



ACE/ACE2 Ratio: A Key Also in 2019 Coronavirus Disease (Covid-19)?

Pasquale Pagliaro* and Claudia Penna

Department of Clinical and Biological Sciences, University of Torino, Turin, Italy

Keywords: RAS, comorbidities, macrophage, exercise, ARDS (acute respiratory distress syndrome), hypoxia

INTRODUCTION

Angiotensin-converting enzyme 2 (ACE2) is an aminopeptidase that converts Angiotensin (Ang) II into Ang (1-7). Coronavirus uses ACE2 as a cellular receptor to invade target cells. In particular, the spike protein of SARS-CoV-2 (the beta-coronavirus responsible for Covid-19) is processed by transmembrane protease-serine 2 (TMPRSS2) and favors the binding of the spike protein to ACE2 (1–3).

It is well-known that Ang II, acting on AT1 receptors, exerts powerful vasoconstrictor, pro-fibrotic, and pro-inflammatory effects. In contrast, Ang (1-7), acting on Mas receptors (MasR), is a potent vasodilator, anti-apoptotic, and anti-proliferative agent (**Figure 1**). Therefore, ACE2 is a negative regulator of classical ACE in the renin-angiotensin system (RAS). The two enzymes are involved in maintaining the homeostasis of RAS and in regulating blood pressure as well as the fluid and salt balance. The human ACE2 gene is located on chromosome Xp22. Moreover, the ACE/ACE2 activity ratio in females is lower than that in the male serum. This different ratio may be partially attributed to the two X chromosomes and to estrogens effect on ACE2 activity (4). In both sexes, ACE2 is largely expressed in lungs, liver, intestine, brain, heart, and kidneys, and also in testes. In almost all the pathological conditions, especially those of the cardiovascular system, there is an increase in the ACE/ACE2 ratio within the organs and systems (5–9). This ACE/ACE2 imbalance is very often due to a downregulation of ACE2 levels, and this ratio alteration is accompanied by disturbance in RAS homeostasis. For instance, it has been found that the ACE/ACE2 ratio is high in the glomeruli in the high-salt diet animals, and it is accompanied by renal dysfunction and oxidative stress (5). Also, in the heart, a high-glucose diet upregulated ACE and downregulated ACE2, leading to the augmentation of ACE/ACE2 ratio (6). Moreover, downregulation of ACE2 has been described in pulmonary arterial hypertension and cigarette smoker patients (7). The ACE/ACE2 ratio increase was also correlated with the systolic blood pressure, the serum creatine level, the fasting blood glucose level, and the proteinuria in humans (8). ACE2 is reduced, and the ACE/ACE2 ratio increased also in Alzheimer's disease in association with increasing amyloid- β and tau pathology. (9). Notably, SARS-CoV-2, which binds with ACE2 to enter the targeted cells, also leads to downregulation of ACE2. All in all, it seems that when ACE2 levels or activity are low and the ACE/ACE2 ratio increases we are in trouble (**Figure 1**) and may be more at risk of having a worse outcome in Covid-19 infection.

COVID-19 AND COMORBIDITIES

The Italian ISS (<https://www.epicentro.iss.it/coronavirus/sars-cov-2-decessi-italia>, accessed on April 26th 2020) reports that among 23,188 SARS-CoV-2 patients dying in Italy, 3.6% patients presented with no comorbidities, 14.4% with a single comorbidity, 21.1% with two, and 60.9% with three or more comorbidities. Among these comorbidities, the most represented is hypertension (69.1%), followed by ischemic heart disease (27.5%), chronic renal failure (21.1%), atrial fibrillation (22%), pulmonary diseases (17.1%), heart failure (16.1%), and some other comorbidities with <15%

OPEN ACCESS

Edited by:

Hsiao-Chi Chuang,
Taipei Medical University, Taiwan

Reviewed by:

Eleni Papakonstantinou,
Aristotle University of
Thessaloniki, Greece
Levent Dalar,
Istanbul Bilim University, Turkey

*Correspondence:

Pasquale Pagliaro
pasquale.pagliaro@unito.it

Specialty section:

This article was submitted to
Pulmonary Medicine,
a section of the journal
Frontiers in Medicine

