Sarcopenia and COVID-19:

A Manifold Insight on Hypertension and the Renin Angiotensin System

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Introduction

The renin-angiotensin system (RAS) is composed of widely interconnected biochemical systems (Figure 1).[1] It plays an important role in the regulation of blood pressure, muscle blood flow, and skeletal muscle metabolism. Specifically, it is known that increased RAS activity plays an important role in the etiopathogenesis of age-related disorders such as hypertension, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, and cancers - in which muscle atrophy and decline of muscle strength, endurance, and physical performance (i.e. sarcopenia) can also commonly be seen.[1, 2]

Angiotensin converting enzyme (ACE) inhibitors (ACEIs) and angiotensin II type 1 (AT1) receptor blockers (ARBs) are commonly used as antihypertensive drugs via inhibiting the classical RAS pathway. The former inhibits ACE, which converts Ang I to Ang II, and the latter blocks the AT1 receptor. Both are equally important regarding blood pressure.[5] The use of ACEIs reduces the RAS activity from an earlier step than ARBs; and although ACEIs and ARBs theoretically act through the RAS, they have fundamentally different mechanisms (Table 1). [2, 3]

The associations of ACEIs/ARBs and coronavirus disease 2019 (COVID-19) have been studied since ACE2 is the entry receptor of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). [4,5] From this point of view, concerns regarding the use of RAS blockers during the COVID-19 pandemic have been reported. It has been put forward that hypertensive patients using ACEIs or ARBs may be at increased risk for COVID-19 mortality.[5] However, discussions regarding the use of ACEIs/ARBs for hypertension and their effects on morbidity or mortality in COVID-19 are still inconclusive. [6]

Accordingly, we would like to provide insight into the interplay among RAS activity-related hypertension, sarcopenia, and COVID-19. First, we would like to describe the role of medications targeted to the classical RAS pathway on COVID-19, and to describe the RAS overactivity and how it affects blood pressure and sarcopenia. We believe that this is noteworthy because hypertension is a significant comorbidity among rehabilitation patients many of whom are elderly with comorbid diseases related to RAS activation.[1] Second, we would like to call attention to the overlooked and beneficial effects of RAS blockers (especially ACEIs) on muscle mass and function. We aim to create awareness among physiatrists (who need to diagnose/treat sarcopenia patients) regarding the deleterious effects of RAS overactivity, as well as the favorable effects of RAS blockers in clinical practice.

What is the goal of the article that we wish to review?

We wish to review the recently published article by Zhang *et al*.[4] The authors studied the association between in-hospital use of ACEIs or ARBs and all-cause mortality in hypertensive COVID-19 patients. The authors retrospectively enrolled 1128 hypertensive adult patients diagnosed with COVID-19 in their multi-center study; 188 were taking ACEI/ARB and 940 were not. They compared all-cause mortality of COVID-19 who were taking ACEI/ARB to those who were not.

What is the conclusion of the article?

The risk of 28-day all-cause mortality was lower in the ACEI/ARB group than the non-ACEI/ARB group (3.7% [7/188] vs. 9.8% [92/940]; p=0.01). After adjusting for (age, gender, comorbidities, and in-hospital medications), the mortality relationship held true (HR, 0.42; 95%

CI, 0.19-0.92; p=0.03). The authors concluded that their inpatient use of ACEI/ARB was associated with a lower risk of all-cause mortality when compared with that of non-users.

Are there important strengths/limitations to the study for interpreting the results?

