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Vasodilators, Enhancers of Prevention through Exercise of COVID-19?

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

The role of the *angiotensin-converting enzyme 2 (*ACE2) receptor in SARS-CoV-2 virus infection and disease progression is complex, and the interaction with exercise is being investigated. However, the virus binds to ACE2. The paper hypothesizes that exceeding the lactic threshold during exercise would cause, through hypoxia, over expression of ACE2. Vasodilators would prevent hypoxia and implicitly this fact. To the complexity of the phenomenon is added the possibility of preventing severe forms of COVID-19 through mitochondrial biogenesis induced by exercise. As a result, the paper examines the ability of antihypertensives used in combination with exercise to treat cardiovascular disease to prevent ACE2 over expression and to stimulate mitochondrial biogenesis. Future research is needed, but it is worth mentioning that some such hypertensives have been proposed for the treatment of COVID-19.

Keywords: Effort intensity; COVID-19; vasodilators.

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1. INTRODUCTION

The COVID-19 epidemic is on the rise, especially in Western countries [1]. For this reason, efforts are being made to elucidate the pathogenesis and the means of treatment. One of the directions is to investigate the relationship between physical exertion and ACE2 receptors. Angiotensin-Converting Enzyme-2 (ACE2) is used as an entry receptor in cells by SARS-CoV-2, being present in cardiac, pulmonary, renal, intestinal and vascular cells [2]. Exercise maintains or restores the natural balance between the ACE2-Ang1-7-Mas receptor axis and the ACE-Ang II-AT1 receptor pathway as a possible means of mitigating COVID-19 susceptibility and subsequent risk upon exposure [3]. High-intensity interval exercise significantly increased plasma levels of ACE2, which is not the case with moderate-intensity continuous exercise [4]. In hypoxic human pulmonary artery smooth muscle cells, ACE2 mRNA and protein levels increased during the early stages of hypoxia [5]. It is likely then that hypoxia created after exceeding the lactic threshold during interval exercises peeks exceeds 80% of the maximum volume of oxygen (VO2 max) cause an increase in plasma ACE2 level. But while ACE2 expression in vascular edothelium and in cardiac, renal, and intestinal tissues may be important for worsening the disease through the spread of cellular infection by the virus, increased airway ACE2 expression may influence the risk of infection. Although, on the other hand, ACE2 is considered to have an anti-inflammatory effect and increased plasma levels may ameliorate the clinical manifestations of COVID-19, and exercise has a positive effect by increasing the ACE2 / Ang (1–7) / Mas axis and reducing the ACE / Ang II / AT1R axis [6], the author of that study admits that future investigations are needed to elucidate these issues. Consequently, I argue based on the arguments in the literature that it is prudent that for the prophylaxis of severe forms of COVID-19 through exercise (one of the objectives being the functional restoration of mitochondria, in order to protect against oxidative stress and consequently to prevent the COVID-19 characteristic inflammatory cascade - [7]) to recommend endurance exercises of moderate intensity (below 80% of VO2 max) that at most to restore normal plasma levels of ACE2 (as might be extrapolated from experimental studies - [8]), without causing its increased expression in the anatomical structures targeted by virus replication. This could prevent an increased risk of infection. The ACE2 receptor protein robustly localizes within the motile cilia of airway epithelial cells, within the upper (nasal) and lower (pulmonary) respiratory tracts [9]. It is accepted that oxygen diffuses through pneumocytes before reaching the pulmonary capillaries [10], so it is unlikely that ACE2 will be expressed in increased amounts in the lungs during exercise. This is not the case with the upper respiratory tract. Therefore, in order to avoid hypoxia during exercise, in addition to dosing the effort and choosing exercise programs during which the lactic threshold should not be exceeded, supplements and even medications could be used. The aim of this paper is to identify substances that prevent hypoxia and are added to physical exertion, as supplements or as a combination of physical therapy - drug therapy. Some may be used as adjuncts to the prophylaxis of severe forms of COVID-19 through exercise.

Supplements and drugs that may potentiate the prophylactic effect against COVID-19 of exercise

A preliminary study in 2017 showed that during strength exercises, individuals who use whey protein supplementation have a different cardiovascular adaptation to exercise, probably caused by nitric oxide (NO)-induced vasodilation that prevents hypoxia [11]. Although it is a preliminary study, the information of which should be used with caution, it opens some doors to understanding the COVID-19 treatment approach. Avoiding deoxygenation induced by intense exertion could prevent increased ACE2 expression in the airways, which would implicitly promote SARS-CoV-2 infection. On the other hand, mitochondrial biogenesis and function are enhanced by nitric oxide [12], which means that protein supplementation can stimulate mitochondrial restoration, a process that is hypothesized to prevent severe forms of COVID-19 [6]. In this case it should be noted NO donors, belonging to different classes, used for the treatment of heart disease [13], possibly, in combination with a beta blocker, as adjuvants of recovery exercises [14]. Calcium antagonists (verapamil and nifedipine), indicated in coronary heart disease and hypertension, lead to a relaxation of smooth vascular muscles and exert a cardiodepressive effect, and during physical exercise VO_2 max and endurance performance are not impaired [15]. Especially for patients who exercise regularly and suffer from mild hypertension, calcium antagonists offer a viable therapeutic alternative to beta-blockers because,