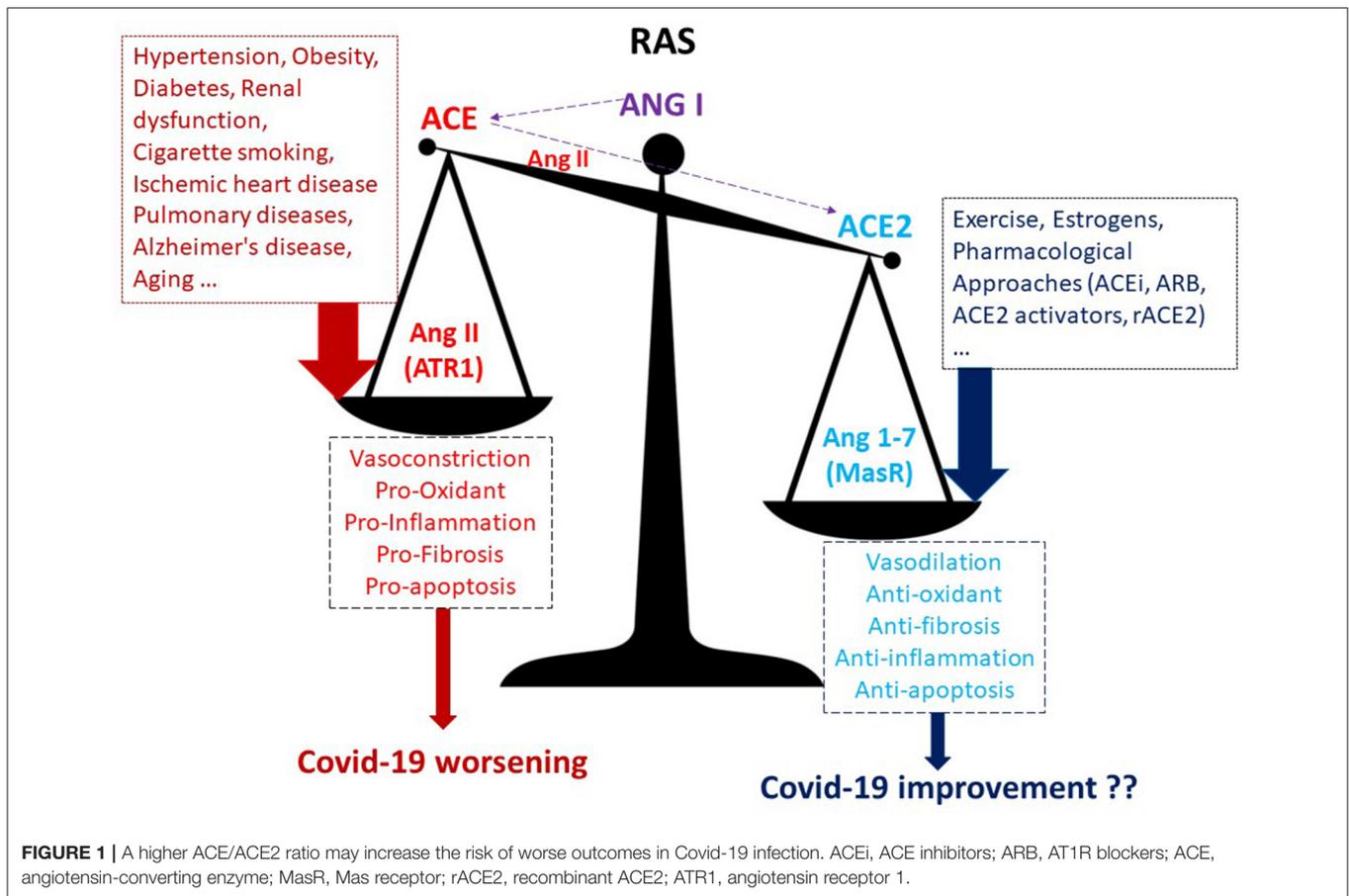
Received: 27 April 2020

Accepted: 05 June 2020

Published: 18 June 2020

Citation:

Pagliaro P and Penna C (2020)
ACE/ACE2 Ratio: A Key Also in 2019
Coronavirus Disease (Covid-19)?
Front. Med. 7:335.
doi: 10.3389/fmed.2020.00335



incidence. Of note is that all these pathologies are characterized by themselves by a downregulation of ACE2 and a high ACE/ACE2 ratio (10–14). The majority of deceased patients were aged (over 60) and obese (in the Italian report, obesity is present in 12.2% of deceased patients). In addition, these two conditions are characterized by an increasing ACE/ACE2 ratio (15, 16). Therefore, we wonder whether the invasion by SARS-CoV-2 and the downregulation of ACE2 are jointly responsible for a high incidence of dramatic acute respiratory distress syndrome (ARDS), cardiovascular complications, and high lethality of Covid-19. Is it worthwhile to try to re-establish an appropriate ACE/ACE2 ratio?

IF YOU CANNOT BREATHE, NOTHING ELSE MATTERS

It has been reported that SARS-CoV-2 has an affinity for ACE2 that is 10 times higher in comparison to SARS-CoV's affinity for this enzyme (2). Is ACE2 like a Trojan horse (1)? Is it a gift of nature that also allows the enemy to enter into cells? Should we therefore say “*timeo Danaos et dona ferentes*”? We believe ACE2 is not an enemy. We believe it is almost an innocent witness to the crime, and we will present here some clues to exculpate it. In our opinion, ACE2 is the key for the virus to enter the organism, but it is not responsible for the injury determined by the virus.

