Cardiac Rehabilitation in COVID-19 Patients

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Recent scientific literature has investigated the cardiovascular implications of COVID-19. The mechanisms of cardiovascular damage seem to involve the protein angiotensin-converting enzyme 2 (ACE2), to which severe acute respiratory syndrome (SARS) coronavirus-2 (CoV-2) binds to penetrate cells and other mechanisms, most of which are still under study. Cardiovascular sequelae of COVID-19 include heart failure, cardiomyopathy, acute coronary syndrome, arrhythmias, and venous thromboembolism.

COVID-19 rehabilitation cardiovascular

1. Introduction

Coronavirus disease 2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). COVID-19 has reached pandemic status and has overwhelmed health care systems, devastated the global economy, and severely restricted everyday life. In this time of crisis, the medical and scientific communities have gathered to understand as much as possible about this disease. Great advances have been made. Knowledge about its pathogenesis, clinical manifestation, preventive care, and therapeutic strategies has grown rapidly [1][2][3][4].

COVID-19 involves systemic inflammation with an increase in the oxidation state to varying degrees, depending on the severity of the symptoms accompanying the disease [5]. The systemic inflammatory state persists over time, defining what the scientific literature today describes as “long COVID“ [6].

Physical exercise, correctly structured and guided or supervised, intervenes in this inflammatory state by promoting the recovery of the antioxidant defenses [7].

Various hypotheses have been put forward regarding the mechanisms of damage at the cardiovascular level, and the most recognized seems to be associated with the transmembrane protein angiotensin-converting enzyme 2 (ACE2) [8][9].

The life cycle of SARS-CoV-2 begins with viral binding to cells via the membrane-bound glycoprotein angiotensin-converting enzyme 2 (ACE2) [10]. Once bound to ACE2, the virus is internalized via endocytosis [11]. The next step is membrane fusion, where the viral RNA genome enters the intracellular compartment, to be translated. The interaction between the encoded proteins and the viral RNA on the membrane of the endoplasmic reticulum and the Golgi apparatus results in viral budding and exocytosis [11][12][13].

SARS-CoV-2 employs ACE2 as a receptor [10][14][15][16] and ACE2 carries out important functions in the cardiovascular system and cardiovascular pharmacology. This surface enzyme is widely expressed in lung tissue [17], in cardiovascular tissue [18] including the endothelia [19], renal, and intestinal tissue [20][21]. Once the virus has penetrated these tissues, it generates multiple damages, probably related to the inhibition of the protective pathways activated by ACE2 [17][22]. Physiologically, ACE2 constitutes a counter-regulator of the renin–angiotensin–aldosterone system, transforming angiotensin II (Ang II) into angiotensin 1–7 (Ang 1–7) (Figure 1). The latter, by binding to a specific Mas receptor, causes a reduction in blood pressure by vasodilatation and by increasing diuresis. In addition, Ang 1–7 carries out the endothelial protective activity by increasing the production of nitric oxide (NO), thus reducing vascular inflammation [23][24], and increasing the stability of the atherosclerotic plaques [25][26]. On the other hand, the inhibition of ACE2, causes an increase in angiotensin II, with its hypertensive and pro-oxidant effects [24][27][28]. However, the role of ACE2 seems to be controversial as according to recent studies, the soluble form of the receptor could have a protective role against coronavirus [29].

2. Exercise Training in the Post-Acute Phase

In both hospital and home settings, it is useful to divide exercise programs into three levels of effort (low, medium, and high) [30][31], based on the patient's condition. A complete initial assessment should include exercise capacity through the 6 Minute Walking Test (6MWT) [32], physical function through the short physical performance battery (SPPB), strength, and also identify existing impairments in basic activities of daily living (ADL) and instrumental activities of daily living (IADL) [33][34]. The following parameters should be constantly evaluated during the exercise [35][36]:

- Saturation: must remain above 92–93% during the whole exercise [36]
- Heart rate: must not increase more than 20 beats per minute from the baseline heart rate during mild intensity exercise (patient's pharmacological therapy should also be carefully considered, especially the use of beta-blockers that limit the physiological increase in frequency during exercise) [36]
- Systolic blood pressure: must be ≥90 mmHg and ≤180 mmHg [36]
- Symptomatology: with use of the Borg scale for dyspnea (must not exceed a score of 4) and of the rate of perceived exertion (RPE) scale for fatigue (must not exceed a score of 11–12) [35][36].

