

## VIEWPOINT

## A Probable Relationship between Physical Exercise and COVID-19 Mediated by the Renin-Angiotensin-Aldosterone System

Renato Aparecido de Souza,<sup>1,2</sup> Priscila Missaki Nakamura,<sup>1,3</sup> Inaian Pignatti Teixeira,<sup>4</sup> Marco Tulio de Souza,<sup>5</sup> Wonder Passoni Higino<sup>1,2</sup>

*Federal Institute of Education, Science and Technology of South of Minas Gerais - Campus Muzambinho,<sup>1</sup> Muzambinho, MG – Brazil.*

*Federal University of Alfenas,<sup>2</sup> Postgraduate Program in Rehabilitation Science, Alfenas, MG – Brazil.*

*São Paulo State University - Institute of Biosciences, Campus Rio Claro,<sup>3</sup> Rio Claro, SP - Brazil*

*University of São Paulo,<sup>4</sup> School of Arts, Sciences and Humanities, São Paulo, SP - Brazil*

*Campinas Medical Center Hospital,<sup>5</sup> Campinas, SP - Brazil*

At the end of 2019, a novel human virus (SARS-CoV-2) causing severe acute respiratory syndrome (SARS) expanded globally from China. In February 2020, the World Health Organization (WHO) officially named this infectious disease coronavirus disease 2019 (COVID-19), and in March 2020, WHO announced COVID-19 a global pandemic. In June 2020, according to an interactive web-based dashboard to track COVID-19 in real time developed by the Johns Hopkins University Center for Systems Science and Engineering (<https://www.eficiens.com/coronavirus-statistics/>), more than 7 million people infected with the new coronavirus and more than 400,000 deaths were confirmed around the world.<sup>1</sup> China and European countries have found solutions to manage and reduce the number of daily infections. However, new COVID-19 cases have risen at alarming rates in many other countries, and today Brazil is the third country in number of cases.<sup>2</sup>

Recently, angiotensin-converting enzyme 2 (ACE2) was identified as an entry receptor for SARS-CoV-2. The binding of the novel coronavirus to ACE2 can reduce (downregulation) the number of ACE2 receptors, causing severe damage to alveolar cells that triggers a series of pulmonary and respiratory reactions that can lead to death.<sup>3,4</sup>

ACE2 is part of a complex and integrated metabolic pathway known as the renin-angiotensin-aldosterone

system (RAAS), which has been the target of several studies that describe physiological adaptations induced by physical exercise. Thus, given the potential role of ACE2 in the pathophysiology of coronavirus infection, this scientific letter sought to establish a probable relationship between physical exercise and COVID-19 through the RAAS and thereby add a contribution to studies on the management and prevention of COVID-19.

### The Pathways of the RAAS

The classical pathway of the RAAS is initiated by the release of angiotensinogen by the liver, which, combined with renin secreted by the kidneys, produces angiotensin I (Angio I). Angio I is converted to angiotensin II (Angio II) by the action of the angiotensin-converting enzyme (ACE) in the lungs. The physiological effects of Angio II are mediated primarily through membrane receptors, especially of the Angio II type 1 (AT1) receptor. These receptors, when stimulated, promote vasoconstriction, hypertrophy and hyperplasia of vascular cells, sodium retention, generation of reactive oxygen species (ROS), and inflammatory, thrombotic and fibrotic processes, which can cause tissue damage.<sup>5</sup>

A counter-regulatory pathway of the RAAS involves the conversion of Angio II to angiotensin 1–7 (Angio-1–7) and membrane receptors (MAS) through the enzymatic activity of angiotensin-converting enzyme 2 (ACE2), which promotes a vasodilatory, anti-inflammatory, anti-fibrotic, and anti-proliferative effect on the tissues.<sup>6</sup> Under appropriate physiological conditions, there is a balance between these two RAAS pathways (Figure 1).

### Keywords

COVID-19; Betacoronavirus; SARS-CoV2; Severe Acute Respiratory Syndrome; Pandemics; Renin-Angiotensin System; Exercise/prevention and control.