Of course, organs that express a high level of ACE2 are the targets of SARS-CoV-2 infection. This virus diffuses and is transmitted through human respiratory droplets. Therefore, the lung is the principal and initial target organ of SARS-CoV-2 infection (3). The subsequent pathogenic mechanisms are not strictly correlated with neither the number/expression of ACE2 and its activity nor with the viremia. For instance, a correlation between viremia and ARDS in patients with severe Covid-19 has not been observed (17). Moreover, estrogen shifts the system toward the ACE2/Ang 1-7 formation and ACE2 activity is higher in female than that in the male serum (18); however, the worst and most lethal Covid-19 infections occur predominantly in males [the Italian ISS (<https://www.epicentro.iss.it/coronavirus/sars-cov-2-decessi-italia>, accessed on April 26th 2020) reports that among 23,188 SARS-CoV-2 patients dying in Italy, women are 8,500 (36.7%)]. We believe that the subsequent inflammation and cytokine storm is responsible for the *primum movens* for Covid-19 worsening rather than viremia. For instance, viroporins-induced NLRP3/inflammasome activation and excessive production of IL-1 β may be important pathological mechanisms (19). After the virus enters the cells, ACE2 is likely to decrease its activity, thus favoring an increase of the ACE/ACE2 balance toward the prevalence of ACE arm in the RAS. First of all, the prevalence of ACE arm determines a direct increase of ROS production, vasoconstriction, and inflammation.

Indeed, Ang II action on its AT1 receptors promotes NAD(P)H oxidase upregulation, oxidative stress, and cytokine production (20). Cytokine storm, ROS, and inflammation lead to vascular permeability, diffuse alveolar damage, pulmonary edema, and, eventually, to ARDS (21, 22). Which cells in the lungs mediate this inflammatory response? It is likely that, among other cells, macrophages may play a pivotal role. Indeed, macrophages express ACE2 receptors (23), and three different macrophage populations have been described by Tan and Krasnow (24) within the respiratory tract. These three populations may respond differently to virus infection, and the different representation of these macrophages may explain the range of clinical scenarios from asymptomatic, to paucisymptomatic, and to dramatic pneumonia. This is a hypothesis that needs to be ascertained. Nevertheless, when the cytokine storm starts and edema/ARDS ensue, hypoxia occurs, which may exacerbate vasoconstriction, through the typical hypoxia-induced vasoconstriction in the pulmonary vessels [for more details on cytokine storm the reader is redirected to (19, 25)]. For some organs, such as the brain and heart, hypoxia represents an intolerable condition that may lead to lethal outcomes. Together a marked increase in macrophage infiltration, hypoxia can mediate the myocardial damage that accompanies the Covid-19 infection. In the heart, multiple different macrophage subtypes have recently been identified (26), and they can mediate the infection-induced injury. From autopsies, it appears that only a third of patients who died for cardiovascular complications, among Covid-19 patients, have evidence of coronaviruses inside the myocardium (27). This is another sign that it is not important how much virus enters but how the organism reacts to the virus.

Chronic hypoxia-driven vasoconstriction contributes significantly to pulmonary hypertension and several pulmonary hypertension-related diseases, including edema, right heart failure, and myocardial ischemic events (28). Paradoxically, hypoxia may exacerbate redox stress through at least two mechanisms: hypoxia-induced hyperventilation and subsequent alkalosis and dysregulation of iron metabolism (29–32). Pulmonary edema hypoxia is not easy to treat. Indeed, oxygen therapy remains the major life-saving concern in intensive care unit (ICU). In ICU-patients, excess oxygen delivery may cause considerable harm in which redox stress plays a pivotal role (33–35). Therefore, additional therapies that limit redox stress and inflammation are needed, including those aimed at improving the ACE/ACE2 ratio.

