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Review

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Is Long COVID Syndrome a Transient Mitochondriopathy Newly Discovered: Implications of CPET

Stefanos G. Sakellaropoulos[a, g], Muhammad Ali[b], Athanasios Papadis[c], Muhemin Mohammed[d], Andreas Mitsis[e], Zaza Zivzivadze[f]

Abstract

The new outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has an impact worldwide, primarily as a medical emergency. Even that the total constellation is considered as a pandemic of acute respiratory disease, coronavirus disease 2019 (COVID-19) gives rise to dysfunction in multiple organs (e.g., brain, lungs, heart, muscles) that impairs cardiopulmonary (CP) function. Parallel to the CP consequences of COVID-19 is a significant reduction in physical activity. Cardiopulmonary exercise testing (CPET) is daily used in clinical practice to define prognosis, provide risk stratification and treatment strategy. As such, the significance of CPET is crucial concerning clinical assessments of COVID-19 patients. Furthermore, new studies aim at understanding the effects of SARS-CoV-2 infection in long term. Multiple studies have investigated the cardiopulmonary function and impairment of exercise endurance in such patients, as well as a possible prolonged physical impairment. With this review, we summarize the COVID-19-associated pathophysiology for the Long COVID (LC) syndrome as well as the importance of performing CPET.

Keywords: Cardiopulmonary exercise test; Long COVID syndrome; Mitochondriopathy

Introduction

Almost 80% of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cases are with no symptoms or with a mild form of the disease. Most of the patients recover within 2 - 4 weeks [1]. Between 2% and 12% of patients report prolonged symptoms, which reflect the Long COVID (LC) [2]. Prolonged illness, lasting up to 2 years, may lead to exercise intolerance, breathlessness, and palpitations [3]. Functional limitations [4] and anatomical or cellular abnormalities (e.g., fibrosis and myocardial inflammation) have been widely reported [5].

Cardiorespiratory fitness (CRF) may be affected following coronavirus disease 2019 (COVID-19) infection [6], due to the fact that the virus has an impact to the systems responsible for it, for example cardiac, pulmonary, and the skeletal muscle one [7]. Cardiopulmonary exercise testing (CPET) can define the quantification of CRF and provides important information concerning ventilatory inefficiency or other pathomechanisms of exercise limitation [8, 9].

Cardiorespiratory Function, Ventilation, Oxygen Delivery and Extraction

Current data indicate that at peak workload the maximal oxygen consumption, tidal volume, as well as peripheral oxygen consumption are found lower in Long COVID-19 patients than healthy individuals. On the other hand, it has been found the respiratory rate was higher. Apart from peak workload, even during submaximal exercise, exercise hyperventilation has been found higher, and as a result, the partial end tidal carbon dioxide has been found lower than healthy individuals [10].

Interestingly, the maximal oxygen consumption at discharge was lower by 30% [11]. The extent of such functional impairment was larger than previous reports, lasted even for 12 months after discharge [12].

Moreover, reduction of oxygen content due to anemia (approximately 8-50% of patients) as well as by impaired peripheral extraction are considered as the main cause of functional limitation. The mechanism of anemia is unknown, most probably in the course of chronic persistent inflammation [13]. This constellation may also reflect the potential direct or indirect myopathic damage rather than isolated muscular disease [14].

Exercise Oscillatory Ventilation (EOV) Following COVID-19 Disease

Unfortunately and relatively often, pulmonary function tests

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[a]Department of Internal Medicine, Cardiology, Cantonal Hospital Baden, Baden, Switzerland
[b]Clinic of Cardiology Salzgitter, Salzgitter, Germany
[c]Swiss Cardiovascular Centre, Bern University Hospital, Bern, Switzerland
[d]Clinic of Internal Medicine, Hospital Affoltern, Affoltern, Switzerland
[e]Cardiology Department, Nicosia General Hospital, Nicosia, Cyprus
[f]Department of Emergency Care, Hospital Affoltern, Affoltern, Switzerland
[g]Corresponding Author: Stefanos G. Sakellaropoulos, Department of Internal Medicine, Cardiology, Cantonal Hospital Baden, Baden, Switzerland.
Email: Stefanos986@hotmail.com

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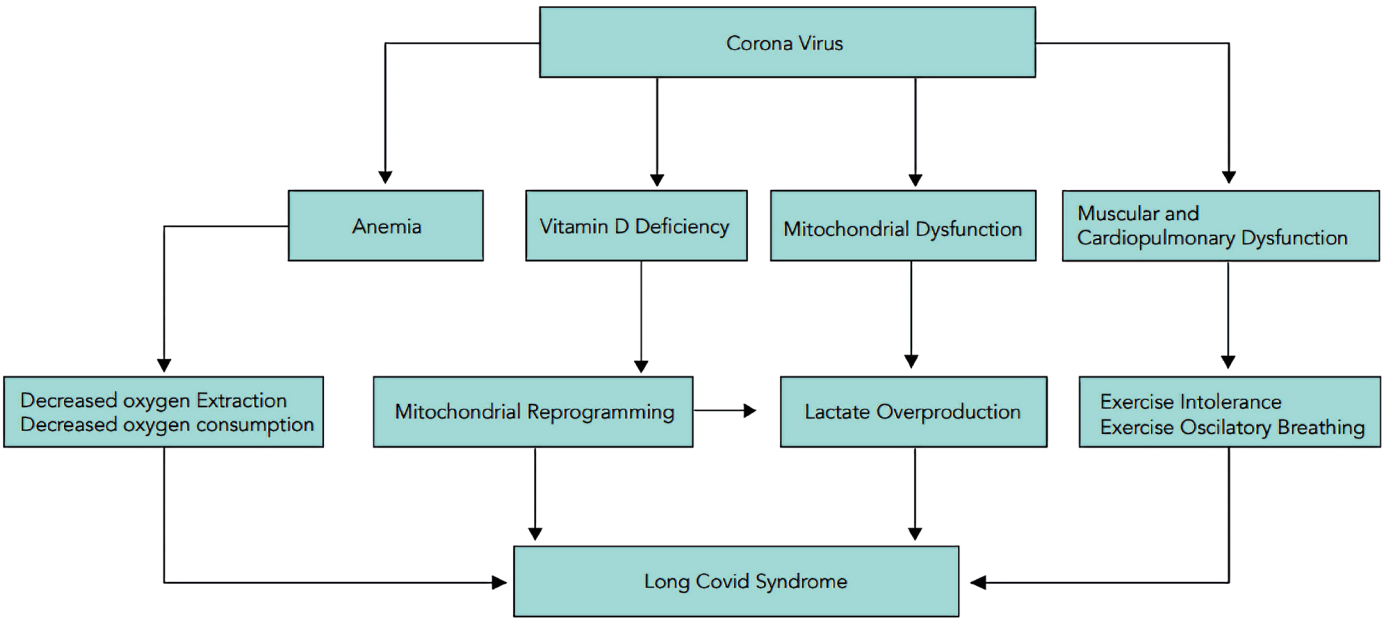

