Potential Harmful Effects of Discontinuing ACE-Inhibitors and ARBs in Covid-19 Patients

Gian Paolo Rossi,[1] Viola Sanga,[1] Matthias Barton[2,3]

[1]Department of Medicine-DIMED, University of Padova, [2]University of Zürich and [2]Andreas Grüntzig Foundation, Zürich, Switzerland

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Corresponding author:
Prof. Gian Paolo Rossi, MD. FACC, FAHA
DIMED– Hypertension Unit
University Hospital
Via Giustiniani, 2
35126 Padova, Italy
Phone: 39-049-821-2279 or 7821
Fax: 39-049-821-7873
E-mail: gianpaolo.rossi@unipd.it

Abstract

The discovery that SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) binds to the angiotensin converting enzyme (ACE)-2, which is highly expressed in the lower airways, explained why SARS-CoV-2 causes acute respiratory distress syndrome (ARDS) and respiratory failure. After this, the news spread that ACEis and ARBs would be harmful in SARS-CoV-2-infected subjects.

To the contrary compelling evidence exists that the ACE-1/angiotensin (Ang) II/ATR-1 pathway is involved in SARS-CoV-2-induced ARDS, while the ACE-2/Ang (1-7)/ATR2/MasR pathway counteracts the harmful actions of AngII in the lung. A reduced ACE-1/ACE-2 ratio is, in fact, a feature of ARDS that can be rescued by human recombinant ACE-2 and Ang (1-7) administration, thus preventing SARS-CoV-2-induced damages to the lung. Based on the current clinical evidence treatment with ACE-inhibitors I (ACEis) or angiotensin receptor blockers (ARBs) continues to provide cardiovascular and renal protection in patients diagnosed with COVID-19. Discontinuing these medications may therefore potentially be harmful in this patients population.

COVID19 Pandemics

The pandemic proportions of Covid-19 (Coronavirus Disease 2019) from the SARS (Severe Acute Respiratory Syndrome) Coronavirus 2 (CoV-2) infecting a million and killing 47,266 people worldwide as of April 2, has fueled enormous interest in the mechanisms whereby this new coronavirus causes acute respiratory distress syndrome (ARDS) and multiorgan failure. The estimated 79% infection rate from undocumented cases in Covid-19 patients (Li et al., 2020), and the high lethality of the infections, along with its enormous socio-economic impact, emphasise the importance of fully understanding these mechanisms for developing effective treatment strategies.

Early in 2020 reports of the full RNA sequence of the SARS-CoV-2 virus highlighted remarkable similarities with the SARS-CoV virus, which was responsible of an outbreak that killed 774 people in 2003 (Xu et al., 2020; Zhou et al., 2020). As the processes whereby the SARS-CoV virus infects the lung cells were already dissected (Kuba et al., 2005), and it was held that SARS-CoV-2 uses identical mechanisms, these discoveries allowed an unprecedented acceleration of knowledge.

Why and how SARS-COV-2 infects the lung?

Since 2005 it was known that the SARS-CoV virus uses the angiotensin converting enzyme (ACE)-2 as a receptor to infect cells. ACE-2 is highly expressed in the vascular endothelium (Kuba et al., 2005) and is highly expressed also in the lung, particularly in the type 2 alveolar epithelial cells (Hamming et al., 2004). The resemblances of SARS-CoV-2 and SARS-CoV include a 76.5% homology in the amino acid sequence of the spike (S) protein of the envelope that both viruses use to infect mammalian cells. Notwithstanding a 4 amino acid residue difference in its receptor binding domain, the SARS-CoV-2 S protein of maintains the 3D structure of the SARS-CoV (Xu et

al., 2020) and, moreover, binds to ACE-2 with an even higher affinity than SARS-CoV (Wrapp et al., 2020), which may explain its virulence and predilection for the lung.