The purpose of physiotherapy in the context of cardiovascular complications of COVID-19 is to trigger the systemic antioxidant response to modulate the inflammatory state generated by the virus, and to intervene in the endothelial dysfunction caused by the same. This can be achieved through exercise training, among which the most used types are:

Aerobic endurance training (Table 1, Point a): provides prolonged training periods lasting at least 20 minutes at sub-maximal intensity from 40–60% of the maximum heart rate reserve (HRR), which can be increased up to 80%

based on the patient's condition [36][37], with a frequency of 3 to 5 times per week. It is now established that regular moderate-intensity aerobic exercise increases dependent endothelial vasodilation in subjects with impaired endothelial function, increasing the bioavailability of NO [38][39][40][41]. The effects of the exercise include the activation of systemic antioxidant mechanisms and anti-inflammatory defenses that induce a decrease of arterial stiffness [42][43], with endothelium-dependent vasodilation induced by NO, and therefore, dose-dependent hypotensive effects [44] in terms of extent and duration [45][46][47].

Table 1. Exercise training and cardiovascular effects. Abbreviations: HRR, heart rate reserve; RPE, rate of perceived exertion; NO, nitric oxide; MET, metabolic equivalent of task; RM, repetition maximum.

Training Type	Exercise Description	Exercise Frequency	Cardiovascular Effects
(a) Endurance training(ET)	• Aerobic • Continuous exercise periods, at least 20 minutes • Low-moderate intensity, 40–80% HRR, RPE = 12	3–5 times per week	• Endothelium dependent vasodilation • Endothelial function improvements • Increased bioavailability of NO • Activation of systemic antioxidant and anti-inflammatory defenses • Decrease in arterial stiffness • BP reduction
(b) Interval training(IT)	• Aerobic • Series of moderate-high intensity exercises, interspersed with rest • Intensity 2–3 METs	3–5 times per week	• Cardiovascular function improvements • Endothelial function improvements (even greater than endurance training)
(c) High Intensity IT(HIIT)	• Aerobic-Anaerobic • Series of high intensity exercises, interspersed with less intense recovery periods	2–3 times per week	• Endothelial function improvements (linked to the intensity variation within the same exercise)

Training Type	Exercise Description	Exercise Frequency	Cardiovascular Effects
	• Usually lasts under 30 minutes		
(d) Resistance training(RT)	• Anaerobic • Series of 8–12 repetitions, with 2–3 minutes of rest (2–4 sets) • Moderate intensity, 8–12 RM • Resistance is offered by an external load (e.g., elastic band) or body weight	2–3 times per week	• Rapid increases in BP and HR, during the exercise • BP reduction that lasts up to 24 h, in post exercise • Endothelium dependent vasodilation (<than ET) • Endothelial function improvements (<than ET)

Interval training (Table 1, Point b): interval exercises alternate training periods with periods of rest and can be carried out at various levels of intensity. As a first approach for more compromised post COVID-19 patients, interval training is preferable and better tolerated at an intensity of 2–3 METs, with a frequency of 3 to 5 times a week. Interval exercises, according to some authors, seem to be responsible for cardiovascular changes and endothelial function, in equal or even greater measure than endurance training [47][48][49].

In the context of interval training, however, there is a great deal of evidence in favor of the cardiovascular benefits of high intensity interval training (HIIT) (Table 1, Point c). HIIT alternates periods of short and intense anaerobic exercise with periods of recovery with less intense aerobic activity. This variation within the same exercise is responsible for improving endothelial function [50][51], however, in patients post COVID-19, high intensity exercises can only be administered after a careful initial evaluation, and in the post-acute phase for a high level of fatigue and respiratory distress with a frequency of 2 to 3 times a week.