Figure 1. Proposed pathophysiology cascade of Long COVID syndrome. COVID: coronavirus disease.

fail to reveal the association between the severity of symptomatology and objective findings in patients after COVID-19 infection [11]. And so, CPET has emerged as the best option to quantify the degree of exercise impairment, while also facilitating differential diagnostics [15, 16]. Up to this day, there is no typical finding of "long COVID pattern" [17-19]. Hyperventilation in LC syndrome has been reported in several studies [20-22]. Current data suggest that approximately a third of post-COVID patients had an abnormal breathing pattern (BrP) or the so called EOV. Patients with an abnormal BrP had lower exercise capacity, lower maximal oxygen consumption and lower peak ventilation [23]. Accordingly, these results demonstrate that abnormal exercise ventilation may at least in part explain the symptomatology of the prolonged exercise intolerance.

Mitochondrial Dysfunction and Vitamin D Deficiency

Recent studies demonstrate the abnormally low fatty acid oxidation (FATox) and increased lactate production as a cause to the functional impairment. With gradual increase of glycolysis under exercise, lactate is oxidized for energy production in mitochondria, primarily in slow-twitch muscle fibers. Like FATox, lactate clearance capacity is an important marker for mitochondrial function. In post-COVID patients, the muscular metabolic disturbances may be worse than in active individuals or in individuals who suffer from metabolic syndrome [24].

Whereas increase of the lactate levels are usually seen during high exercise intensity, high blood levels at lower exercise intensity point out an underlying mitochondrial dysfunction. Increased arterial lactate levels at relatively low exercise intensity (e.g., .9 mM at 150 W) suggest the premature transition from FATox to carbohydrate oxidation (CHOox), showing metabolic reprogramming and dysfunctional mitochondria in long COVID-19 syndrome [25] (Fig. 1).

Current data indicate a significant association between vitamin D deficiency and COVID-19 susceptibility and severity. Numerous studies have suggested the benefit of vitamin D intake on ameliorating respiratory infections and COVID-19. Vitamin D supplementation is strongly recommended in order to avoid a cardiovascular outcome, optimize innate and adaptive immunity [25]. Current evidence suggests that taking a vitamin D supplement of at least 30 ng/mL can help reduce the risk of SARS-CoV-2 infection and its severe outcomes, including mortality.

On cellular basis, vitamin D inhibits apoptosis, predominantly of adipocytes by reducing expression of the mitochondrial uncoupling protein 2. Mitochondrial dysfunction due to vitamin D deficiency is critical in debilitated conditions because it decreases adenosine triphosphate formation and increases reactive oxygen species (ROS) generation. Moreover, vitamin D regulates the expression of adiponectin, a hormone with insulin-sensitizing and anti-inflammatory actions. In overall, cellular and systemic alterations due to vitamin D deficiency impair mitochondrial function, contributing to the progression and severity of COVID-19 [26].

Conclusions

CPET is especially useful tool to objectively identify the pathophysiology of exertional dyspnea, including in LC. A CPET with normal findings can provide increased comfort with physical activity. Furthermore, unresolved epidemiologic problems about the prevalence of decreased exercise capacity require further investigations and research in a larger scale. Since all CPET variables can provide a synergistic prognostic discrimination, it can certainly be used for further diagnostic

approach, risk stratification and treatment strategy [27].

In overall, the summery of the current data suggest that exercise capacity is reduced after SARS-CoV-2 infection especially 3 - 6 months after hospitalization as well as among those with LC. We recommend further research studies in a larger scale to further clarify the trajectory of exercise capacity. Of special importance will be studies that will shed the light on potential therapies, improving conditioning, metabolic normalization, and recovering of mitochondrial function, as supplementation of vitamin D contributes to the normalization of mitochondrial function.

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Conflict of Interest

None to declare.

Author Contributions

Stefanos G. Sakellaropoulos: main text, mitochondriopathy pathomechanisms, exercise oscillatory ventilation, illustration formation. Muhammad Ali, Athanasios Papadis, Muhemin Mohammed, Andreas Mitsis and Zaza Zivzivadze contributed to the review of main text.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

Abbreviations

BrP: breathing pattern; CHOox: oxidation of carbohydrates; CP: cardiopulmonary; CPET: cardiopulmonary exercise test; COVID19: coronavirus disease 2019; CRF: cardiorespiratory fitness; FATox: oxidation of fatty acids; LC: Long COVID; ROS: reactive oxygen species; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

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