#### Mailing Address: Renato de Souza

Rua Dinah, 75, Canaã. Postal Code: 37890-000, Muzambinho, MG – Brazil.

E-mail: renato.souza@muz.ifsuldeminas.edu.br

## Physical Exercise and the RAAS

Previous studies, especially experimental studies, have shown that physical exercise can reduce the activation of the classic RAS pathway and increase the activation of the components of the counter-regulatory pathway (ACE2/Angio-1-7/MAS) (Figure 2).<sup>7-13</sup>

However, the literature is still scarce about the effects of physical exercise on the ACE2/Angio-1-7/MAS pathway, mainly on ACE2 (the primary receptor site of SARS-CoV-2). In short, it was shown in rodents that physical exercise increased the expression of MAS receptors in aortas, thereby improving the vasodilatory effect of Angio-1-7.<sup>9</sup> Deficiency of ACE2 has been shown to be related to impaired physical performance and adaptations of the cardiac and skeletal muscles.<sup>10</sup> In addition, swimming improved oxidative capacity<sup>11</sup> and sensitivity to insulin in muscle tissue,<sup>12</sup> and in all these studies, a role of the ACE2/Angio-1-7/MAS pathway has been suggested to be involved in the adaptive process. In humans, it was shown that aerobic physical exercise acutely increased the activity of the ACE2/Angio-1-7/MAS pathway, leading to increased plasma and urinary levels of ACE2, especially with a continuous moderate exercise protocol.<sup>13</sup>

In addition, evidence from genetic studies have shown the relationship between physical exercise and RAAS modulation. Among the main findings, it has been highlighted that physical exercise affects the cardiovascular system, by lowering blood pressure, inhibiting the interactions between ACE, Angio II, and AT1 receptors activated by the classical RAAS pathway, and increasing the expression of ACE2.<sup>14,15</sup>

## COVID-19 and Physical Exercise

The lethality of COVID-19 has been associated with a decrease in the number of ACE2 receptors, impairing the activation of this important lung-protective protection pathway.<sup>3,4</sup> With less ACE2 available to convert Angio II to Angio-1-7, preventing the anti-inflammatory and anti-fibrotic effects of the ACE2/ Ang-(1-7)/Mas pathway, more angiotensin is produced via the ACE/Ang-I/AT1 pathway, leading to a heightened inflammatory milieu and lung damage.<sup>16</sup>

With respect to therapeutic research on COVID-19, at least three clinical approaches targeting ACE2 receptors have been described: vaccines, Angio II receptor blockers, and by increasing the levels of the soluble form of ACE2.<sup>4</sup>