Upon binding to ACE-2, both SARS-CoV and SARS-CoV-2 activate the transmembrane serine protease-2 (TMPRSS2), which is also highly expressed in the lung. Through fusion of its envelope with the cell membrane the virus penetrates into the cells (Central figure panel A) (Heurich et al., 2014; Hoffmann et al., 2020). Of note, SARS-CoV-2 entry can be prevented by SARS convalescent sera containing neutralizing antibodies, or by TMPRSS2 inhibitors as camostat (Hoffmann et al., 2020) and nafamostat mesylate, both approved in Japan for clinical use for other indications (Yamamoto et al., 2016). These seminal discoveries suggested several potential therapeutic strategies to prevent SARS-CoV-2 entry into alveolar epithelial cells (Zhang et al., 2020a) (Central figure, panel A).

What is the role of ACE-1 and ACE-2 enzymes in infections with SARS-COV-2 and SARS-COV?

Are there similarities between ACE-1 - the target of ACEis - and ACE-2 - the target of SARS-CoV-2 and SARS-CoV? This is the obvious essential question for physicians using ACEis or ARBs which are frequently prescribed in elderly patients.

Both ACE-1 and ACE-2 cleave angiotensin peptides. However, they differ markedly: ACE-1 cuts the dipeptide His-Leu from angiotensin I, thus generating angiotensin (Ang) II, which causes vaso- and broncho-constriction, increased vascular permeability, inflammation, and fibrosis and thereby promotes the development of ARDS and lung failure in patients infected by the SARS-CoV and SARS-CoV-2 (Yang et al., 2014) (Central figure, panel B).

Compelling evidence from animal models of ARDS, lung fibrosis, asthma, and chronic obstructive lung disease, indicate that these effects are essential for ARDS to develop and that both ACEis and

ARBs block the disease-propagating effect of Ang II (Dhawale et al., 2016; Imai et al., 2005; Kaparianos and Argyropoulou, 2011).

ACE-2, which is expressed more abundantly on the apical than the basolateral side of polarized alveolar epithelial cells (Jia et al., 2005), shares only 42% amino acid sequence homology with ACE-1 (Harmer et al., 2002). It cleaves only one amino acid residue (Leu or Phe) from Ang I and Ang II, respectively, to generate Ang (1-9) and Ang (1-7) (Central figure, panel B). Ang (1-7) counteracts the AT_1R-mediated aforementioned detrimental effects induced by Ang II in the lung. Accordingly, genetic deletion of ACE-2 worsened experimental ARDS (Kuba et al., 2005), while Ang (1-7) and ACEIs or ARBs administration improve it (Imai et al., 2005; Wösten-Van Asperen et al., 2011). Thus, blunting the ACE-1/Ang II/ATR1 axis, and/or enhancing the ACE-2/Ang (1-7)/AT_2R/MasR axis protect from ARDS triggered by pathogens, including the Coronaviruses (Dhawale et al., 2016; Imai et al., 2005; Kaparianos and Argyropoulou, 2011; Meng et al., 2014).

Do ACEIs or ARBs facilitate SARS-COV-2 pathogenicity and the clinical course of Covid-19?

After ACE-2 was identified as the SARS-CoV-2 receptor (Hoffmann et al., 2020; Yan et al., 2020), unexpectedly, and almost immediately, it was contended that treatment with ACEis and ARBs would be harmful for the Covid-19 patients. This hypothesis was quickly spread in the public, causing confusion and fear in patients taking these drugs, who started asking themselves, and their doctors if they should discontinue these medications and replace them with of antihypertensive drugs of other classes.

The trigger to this spread of the news were two published commentaries. In one ACE-2 was suggested to be secreted at higher amount in patients with cardiovascular disease than in healthy individuals and it was also stated that '*ACE-2 levels can be increased by the use of ACEis*' (Zheng et al., 2020), albeit no evidence of this occurring in the lung exists. These hypothetical phenomena

were put forward as to enhance susceptibility to SARS-CoV-2 infection, and thus to warn patients about taking these drugs.