Resistance training (Table 1, Point d): is an anaerobic exercise mode characterized by the presence of an external load, or the body weight itself. Typically, it is more used in the treatment of sarcopenia [52] than for cardiovascular pathologies. We can distinguish two kinds of training: resistance training, which involves specific muscle groups, and circuit training, which includes the whole body, thus generating a more important hypotensive response [53]. As part of the cardiac rehabilitation programs for post COVID patients, resistance training should be offered at moderate intensity equal to 8–12 repetition maximum [36] at a frequency of 2–3 times a week. However, intensity and frequency, as in the case of HIIT must be modulated in relation to the clinical and hemodynamic conditions of the patients [54]. From a cardiovascular point of view, resistance training during exercise is accompanied by significant increases in blood pressure and heart rate [55]. At the same time, there is a reduction in post-exercise pressure that lasts up to 24 hours [53]. In a study conducted on hypertensive rats, it appears to have induced

improvements in endothelial function mediated by an increase in NO, together with a reduction in systemic inflammation [56], even though these results are considered to be of lesser extent than endurance training [57].

Despite the low incidence of adverse events during cardiac rehabilitation, in post-COVID patients it is appropriate to keep in mind the following elements, which require further study, and a possible suspension of the physiotherapy [36][58][59]:

- Saturation <88–93%
- Heart rate <40 beats per minute, or >120 beats per minute
- Systolic blood pressure <90 mmHg and >180 mmHg
- Body temperature fluctuations >37.2 °C
- Respiratory symptoms and fatigue that worsen during exercise and are not alleviated after rest
- Symptoms such as chest tightness or pain, difficulty in breathing, severe cough, dizziness, headache, unclear vision, palpitations, sweating and instability.

These parameters must be targeted to the specific risk profile of the patient, according to the response obtained at the 6MWT performed during the physiotherapy evaluation.

Exercise training is therefore a powerful tool in physiotherapy that is capable of inducing significant changes in the cardiovascular system and functional to the recovery of the endothelial dysfunction, which is now recognized as responsible for numerous pathologies [60]. Evidence highlights the clinical outcomes of cardiac rehabilitation on endothelium and myocardium in patients with acute myocardial infarction or who have undergone coronary artery bypass graft surgery (CABG) surgery, percutaneous coronary intervention (PCI), heart transplantation, heart valve surgery, and in patients with chronic heart failure (CHF) [61]. In particular, clinical effects of exercise have been reported on coronary endothelial function in patients with coronary artery disease (CAD) [62], demonstrating that 4-weeks of exercise training was effective in attenuating the paradoxical arterial vasoconstriction in epicardial conduit vessels by −54% and increasing average peak flow velocity by +78%. In addition, Belardinelli and colleagues [63], who performed an exercise training program in heart failure (HF) patients for >10 years, demonstrated an improvement in quality of life and a reduction in major cardiovascular events, including hospitalizations for chronic heart failure and cardiac mortality. Finally, Ades et al. [64] have clearly reported the clinical outcomes that can be obtained by a cardiac rehabilitation program, classifying them as: (1) primary clinical outcomes, (2) intermediate clinical outcomes, (3) quality-of-life, and they defined the improvement measurable at different levels: cardiovascular, metabolic, skeletal muscle and psychologic [64].

Due to the wide variety of possible exercise programs that can be obtained by combining intensity, duration, speed of execution, and exercise mode in various ways, and defining the program on the basis of constant patient

monitoring, exercise training is well suited to the treatment of post-COVID patients with impaired cardiovascular system of various degrees.

3. Conclusions

Owing to the recent onset of the disease, evidence concerning the rehabilitation treatment of cardiovascular complications from COVID-19 is scarce in the literature. The primum movens of cardiovascular complications seems to be endothelial dysfunction [65][66], and also connected to the severe thromboembolic complications at venous, pulmonary and cerebral level that have been recorded in many patients [66][67][68], including also young patients [69]. It is important to keep in mind that, although the exercise exerts beneficial effects on endothelial function as evidenced in acute myocardial infarction, CAD, and HF patients and contributes to the reduction of cardiovascular alterations [70], whether it actually translates into improved clinical outcomes in COVID-19 patients remains to be demonstrated.

Thus, any patient with COVID-19 would require a complete assessment of their symptoms, exercise capacity, function, and potential impairments [36]. Depending on the patient's initial assessment and their clinical and cardiovascular risk profile, an exercise program should be developed that considers all clinical features of the patient. Exercise is considered to be a biological drug [71], so we must pay close attention to ensure the right dose is administered to our patients. Exercise can be modulated in terms of intensity, frequency and speed of execution in order to adapt programs to this novel group of patients that is emerging as a result of the COVID-19 pandemic.

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