APPROACHES TO IMPROVE ACE/ACE2 RATIO

All the above data support the idea that an imbalance in the ACE/ACE2 ratio may be a predisposing cause to the worsening of the Covid-19. It has also been suggested that the increased concentration of ACE2 receptors in the lungs of children may have a protective effect on severe clinical manifestations due to SARS-CoV-2 invasion (36). Also, these data support a negative correlation between ACE2 expression and Covid-19 severe outcomes. Perhaps, therapies improving

this ratio may be useful in infected patients (37–40). The RAS is quite complex, and several pharmacological approaches are under evaluation to benefit from ACE downregulation and ACE2 upregulation in a variety of pathological conditions, especially cardiovascular diseases. ACE inhibitors (ACEi) and AT1R blockers (ARB) upregulate the expression of ACE2 (37–40). Potential direct activators of ACE2 are *diminazene aceturate*, *resorcinolnaphthalein*, and *xanthenone* (41). Since SARS-CoV-2 spreads *via* the bloodstream to infect other organs, recombinant ACE2 (rhACE2) has been proposed as a therapeutic approach in pneumonia and Covid-19 (42–44). The soluble rhACE2 may be a promising approach to quench the virus when it is in the bloodstream (43, 44). However, it must be tested with caution, as soluble ACE2 is not always associated with beneficial effects (45). For instance, soluble ACE2 has a high level in men suffering from heart failure (45, 46). However, as said above, this is a condition associated with Covid-19 worsening; and this therefore suggests that soluble ACE2 may not be sufficient to protect patients. Membrane-bound ACE2 has greater anti-inflammatory effects (47).

A natural way to upregulate membrane bound ACE2 and to lower the ACE/ACE2 ratio is to exercise. It has been reported several times that physical training, and especially aerobic training may decrease ACE/Ang II, and synergistic upregulates ACE2/Ang (1-7) axis (48, 49). Although someone has put forward the hypothesis that excessive exercise is a way to increase Trojan horses (ACE2) for SARS-CoV-2 invasion, the evidence for the beneficial effects attributable to regular exercise are overwhelming.

DISCUSSION AND CONCLUSIONS

All in all, the majority of data are in favor of the idea that a high ACE/ACE2 ratio may be detrimental for Covid-19 infection. ACE/ACE2 ratio is increased in many pathologies (especially dis-metabolisms and cardiovascular diseases) and conditions (obesity and aging) that exacerbate Covid-19 symptomatology and worsen outcomes. Moreover, ACE2 is upregulated and the ACE/ACE2 ratio is lower in many subjects at low risk for cardiovascular diseases, such as females, exercise-trained individuals, and patients well-treated with ACE inhibitors. Since most of the deceased Covid-19 patients had hypertension, further consideration is needed for ACEi and ARBs. The use of these drugs has been questioned, but the majority of authors are in favor of the use of these drugs (37–42). We agree that if used correctly they reduce the ACE / ACE2 ratio and should also be recommended to Covid-19 patients.

Are these subjects with a higher ACE2 and lower ACE/ACE2 ratio also protected against Covid-19 exacerbation? ACE2 expression could influence the course of Covid-19 in different ways: increased expression might promote viral entry, whereas ACE2 increased expression may be beneficial due to ACE2 anti-inflammatory and other beneficial effects (**Figure 1**) that could prevent pulmonary edema, ARDS, hypoxia, and redox stress development. It is likely that viral load is not strictly related to disease severity, and so it is likely that ACE2 overexpression is

not responsible for Covid-19 worsening but that there is, rather, some other mechanism within the complex RAS or outside of RAS (such as a different macrophages population or a different immune response) that may play a role. Covid-19 is associated with an exaggerated and dysregulated systemic inflammatory response involving several inflammatory cells and leading to overproduction of several cytokines. We recently discussed in a Review article (25) the cells and the cytokines likely involved in the exacerbation of Covid-19. We pointed out how cytokine storms on cardiac and vascular endothelium may facilitate the onset of coagulopathies, thereby increasing the probability for organ ischemia and for multiple pulmonary and cardiovascular complications. The virus downregulates ACE2, exacerbating the pro-inflammatory milieu of high ACE/ACE2 ratio.

Membrane-bound ACE2 has an anti-inflammatory role, and an imbalanced and high ACE/ACE2 ratio is not recommended (Figure 1): it is better to have a low ACE/ACE2 ratio. Whether increasing the ACE2/Ang (1-7) axis by pharmacological intervention or by regular exercise may limit Covid-19 worsening remains to be ascertained. Of course, these hypotheses deserve to be studied and must be confirmed with *ad hoc* researches. Nevertheless, currently there are no effective and definitively

approved drugs for the treatment of Covid-19. Therefore, understanding the molecular and cellular mechanisms that favors or exacerbates the Covid-19 in patients with altered ACE/ACE2 ratio and with comorbidities in general is urgent and necessary to design some truly effective therapies. In the meantime, we await a therapy or a vaccine; we can exercise, though we recommend to do this at home or alone to limit the diffusion of this terrible pandemic.

AUTHOR CONTRIBUTIONS

PP and CP made contributed to the conception and design of the work. PP drafted the work and revised it critically for important intellectual content. CP helped in finding the references and revised the manuscript critically for important intellectual content. All authors approved the version to be published.

FUNDING

The authors are supported by University of Turin, MIUR, and Intesa San Paolo Fondo Beneficenza (CP).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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