A correspondence to the Lancet Respiratory Medicine suggested that patients with cardiac diseases, as hypertension and/or diabetes treated with *'ACE-2-increasing drugs'* would be at higher risk for severe SARS-CoV-2, because treatment with ACEis and ARBs would raise ACE-2 (Fang et al., 2020). To support their contention the authors quoted a review article that reported no such evidence (Li et al., 2017). To the contrary, a search of the literature revealed that no data that would support such notion exist. In fact, evidence of ACE-2 upregulation applies to the heart, likely as a compensatory phenomenon to underlying conditions, for example myocardial infarction (Burrell et al., 2005; Ishiyama et al., 2004; Ocaranza et al., 2006), rather than to the drug treatment per se.

Moreover, in neither commentary the authors considered the fact that increased plasma levels of ACE-2 (generated by delivering soluble forms of rhACE-2 and/or shedding of ACE-2 from the cell membrane) can bait the S protein of SARS-CoV-2 (and SARS-CoV) in plasma, thus preventing the virus from binding to lung cells, two strategies that have been suggested to protect against SARS-CoV-2 infection of the lung (Kruse, 2020; Zhang et al., 2020b) (Central figure panel A).

Nonetheless, the publication of simple hypotheses unsubstantiated by any data spread so fast in public and news portals that scientific societies, including the European Society of Hypertension (ESH) and the Italian Society of Cardiology and the Italian Society of Arterial Hypertension were required to release statements to confirm that there is no evidence that ACEis and ARBs could jeopardize Covid-19 patients and there is no need not to recommend discontinuing treatment. To date Italy is the country with the highest number of SARS-CoV-2-positive individuals in the European Union and the highest official number of deaths in the world. On March 17th, 2020 a

joint statement of the presidents of the HFSA/ACC/AHA (Bozkurt et al., 2020), followed by one of the European Medicines Agency (European Medicines Agency, 2020), and several experts' opinion articles reported affirmed that there were no evidences for discontinuing ACEis and ARBs (Danser et al., 2020; Greene et al., 2013; Perico et al., 2020) in accordance with the Editors of the New England Journal of Medicine (Rubin et al., 2020).

In our view these neutral recommendations could be an understatement. In fact, in two large meta-analysis, and a case-control study involving over 21,000 patients in several high-risk categories of patients, including stroke survivors (Shinohara and Origasa, 2012), Asians (Caldeira et al., 2012; Liu et al., 2012), and also in patients with Parkinson's disease (Wang et al., 2015), ACEis were superior to other antihypertensive agents in pneumonia prevention.

The experimental data obtained for the SARS-CoV virus also showed that these drugs can be protective rather than harmful, which lead to the proposition of specifically enhancing the protective arm of the renin-angiotensin system as a novel therapeutic strategy for pulmonary diseases (Tan et al., 2018). Moreover, abrupt withdrawal of RAAS inhibitors in high-risk patients, including those who have stage 3 arterial hypertension, heart failure or have had myocardial infarction, may result in clinical instability and adverse health outcomes as recently pointed out (Vaduganathan et al., 2020).

ACE inhibitors and ARBs are beneficial in Acute Respiratory Distress Syndrome (ARDS)

The AT_1R-mediated detrimental effects of Ang II were demonstrated in several models of ARDS SARS-CoV-induced acute respiratory failure (Imai et al., 2005; Kuba et al., 2006, 2005). Moreover, with its vasodilatory, anti-inflammatory, anti-proliferogenic and antifibrotic effects activation of the ACE-2/Ang (1-7)/AT_2R/MasR pathway counterbalances the harmful effects of the ACE-1/Ang II/ATR-1 pathway on the lung. A reduced ratio of ACE-1/ACE-2 has been documented in ARDS;

furthermore, experimentally ARDS and lung fibrosis can be prevented by administration of Ang (1-7) (Cao et al., 2019), or an ARB (Wösten-Van Asperen et al., 2011), indicating that ACE-2 activation limits pulmonary disease progression. This implies not only that ACEis and ARBs are unlikely to be detrimental in Covid-19 patients, but rather that they will be protective. Whether the same applies to drugs that block the mineralocorticoid receptor and antagonize aldosterone, another downstream mediator in the ACE-1/Ang II/AT1R pathway remains unknown.