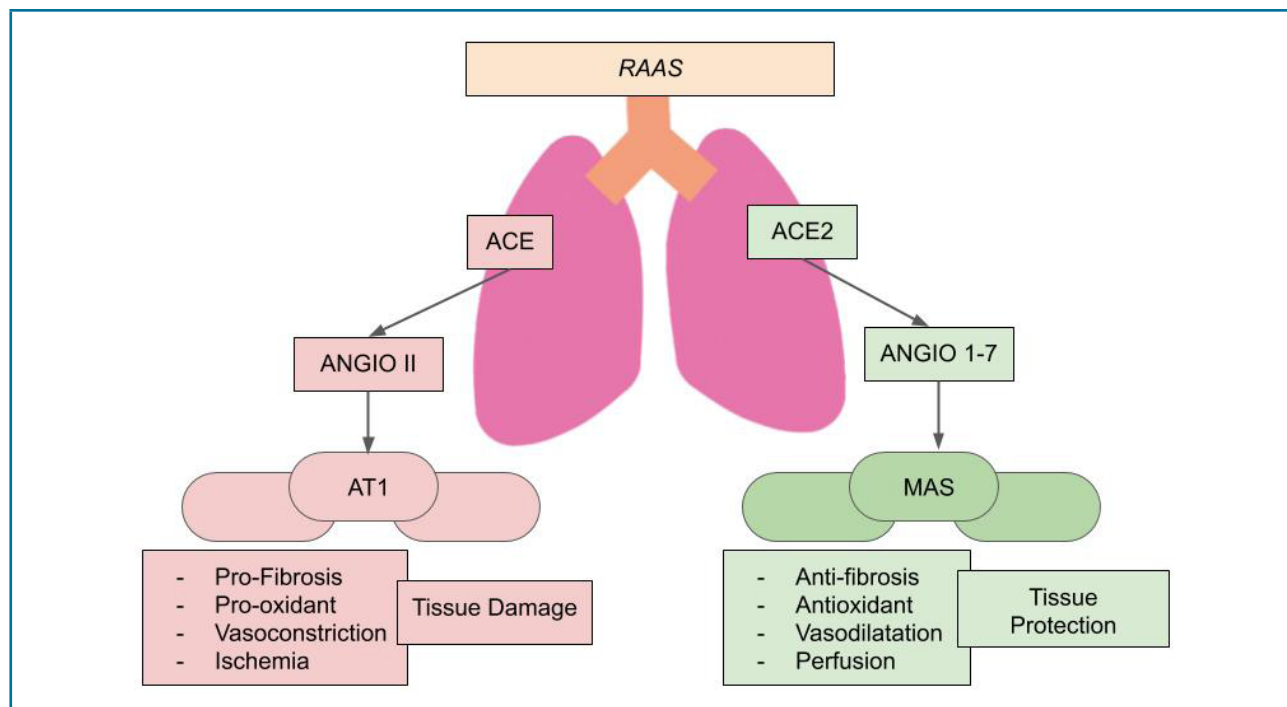
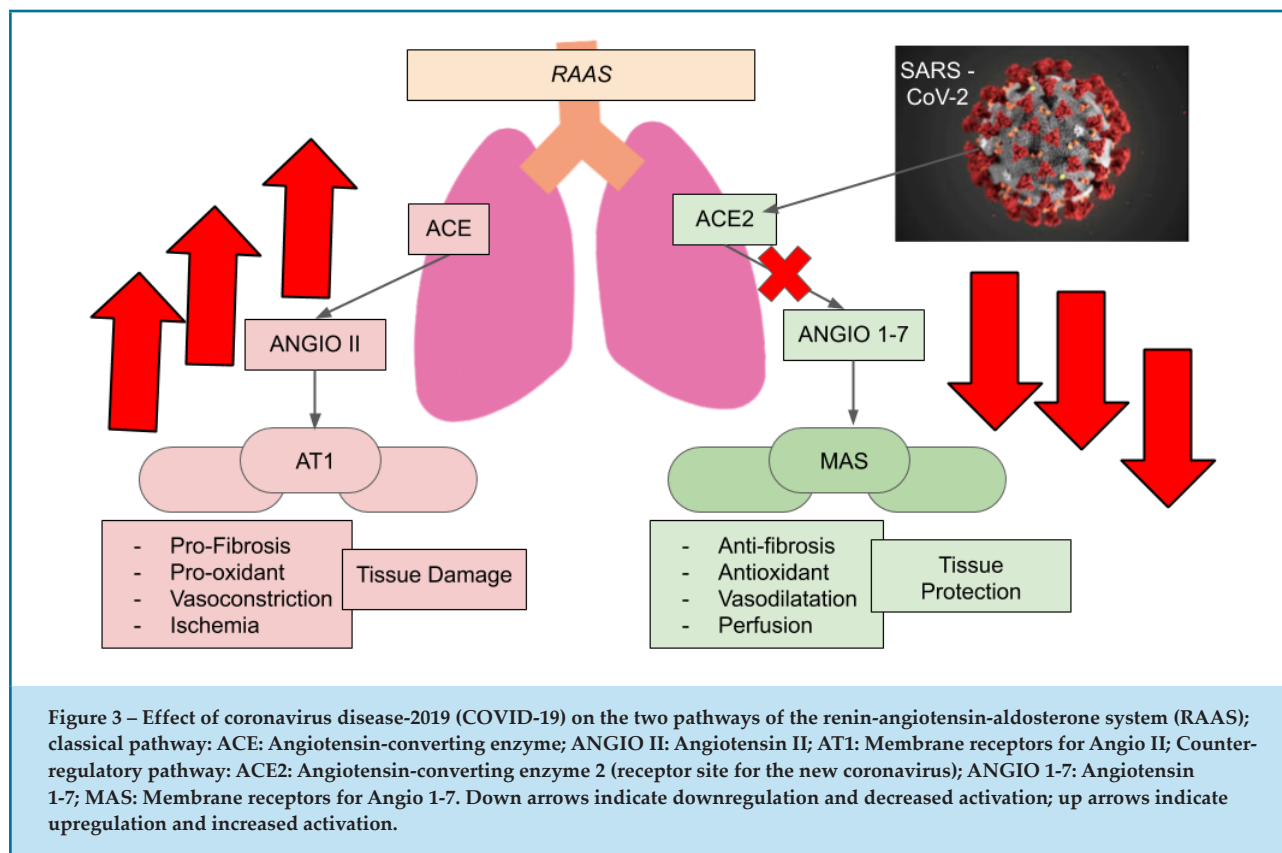
