Angiotensin-converting enzyme-2 in SARS-CoV-2 infection: good or bad?

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Patients with previous cardiovascular disease, hypertension and diabetes have an increased risk of dying of infection with SARS-CoV-2 [1]. A common factor might be the use of inhibitors of the renin–angiotensin system (RAS), that is, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), by such patients. This has frequently been suggested once it became common knowledge that ACE2, especially in the respiratory tract, facilitates SARS-CoV-2 cell invasion via binding of a viral spike protein to ACE2 [2–4]. In fact, this had already been established during an earlier SARS-CoV outbreak with a variant showing large similarity with the current virus, therefore, now referred to as SARS-CoV-2.

Several groups, including recently Esler and Esler in the *Journal of Hypertension*, even warned that ACE inhibitors and ARBs could be harmful in SARS-CoV-2 patients [3,5,6]. Yet, is this really the case? Here, we propose that rather the opposite is expected. In patients with cardiovascular and pulmonary disease, ACE2 expression is often already low [7,8]. SARS-CoV2 infection can downregulate local ACE2 even further [9,10], which may then result in worse pulmonary and cardiovascular outcomes. If anything, RAS blockers would be the preferred drugs to treat such patients once infected to prevent tissue damage.

ACE and ACE2 are less related than the names suggest (homology ~40%). ACE or ACE1, the target of ACE inhibitors, converts angiotensin I into angiotensin II, a peptide leading to a rise in blood pressure primarily by vasoconstriction and release of aldosterone. ACE inhibitors, therefore, not only lower blood pressure but also have beneficial 'local' effects, for instance on cardiac remodelling after infarction. The carboxypeptidase ACE2 degrades angiotensin I to angiotensin-(1–9) and angiotensin II to angiotensin-(1–7), and has multiple substrates outside the RAS. Angiotensin-(1–7) and angiotensin-(1–9) have been suggested to counteract some or all of the deleterious effects of angiotensin II, such as inducing inflammation and fibrosis. However, their in-vivo levels are low and pharmacological strategies targeting these pathways, so far, have been disappointing [11,12]. More likely, therefore, ACE2 is simply one of many angiotensin-degrading enzymes. Yet, it may have multiple other effects via its other substrates, including apelin, bradykinin, and opioids.

ACE inhibitors do not block ACE2 [13]. Indirect effects of ACE inhibitors on ACE2 expression and activity show conflicting results but overall, these effects appear to be neutral [14,15]. ARBs are suggested to upregulate the pathway involving ACE2 and angiotensin-(1–7) but again data are conflicting, and differ per ARB and per organ [15–17]. For instance, ARBs may increase ACE2 activity but not its expression, which is most important for binding of virus particles [14]. Importantly, reduced ACE2 expression associates with worse cardiovascular and pulmonary outcomes, for example, in acute respiratory distress syndrome (ARDS) and shock [18,19]. After the SARS epidemic in 2003, studies were done concerning ACE2. Here it is of interest to note that SARS-CoV binding lowers ACE2 expression, thereby deteriorating ARDS in a mouse model [10]. Diminished myocardial ACE2 expression also facilitates inflammation and damage [20], and low ACE2 activity predisposes for hypertension and diabetes and their cardiovascular complications [21,22].

From this perspective, cardiovascular patients with low ACE2 expression would actually be least susceptible to SARS-Cov-2 infection. However, once the infection occurs, lower ACE2 activity as a consequence of virus particle binding would rapidly deteriorate their situation. Simultaneously, RAS blockers, if exerting their effects in these patients via ACE2 upregulation, would be the most desirable drugs [21,23]. Of course, none of this is clinically proven.

At this stage, we urgently need detailed data (blood pressure, drug treatment) on the hypertensive and diabetic patients dying from SARS-Cov-2 infection. Until that time, there is no reason to abandon RAS blockers as recently underlined by societies, such as the European Society of Hypertension (https://www.eshonline.org/spotlights/esh-statement-on-covid-19/) massively stopping RAS blockers could potentially lead to: uncontrolled blood pressure, worse cardiovascular outcomes, and death. To study the role of ACE2 expression in the clinical course of SARS-CoV-2, future studies should determine ACE2 expression, particularly after virus exposure. If indeed lower ACE2 is confirmed, RAS blockers might be the drugs of first choice. In summary, the current knowledge gaps are whether ACE2 quantity determines the degree of SARS-Cov-2 infection, whether such infection further lowers ACE2, whether low ACE2 quantity in cardiovascular patients truly relates to outcome, and whether the proven beneficial effects of RAS blockers in these patients is related to ACE2 regulation. The current pandemic is a major challenge for global health care. Therefore, unravelling the pathogenic pathways should be the highest priority to enable therapeutic options to improve outcomes.

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Conflicts of interest

There are no conflicts of interest.

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