Once in the lung type 2 alveolar epithelial cells, SARS-CoV-2 downregulates ACE-2 (Kuba et al., 2005), and thereby the Ang (1-7)/AT2R/MasR pathway (Imai et al., 2008). Bona fide this would also suggest that ACEis and ARBs can be beneficial by blunting the ACE-1/Ang II/AT_1R pathway and counterbalancing the down-regulation of ACE-2. Theoretically, administration of recombinant human ACE-2 (rhACE-2) to bait SARS-COV-2 in the bloodstream prevent its binding to lung cells, and enhance ACE-2 activity in lung tissue (Central figure panel A), could be beneficial for SARS-CoV-2 -infected ARDS patients, possibly even at a late stage of the infection for patients in intensive care requiring assisted ventilation. Along this line, in 2017 a pilot trial in ARDS patients in ten U.S intensive care units supported the value of this strategy in that rhACE-2 increased levels of Ang (1-7) and alveolar surfactant protein D levels, and tended to lower the concentrations of the proinflammatory cytokine interleukin-6 (Khan et al., 2017).

Conclusions and perspectives

In summary, a disbalance between the ACE-1/Ang II/AT_1R and the ACE-2/Ang (1-7)/AT_2R/MasR contributes to the pathogenesis of ARDS and acute lung failure in Covid-19 patients. Therefore, is seems reasonable to conclude that rebalancing the system by blunting the ACE-1 with ACEis and ARBs, and enhancing the ACE-2 axis is a valuable strategy to minimize the harmful effects of SARS-CoV-2 on the lung. In the majority of patients with cardiovascular diseases, mainly hypertension

and/or heart failure and/or after a myocardial infarction, who are on ACEis or ARBs and are at risk of getting infected, or have been infected by SARS-CoV-2 but do not need invasive ventilation, while there is no evidence that discontinuing these drugs is beneficial, discontinuing these life-saving medications potentially can be harmful.

