xiong, Y. Luo, C. Gao, W. Zeng, Chest CT severity score: an imaging tool for assessing severe COVID-19, Radiol. Cardiothorac. Imaging 2 (2020) 200047, https://doi.org/10.1148/rcyt.2020200047.

D. Colombi, F.C. Bodini, M. Petrini, G. Maffi, N. Morelli, G. Milanese, M. Silva, N. Sverzellati, E. Michieletti, Well-aerated lung on admitting chest CT to predict adverse outcome in COVID-19 pneumonia, Radiology 296 (2020) E86-E96, https://doi.org/10.1148/radiol.2020201433.

I.M. Weisman, D. Marchini, F.J. Martinez, F. Scliaurba, D. Sue, J. Myers, R. Casaburi, D. Marchini, K. Beck, J. Zeballos, G. Swanson, J. Myers, F. Scliaurba, B. Johnson, B. Whipp, J. Zeballos, I.M. Weisman, K. Beck, D. Mahler, J. Cotes, K. Sietsema, ATS/ACCP Statement on cardiopulmonary exercise testing, Am. J. Respir. Crit. Care Med. 167 (2003) 211–277, https://doi.org/10.1164/rccm.167.2.211.

R.F. Rinaldo, M. Mondoni, S. Comandini, P. Lombardo, B. Vigo, S. Terraneo, P. Santos, S. Carugo, S. Centanni, F. Di Marco, The role of phenotype on ventilation and exercise capacity in patients affected by COPD: a retrospective study, Multidiscip. Respir. Med. 15 (2020) 13–19, https://doi.org/10.4081/mrm.2020.476.

Z. Zhai, K. Murphy, H. Tighe, C. Wang, M.R. Wilkins, J.S.R. Gibbs, L.S. Howard, Differences in ventilatory inefficiency between pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension, Chest 140 (2011) 1284–1291, https://doi.org/10.1378/chest.10-5357.

Y. Zhao, Y. Shang, w. Song, Q. Lie, H. Xiee, Q. Xu, j. Jia, I. Li, M. Zhou, H. Luod, Y. Gaob, A. Xu, Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery, EClinicalMedicine 25 (2020) 100463, https://doi.org/10.1016/j.eclinm.2020.100463.

L. Gattinoni, D. Chiurillo, P. Cairoani, M. Busana, F. Romitti, L. Brazzi, L. Caporota, COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med. 46 (2020) 1099–1102, https://doi.org/10.1007/s00134-020-06033-2.

G. Morelli, M. Braggio, D. Gabbiani, F. Bisti, M. Caminati, G. Senna, D. Girelli, P. Laveneziana, M. Ferrari, G. Sartori, L. Dalle Carbonare, E. Cremolini, behalf of the RESPICOVID study investigators, Importance of cardiopulmonary exercise testing amongst subjects recovering from COVID-19, Diagnostics 11 (2021) 507, https://doi.org/10.3390/diagnostics11030507.

M. Liu, F. Lv, Y. Huang, K. Xiao, Follow-up study of the chest CT characteristics of COVID-19 survivors seven months after recovery, Front. Med. 8 (2021) 636298, https://doi.org/10.3389/fmed.2021.636298.

K.C. Ong, A.W.K. Ng, L.S.U. Lee, G. Kaw, S.K. Kweek, M.K.S. Leow, A. Earnest, Pulmonary function and exercise capacity in survivors of severe acute respiratory syndrome, Eur. Respir. J. 24 (2004) 436–442, https://doi.org/10.1183/09031936.04.000716.