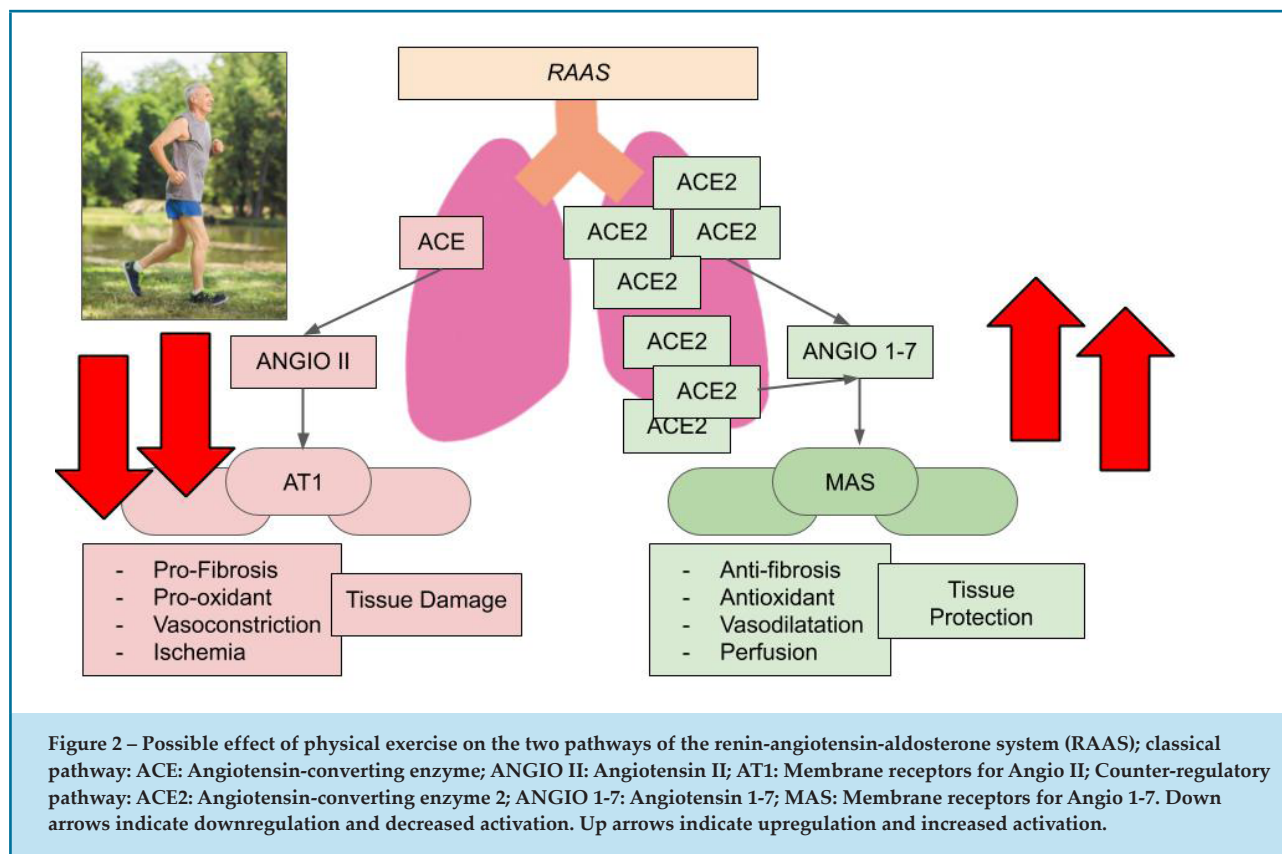


