Title: COVID-19 and the RAAS

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Dear Editor:

Further to Thomas Hanff *et al* [1] timely call for epidemiological and clinical investigations of COVID-19 infectious disease, measurements of the renin angiotensin aldosterone system (RAAS) components, as sub-studies would be insightful of this pandemic. Angiotensin-converting enzyme 2 (ACE 2) participates in the coronavirus (SARS-CoV-2) cell entry. This infection down regulates ACE 2. Drugs that block RAAS also affect ACE 2 expression: it is down regulated by renin inhibition (RI) and up regulated by angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) (1) and mineralocorticoid receptor antagonists (MRAs) [2]. Other likely regulatory factors are age, type II diabetes and sex difference [3]. These interactions would directly affect the balance between the beneficial and deleterious angiotensins (Angs), such as, Ang (1-7) and Ang (1-9) versus excess Ang II. Such perturbations would also indirectly influence other RAAS components, and the coordination between circulating and local tissue expressions, as shown in **Figure 1 (a)** and **(b)**.

ACE 2 is distributed throughout the body and is abundantly expressed in the lung, small intestine, and in blood vessels of many organs including the brain, heart, kidney and testis [4]. These organs and blood vessels are potential sites of infection. The down-regulation of ACE 2 would reduce the production of Ang (1-7) and Ang (1-9), and concurrently prevent the reduction of the Ang II, tilting the balance to Ang II accumulation that may lead to toxicity [1], **Figure 1 (b)**. Such dysregulation likely contributed to reported cases of acute respiratory distress syndrome (ARDS) [1],

inflammation, myocardial injury [5], neurological incidences [6] and gastrointestinal manifestations [7].

Other components and the crosstalk between the systemic circulation and local tissue renin angiotensin system would also be disrupted. Changes in circulating Ang II concentration alter renin secretion through a negative feedback loop, Figure 1 (a), as Ang II decreases renin secretion increases and consequently affect renin concentration and plasma renin activity (PRA). Renin converts angiotensinogen to angiotensin I (Ang I) and PRA is a measure of this rate. Renin catalytic activity is enhanced when bound to its receptor (PPR) [8]. The inhibition of renin or ACE reduces circulating Ang II with an increase in renin concentration. It is conceivable that circulating renin could bind to PPR, where expressed, and activate local tissue renin angiotensin system. Ang II changes would also affect aldosterone stimulation and angiotensin IV (Ang IV) production. Ang IV through its receptor AT_4 has opposite biological effects to Ang II *via* receptor AT_1. We therefore suggest the measurement [9] of potential affected RAAS components, Ang (1-7), Ang (1-9), Ang II, circulating ACE 2 and PRA, from which Ang I can be derived. Such results would characterize the impact of the COVID-19 infection on the RAAS.

I appreciate and thank Dr. Maryam Cassim for reading and making constructive suggestions to this letter.

The author has no potential conflicts.

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Figure 1 (a) and (b) Legend:

(a) Flow diagram showing the renin angiotensin aldosterone system (RAAS) with coronavirus 2019 (SARS-CoV-2) infection and points of RAAS drug blockade and (b) implications of angiotensin converting enzyme 2 (ACE 2) perturbations on directly affected angiotensins (Angs). Changes in ACE 2 expression would impact the beneficial, deleterious and other components of the RAAS. Physiologically, the RAAS maintains blood pressure and body water balance. ACE 2 is down regulated by SARS-CoV-2 viral infection and renin inhibition (RI), and up regulated by angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and mineralocorticoid receptor antagonists (MRAs). Renin is secreted from the kidney which transforms angiotensinogen to angiotensin I (Ang I), the rate-limiting step. Circulating renin can also bind to (pro)renin receptor (PRR) with likely activation of local tissue renin angiotensin system throughout the body. Ang I is converted to angiotensin II (Ang II) by angiotensin-converting enzyme (ACE) and by a second enzyme, chymase. ACE also converts bradykinin (1-9) to bradykinin (1-7) (Bk (1-7)). Ang II is further transformed to Ang III, Ang IV and Ang V. A negative feedback loop controls Ang II concentration changes with renin secretion that responds in the opposite direction. Ang II stimulates the release of aldosterone. However, excessive Ang II is deleterious and is associated with hypertension, congestive heart failure and chronic kidney disease. ACE 2 transforms Ang I and Ang II, that is, Ang I to Ang (1-9), and Ang II to Ang (1-7). Ang (1-9) and Ang (1-7) have protective effects balancing the deleterious Ang II, when in excess.

Figure 1