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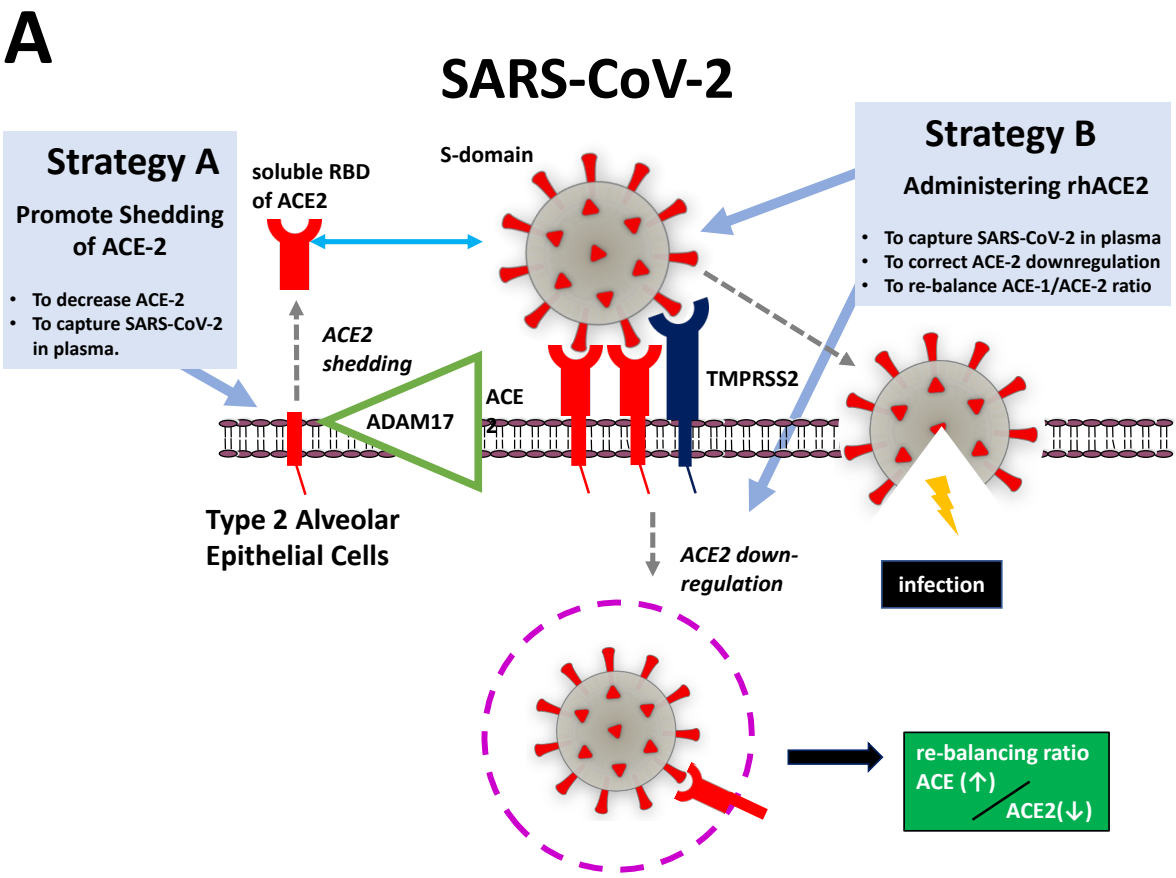
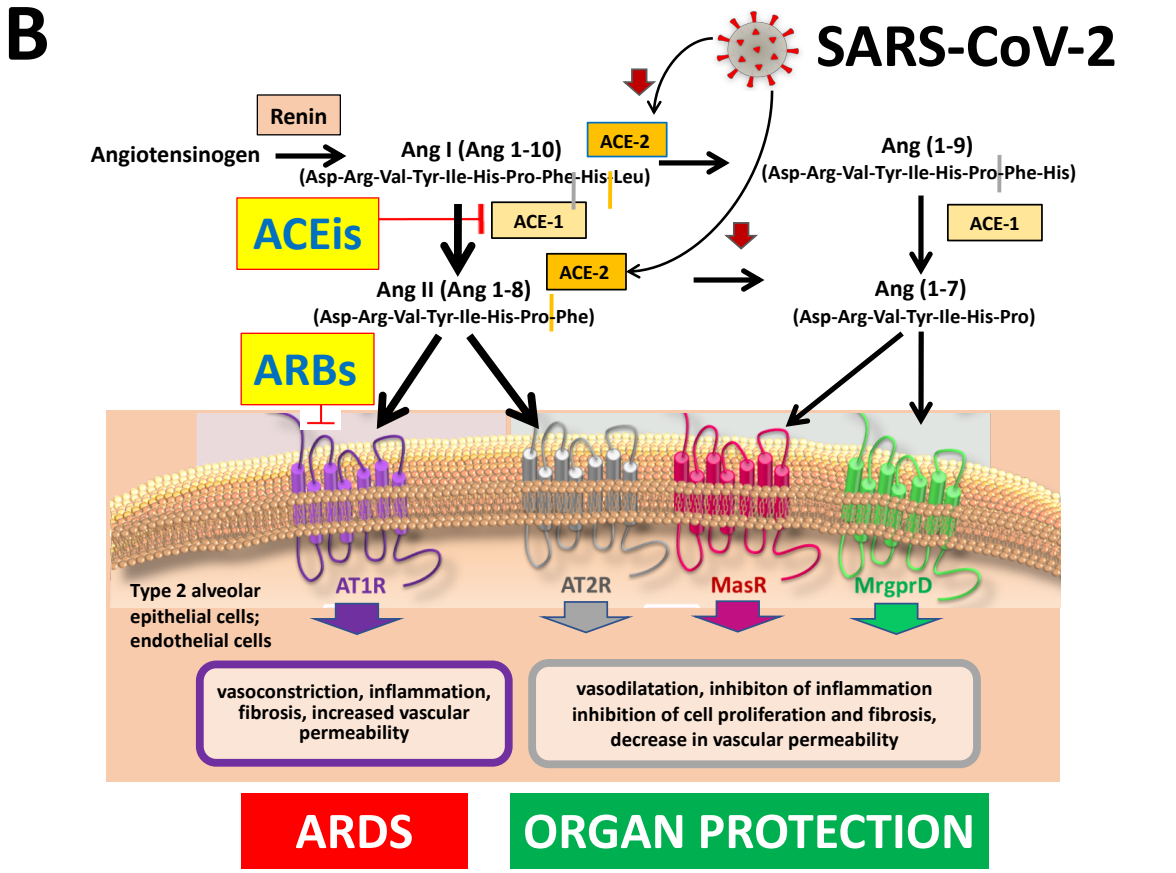