compared to taking only calcium antagonists, the combination of calcium antagonists and beta-blockers affects physical performance [15]. Due to the avoidance of hypoxia by vasodilation, we can assume that they also prevent the overexpression of ACE2 and consequently decrease the chances of infection with SARS-CoV-2 in patients undergoing a cardiovascular rehabilitation program. Beta-adrenergic blockers not only prevent hypoxia by vasodilating effect, but by downregulating ACE2 receptors have been proposed in the treatment of COVID-19 [16]. They may be a factor in the prevention of SARSCOV-2 infection in hypertensive patients undergoing motion therapy with the addition of beta-adrenergic blockers [17]. Unfortunately beta-adrenergic blockers (metoprolol) aggravate mitochondrial dysfunctions [18], which raises questions about their effectiveness in the prophylaxis of severe forms of COVID-19. The effects of renin inhibitors on ACE2 and implicitly on the evolution of COVID-19 continue to be a matter of dispute, but it still appears that the administration of these vasodilators has rather beneficial effects [19,20]. Although the entry of the virus into the cell is facilitated by ACE2, depletion of ACE2 by infection prevents vasodilation with antithrombotic and anti-inflammatory role [19]. So this balance seems to lean towards the protective role of ACE2. Renin inhibitors increase energy production and protect the structure of mitochondria, having the potential to treat diseases characterized by mitochondrial dysfunction (hypertension, diabetes) [21]. Mention should be made of the involvement of mitochondrial dysfunctions in the pathogenesis of COVID-19 [22], diabetes and hypertension being known risk factors for the development of severe forms of the infection. Angiotensin receptor blockers and angiotensin converting enzyme inhibitors induce ACE2 overexpression in cell membranes, and their effect on COVID-19 infection appears to be a double-edged sword (being under investigation) [23]. Hydralazine should be discussed among direct acting vasodilators. In an animal study of (Brojakowska A et al., 2020) using rats it was found that hydralazine does not increase ACE2 expression [24]. Hydralazine is used as an adjunct to exercise recovery in patients with chronic severe aortic insufficiency [25]. Moreover, hydralazine improves mitochondrial function [26], which emphasizes its potential to help prevent infection and severe forms of COVID-19. Phosphodiesterases inhibitors have already been proposed for the treatment of

Table 1. Effects of antihypertensive drugs on ACE2 expression and mitochondrial biogenesis

Drug class	stimulating effect on ACE2 expression	inhibitory effect on ACE2 expression	stimulating effect on mitochondrial biogenesis	inhibitory effect on mitochondrial biogenesis
NO donors		↑ (presumably by preventing hypoxia)	↑	
calcium antagonists		↑ (presumably by preventing hypoxia)		
beta-adrenergic blockers		↑[16]		↑ (aggravates mitochondrial dysfunction) [18]
renin inhibitors	unknown, but administration appears to have beneficial effects on the evolution of COVID-19 [19, 20]		↑	
angiotensin receptor blockers and angiotensin converting enzyme inhibitors	↑ [23]			
direct acting vasodilators (hydralazine)		(does not increase ACE2 expression) [24]	↑[26]	
phosphodiesterases inhibitors	unknown, but are proposed for the treatment of COVID-19 [27])		↑[28,29]	

COVID-19 [27]. Previous animal studies done using rats had been shown that phosphodiesterase inhibitors and moderate-intensity preconditioning training decreased the release of prooxidants and improved the activity of antioxidant enzymes thus preventing systemic oxidative stress [28]. In addition, experimental data suggest that specific phosphodiesterase inhibitors that increase cyclic guanosine monophosphate (*cGMP*) are inducers of mitochondrial biogenesis in vitro and in vivo [29]. Table 1 summarizes some antihypertensives that by their vasodilating effect influence tissue oxygenation, mentioning their effect on ACE2 expression and mitochondrial biogenesis. The paper did not aim to discuss the influence of exercise or drugs on immunity, but it is known that immunity is not affected by the performance of 45 minutes of moderate physical exertion [30].

2. CONCLUSIONS

Due to the danger of stimulation of ACE2 expression (SARSCOV-2 receptor) by hypoxia, the intensity of exercise recommended for the prophylaxis of severe forms of COVID-19 does not appear to exceed 80% maximum volume of oxygen. In this sense, medium intensity endurance exercises are indicated. It seems that deoxygenation during high-intensity exercise can be alleviated by using whey protein supplements, due to the vasodilating effect of nitric oxide. Of the vasodilators used in combination with motion therapy to treat various conditions, only nitric oxide donors and hydralazines appear to simultaneously meet the conditions to inhibit or at least not stimulate ACE2 expression (which may prevent the risk of SARSCOV-2 infection) and stimulate mitochondrial biogenesis (a factor that can prevent the development of severe forms of infection). Due to the multitude of variables and unknowns in the pathogenesis of COVID-19, future research on this subject is indicated.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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