

**LETTER****CARDIOVASCULAR MEDICINE**

# On the imbalanced protective arm of RAS in COVID-19: Lesson from rare genetic tubulopathies

The critical role of the renin-angiotensin system (RAS) in COVID-19 has been recently reviewed<sup>1</sup> and, as in other reports since the beginning of the COVID-19 pandemic, it is suggested that SARS-CoV-2, which has ACE2 as a primary target for initiating the cell infection process, compromises the ACE2 production of angiotensin-(1-7) and angiotensin-(1-9) leading to decreased Mas and Angiotensin II (Ang II) AT2-receptors (AT2Rs) stimulation. In addition, SARS-CoV-2 effects on ACE2 lead to overstimulation of Ang II AT1-receptors (AT1Rs) by less degradation of Ang II.<sup>1</sup> Thus, the pathology of COVID-19, eg, excessive immune response, endothelial dysfunction, increased clotting, thromboses, and stroke may be linked to an imbalance of the two arms of the renin-angiotensin system (RAS), where the ACE2 counterregulatory linked arm has numerous beneficial actions including anti-inflammatory, anticoagulative, anti-fibrotic effects along with endothelial, and neural protection that opposes the deleterious effects caused by heightened stimulation of the Ang II AT1Rs RAS regulatory arm.<sup>2</sup> Of note, preclinical studies with AT2Rs agonists suggest that AT2Rs stimulation may be a therapeutically effective treatment of the various organ disorders in the lung, vasculature, or brain caused by SARS-CoV-2 infection.<sup>1</sup>

We would like to point out results from several decades' of our research on Gitelman's and Bartter's syndromes (GS/BS) patients that provide *in vivo* human data that directly address the role of RAS system balance and suggest that increased ACE2 has beneficial effects with respect to COVID-19.

GS/BS patients are rare genetic tubulopathies and are characterised by hypokalemia, metabolic alkalosis, endogenously activated RAS, and high Ang II levels; yet, they usually present normotension or hypotension, along with blunted Ang II-mediated cardiovascular-renal effects.<sup>3</sup> Moreover, they have the activation of Ang II signalling via AT2Rs,<sup>3,4</sup> which likely represents a major factor in the mechanism(s) that produces the blunted Ang II signalling via AT1R and related pathways<sup>3,4</sup> and may also explain their elevated anti-inflammatory, antiapoptotic, antiproliferative, and antiatherosclerotic defences, decreased oxidative stress and Rho kinase signalling.<sup>3-5</sup> Note that this list of effects present in GS/BS patients mirrors those suggested as enhancing protective RAS via Ang II AT2Rs agonists.<sup>1</sup> Of particular interest is that GS/BS patients have increased levels of ACE2 that correlate with their increased Ang 1-7,<sup>3,6</sup> which also fits with GS/BS having an endogenous antagonism of Ang II signalling via AT1Rs.<sup>3-6</sup>

Given their endogenously higher ACE2 levels, GS/BS patients might be expected to differ in their response to SARS-CoV-2

exposure and/or infection. With this in mind, we have recently performed a telephone survey on more than 100 of our GS/BS patients' cohort living in Italian COVID-19 hot spots (Lombardia, Veneto, and Emilia Romagna) asking them if they had any COVID-19 symptoms (fever, cough, sore throat, asthenia, dyspnea, myalgia, anosmia/hyposmia, or ageusia). We found none, data that were statistically significant when analysed using those Regions COVID-19 prevalence as estimated by Signorelli et al at the time of the survey (April 2020).<sup>7</sup> The interpretation of our results is limited by the small cohort, in line with the rare nature of their syndromes, and that all of our GS/BS patients had not been tested for SARS-CoV-2 infection. However, accepting that we may have missed SARS-CoV-2 infections in our cohort, our findings are consistent with their ACE2 levels rendering BS/GS either asymptomatic, ie, resistant to COVID-19 or in fact resistant to SARS-CoV-2 infection, both of which interpretations point to ACE2 levels as key to SARS-CoV-2/COVID-19. (Manuscript submitted).

Another feature of GS/BS patients that may affect ACE2 is their metabolic alkalosis.<sup>3</sup> This alkalosis may relate to the effects of Chloroquine (CQ) and hydroxychloroquine (HCQ) affecting ACE2.<sup>8,9</sup> Central to CQ and HCQ effects are that they alkalize the *trans*-Golgi Network/post-Golgi pathway which then compromises ACE2's glycosylation. This effect, while not affecting ACE2 membrane expression, significantly reduced viral binding/infectivity of SARS-CoV.<sup>8</sup> We suggest that the GS/BS patients' metabolic alkalosis might increase the endosome pH, mimicking CQ's and HCQ effect, and thereby bring about aberrant ACE2 glycosylation resulting in an environment hostile also to SARS-CoV-2 infection or COVID-19 symptoms.<sup>9</sup> Of note, both patients treated with CQ and HCQ and GS/BS patients can exhibit a prolonged QT interval, which further suggests that both likely affect similar systems.<sup>3,10,11</sup> Whether there is altered ACE2 glycosylation in addition to increased ACE2 found in GS/BS patients is the subject of an ongoing study in our laboratory.

**DISCLOSURE**

The authors have declared no conflicts of interest for this article.

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