
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.

Medical Hypotheses 142 (2020) 109835

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

# Exercise as medicine for COVID-19: An ACE in the hole?

ARTICLE INFO

*Keywords:*
Exercise
Angiotensin converting enzyme
COVID-19

The COVID-19 pandemic is currently exacerbating another established global pandemic – physical inactivity [1]. The World Health Organization attributes approximately 3.2 million deaths per year to sedentary behavior. For many, social distancing and quarantine coupled with the systemic closure of fitness centers and public parks have imposed unique structural barriers to maintaining a physically active lifestyle. From a public health perspective, the importance of not conflating shelter-in-place with staying-in-place needs to be reinforced. Herein, exercise will be discussed as a possible therapeutic strategy to bolster resilience against COVID-19 via effects on ACE2.

Since the angiotensin converting enzyme-2 (ACE2) receptor has been acknowledged as an important cellular entry point for SARS-CoV-2, controversy has ensued regarding use of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) in the management of COVID-19 patients with hypertension. Animal studies suggest that ACEi/ARBs may upregulate expression of ACE2 receptors. As such, concern arose that use of ACEi/ARBs by hypertensives might increase risk for developing COVID-19, exacerbate severity of COVID-19 morbidity and lead to increased fatal events with some further advocating for ACE2 blockade (or angiotensin II administration) as a potential strategy to mitigate viral entry of SARS-CoV-2 into ACE2 expressing cells [2]. Zhang et al. recently examined the association of in-hospital ACEi/ARB use with all-cause mortality in a sample of 1128 COVID-19 patients with hypertension. Results highlight that in-hospital use of ACEi/ARBs by hypertensives with COVID-19 was associated with lower mortality risk compared to hypertensives not using these agents. Given the inherent limitations of a retrospective cohort study, care should be taken with interpretation of findings. Nonetheless, results are provocative and shine a light on the complexity of ACE2 in COVID-19 pathophysiology.

ACE2 via the production of Angiotensin 1–7 has anti-inflammatory and antifibrotic effects via the Mas receptor. Thus, the ACE2-Ang1-7-Mas receptor axis and the ACE-Ang II-AT1 receptor pathway may be viewed as two opposing yet complementary pathways; a duality whose balance is needed for optimal health. The binding of COVID-19 to the ACE2 binding site downregulates ACE2 and thus the ACE2-Ang1-7-Mas receptor axis, essentially over-activating the ACE-Ang II-AT1 receptor pathway. With less ACE2 available to convert angiotensin to Ang1-7 and effect anti-inflammatory and antifibrotic pathways, more angiotensin is produced via ACE leading to a heightened inflammatory milieu and lung injury [3]. As an illustrative example, ACE2 gene deletion in wildtype mice worsens Bleomycin-induced lung injury via increased expression of the profibrotic genes α-smooth muscle actin and TGF- ß1 while treatment with intraperitoneal recombinant human ACE2 protects against Bleomycin-induced fibrosis [4]. Thus, discontinuation of ACEi/ARBs by individuals with hypertension is not advised at this time and indeed may lead to higher mortality rates in COVID-19 patients [5]. Indeed, use of ACEi/ARBs may be protective.

The question arises – what can be done to maintain or restore 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? [6] In one word – *exercise*. Exercise training can augment the ACE2-Ang1-7-Mas receptor axis while simultaneously inhibiting the ACE-Ang II-AT1 receptor pathway [7]. Whether COVID-19 causes long term cardiopulmonary damage will require study. If cardiopulmonary rehabilitation is indeed needed, exercise may be the therapy of choice as activation of the ACE2-Ang1-7-Mas receptor axis with exercise training reduces pulmonary fibrosis [8]. Among the factors responsible for the pulmo-protection are reductions in TGF- ß1.

At a time when many individuals are choosing to move less, the message that exercise is medicine is needed more. Exercise may be an ACE in the hole to help lower risk of COVID-19 infection and minimize the cardiopulmonary sequela during recovery.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.109835.

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Received 23 April 2020; Accepted 11 May 2020

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Kevin S. Heffernan[a,*], Sae Young Jae[b]
[a] *Department of Exercise Science, Syracuse University, Syracuse, NY, USA*
[b] *Department of Sports Sciences, University of Seoul, Seoul, South Korea*
*E-mail address:* ksheffer@syr.edu (K.S. Heffernan).

* Corresponding author at: The Human Performance Laboratory, Department of Exercise Science, Syracuse University, Syracuse, NY 13244, USA.