A
SARS-CoV-2
Strategy A
Promote Shedding of ACE-2
To decrease ACE-2
To capture SARS-CoV-2 in plasma.
soluble RBD of ACE2
S-domain
Strategy B
Administering rhACE2
To capture SARS-CoV-2 in plasma
To correct ACE-2 downregulation
To re-balance ACE-1/ACE-2 ratio
ACE2 shedding
ADAM17
ACE 2
TMPRSS2
Type 2 Alveolar Epithelial Cells
ACE2 down-regulation
infection
re-balancing ratio
ACE (↑)
ACE2(↓)


B
SARS-CoV-2
Renin
Angiotensinogen
Ang I (Ang 1-10)
(Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu)
ACE-2
Ang (1-9)
(Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His)
ACEis
ACE-1
ACE-1
ACE-2
Ang II (Ang 1-8)
(Asp-Arg-Val-Tyr-Ile-His-Pro-Phe)
Ang (1-7)
(Asp-Arg-Val-Tyr-Ile-His-Pro)
ARBs
AT1R
AT2R
MasR
MrgprD
Type 2 alveolar epithelial cells; endothelial cells
vasoconstriction, inflammation, fibrosis, increased vascular permeability
vasodilatation, inhibiton of inflammation inhibition of cell proliferation and fibrosis, decrease in vascular permeability
ARDS
ORGAN PROTECTION

Caption

Central figure. Panel A: the cartoon depicts the sequence of events by which the SARS and SARS-COV-2 viruses can infect the lower airways cells. By binding to type 2 alveolar epithelial cells that express ACE-2 at high levels, the viruses activate proteases, as TMPRSS2. This allow fusion of the viruses' envelope to the cell membrane which allows them to enter and infect the cells. Of note, the type 2 alveolar epithelial cells are well equipped with a molecular machinery that allows rapid replication of the viruses thus enhancing spreading of the infection through the lung. Once infected by SARS and SARS-COV-2 the lung cells downregulate their ACE-2. Therefore, the lung remains exposed to, and is unprotected from, the detrimental actions of angiotensin II acting via the AT1R (Panel B). Thus, the potentially beneficial effects of ACEis and ARBs, as well as those of providing soluble recombinant human ACE-2, entail rescuing the downregulated ACE-2/AT2R/MasR pathway in the lung and baiting the virus in the circulation, thus impeding it binding to the lung cells and damaging the lung.

Abbreviations: RBD: receptor binding domain; ACE-1: type 1 angiotensin-converting enzyme; ACE-2: type 2 angiotensin-converting enzyme; ACEis: type angiotensin-converting enzyme inhibitors; ARBs: type 1 angiotensin receptor; ADAMS 17: ADAM metallopeptidase Domain 17; TMPRSS2: Transmembrane Serine Protease 2.