This article will be helpful for the management of hypertension during the COVID-19. However, although mentioned by the authors, enrolling 383 patients (34%) with hypertension who did not receive antihypertensive drugs into the non-ACEI/ARB group may contribute to bias. Moreover, they mentioned that the sample size was modest and did not have the power to detect if there was a differential effect between ACEI and ARB. There were a total of 99 deaths i.e. 7 out of 188 patients (3.7%) from the ACEI/ARB group and 92 out of 940 patients (9.8%) from non-ACEI/ARB. To improve upon this study, death rates among 4 groups (ACEI users, ARB users, other antihypertensive drug users, and nondrug users) could be compared. Although the protective role of antihypertensive drugs including ACEI/ARB against COVID-19 has been shown; elucidating the separate mortality rates of ACEI and ARB users, against other antihypertensive drug users and those who are not using any antihypertensive drugs would have been more instructive. Therefore, the main limitation is the lack of comparison between hypertension patients who had been treated with ACEIs and those who had been treated with ARBs. In this sense, we believe that evaluating further analyses on the individual mortality rates of different antihypertensive drugs against no drug in hypertensive patients with COVID-19 would be noteworthy.

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What are the relations of ACEIs/ARBs to COVID-19 mortality?

Concerning the interplay among ongoing COVID-19 pandemic, hypertension, ACEIs/ARBs, and ACE2 activity (the entry receptor of SARS-CoV-2); it was initially believed that ACEIs/ARBs were associated with increased risk of COVID-19, but this has been disproven. There have been only select preclinical studies about increased ACE2 expression and safety in patients with CoVID-19[7] and it is important to clarify the clinical effects of ACEIs and ARBs on COVID-19. As such, the clinical effects still need to be deciphered by prompt comparison of ACEI vs. ARB users in this regard.

In light of the available evidence, withdrawal of ACEIs or ARBs in high-risk patients (i.e. coronary heart disease, myocardial infarction, heart failure) particularly in the elderly, can cause clinical instability and adverse health outcomes.[7] In short, the RAS inhibitors should be continued in patients with COVID-19.[7]

How and why is the current article relevant for physiatrists and how will it change the clinical practice?

Sarcopenia is the age-related loss of muscle mass and function as well as a significant determinant of physical frailty.[8] Sarcopenia is a major global health problem that is highly common in elderly. It has been suggested that the classical RAS pathway plays an essential role in mechanisms causing muscle wasting in chronic disease states.[9] Besides, in an experimental model, it has been shown that deletion of ACE2 resulted in an earlier appearance of sarcopenia.[10] The pro-fibrotic/atrophic stimuli of the classical pathway of RAS are counterbalanced by the positive metabolic effects on the muscular tissue induced by the non-classical pathway (Fig. 1).[1, 2, 10]

In this regard, hypertension is a 'silent killer' causing significant comorbidity among elderly rehabilitation patients. A recent study investigating the prevalence of sarcopenia in the elderly by using machine learning found that (in order of importance), age, arterial hypertension, mini-nutritional assessment, number of chronic diseases and blood sodium level determined the sarcopenia.[11] Physiatrists need to consider advising their patients to continue RAS blockers (especially ACEIs) during the COVID-19 pandemic,[7] and they should also be aware of the RAS inhibitors' roles in sarcopenia.[12,13] The ACEIs can be protective against loss of muscle mass and physical performance.[12,13] It has been found that ACEI users had higher lower limb muscle mass than those using other antihypertensive drugs.[8] Additionally, continuous use of ACEIs have been found preventive in terms of gait speed and knee extensor muscle strength after a 3-year follow-up.[12,13]

In conclusion, RAS inhibitors (especially ACEIs) seem to have beneficial effects on not only reducing the blood pressure but also on preventing sarcopenia. ACEIs/ARBs have emerging evidence that they do not cause increased COVID-19 risk. However, future studies elucidating the separate mortality rates as regards ACEI vs. ARB users in COVID-19 would provide further clarity. Last but not least, similar to many other drugs used by rehabilitation patients, physiatrists should also be aware of the pros and cons of these antihypertensive drugs. This article may assist them in discussing such issues with their patients as well since these drugs do seem to have a direct impact on the neuromusculoskeletal system.