Figure 1 – Balance between the two pathways of the renin-angiotensin-aldosterone system (RAAS) and their general effects. Classical pathway: ACE: Angiotensin-converting enzyme; ANGIO II: Angiotensin II; AT1: Membrane receptors for Angio II; Counter-regulatory pathway: ACE2: Angiotensin-converting enzyme 2; ANGIO 1-7: Angiotensin 1-7; MAS: Membrane receptors for Angio 1-7.



This last strategy has been suggested based on the fact that soluble ACE2 could prevent the binding of the coronavirus to the full-length ACE2, and thereby not only neutralize the virus but also rescue ACE2 cellular activity, counter-regulating RAAS and protecting pulmonary tissue.<sup>17</sup>

Thus, based on the above, the potential link between physical exercise and COVID-19 is the following: while the new coronavirus is capable of compromising the ACE2/Angio-1-7/MAS pathway (Figure 3), physical exercise would be able to stimulate it, and hence prevent the RAAS imbalance and associated lung injury.<sup>18</sup>

In addition, considering that (i) chronic diseases, such as diabetes, obesity, dyslipidemia and hypertension, are important risk factors that increase the lethality of COVID-19, (ii) the elderly population is the group with the highest COVID-19 mortality rates,<sup>3</sup> (iii) the aging process reduces the expression of ACE2, and the classical pathway of RAAS is involved in the pathophysiology of many chronic diseases, and that (iv) there is scientific evidence supporting the benefits of regular physical exercise for the elderly population and people with chronic non-transmissible diseases,<sup>19,20</sup> a protective effect of physical exercise against the effects of COVID-19 may be suggested.

However, until now, there has been no scientific study evaluating the preventive effects of exercise on COVID-19 or studies with patients with COVID-19 submitted to physical exercise. In fact, the American College of Sports Medicine (ACSM) recently published a brief position recommending that people exercise during the COVID-19 pandemic.<sup>21</sup>

Given the scientific basis presented here, it seems reasonable to consider a protective effect of physical exercise in relation to COVID-19, by restoring or maintaining an appropriate balance between the classical

and counter-regulatory pathways of the RAAS. Future studies are needed to clarify the relationship between physical exercise and COVID-19. For now, in addition to the widespread use of preventive measures, such as the correct hand washing, use of gel alcohol and face masks, and social isolation/distancing, physical exercise should also be considered for COVID-19 prevention.

## Author Contributions

Conception and design of the research: Souza RA, Nakamura PM, Teixeira IP, Souza MT, Passoni WH. Analysis and interpretation of the data: Souza RA, Nakamura PM, Teixeira IP, Souza MT, Passoni WH. Writing of the manuscript: Souza RA, Nakamura PM, Teixeira IP, Souza MT, Passoni WH. Critical revision of the manuscript for intellectual content: Souza RA, Nakamura PM, Teixeira IP, Souza MT, Passoni WH.

## Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

## Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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## Study Association

This study is not associated with any thesis or dissertation work.

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