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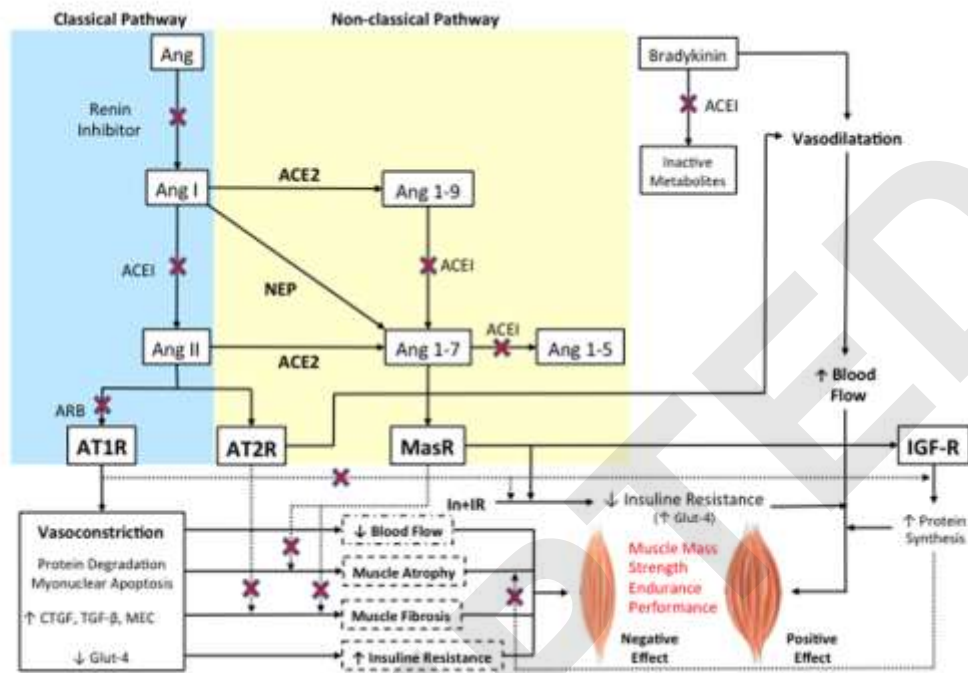
Figure Legend

Figure 1. Renin-Angiotensin System Pathway and Skeletal Muscle: A Complex Interaction.

Schematic drawing shows the classical *(blue)* and non-classical *(yellow)* pathway of the renin-angiotensin system and their multiple effects on the skeletal muscle. The pro-fibrotic/atrophic stimuli of the Ang II/AT1R axis are counterbalanced by the positive metabolic effects on the muscular tissue induced by the Ang 1-7/Mas receptor (MasR) axis. Of note, the ACEIs/ARBs modulate such an intricate "biochemical tangle" at specific and multiple levels with different consequences from each other, especially as regards the neuromuscular system.

In+IR; insulin and insulin receptor, ARB; angiotensin (Ang) II receptor type I (AT1R) blocker, IGF-R; insulin-like growth factor receptor

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Figure 1

Table 1. Comparison of the mechanisms and effects of ACEIs and ARBs

	ACEIs	ARBs
Mechanism	• Inhibit ACE which converts Ang I to Ang II, an earlier step of the RAS	• Block specifically angiotensin II type I receptors
Blood Pressure Effects	• Inhibit the formation of Ang II • Inhibit sympathetic activity • Increased level of bradykinin, a potent vasodilator	• Do not inhibit the formation of Ang II, only block the effects of AT1 receptors • Do not inhibit central sympathetic outflow or act • Do not affect bradykinin levels
Effects on Muscle	• Eliminate the fibrotic, inflammatory, and atrophic effects of Ang II • Promote muscle blood flow, reduce plasminogen activator inhibitor-1 as well as inhibit endothelial apoptosis, i.e. preserve endothelial function and anti-oxidant effects via increasing bradykinin levels and inhibiting the sympathetic activity	• Eliminate the fibrotic, inflammatory, and atrophic effects of Ang II • Do not change bradykinin levels

ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; Ang: Angiotensin II: RAS: Renin-angiotensin system; AT: Angiotensin