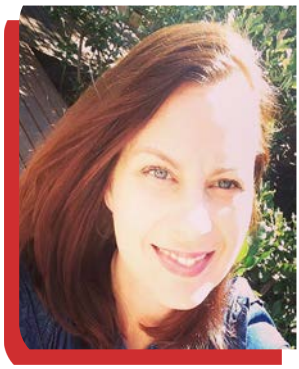
# THE CURRENT COVID-19 PANDEMIC AND HYPERTENSION

## COVID-19 and hypertension

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As the COVID-19 pandemic intensified, an early report from Italy indicated that patients with hypertension were at greater risk of developing severe illness, of being admitted to intensive care units, and of succumbing to their illness[1]. This is perhaps a real and independent phenomenon[1] but, alternatively as suggested by the well-designed study of Mancia and colleagues in the same region of Italy[2], more likely results from confounding by the age-dependence of hypertension, and from associated comorbidities in the Lombardy communities[2]. If patients with hypertension are at particular risk for severe COVID-19 this would be unexpected, as hypertension does not appear to impact other infections. But some medical scientists, including the authors, were not convinced that multivariate analyses of clinical data bases in COVID-19 trouble spots[2] totally cancels out a possible independent effect of hypertension on disease severity, although at first there were no clues why, for hypertensive patients, the COVID-19 pandemic should be a special case.

### Is Pharmacological Renin-Angiotensin Blockade Harmful in COVID-19 ?

Unlike other infectious agents, SARS-CoV-2 interacts directly with a cardiovascular regulatory enzyme, ACE2. Viral entry into pulmonary and other cells occurs via membrane ACE2 binding[3]. This came as a revelation to many, especially those working in cardiovascular medicine. Cardiologists and hypertension specialists familiar with ACE2 wondered whether the method of pulmonary cell entry by the coronavirus could perhaps be significant in the morbidity and mortality profile of the illness, particularly in the context of hypertension co-morbidity.

Given the importance of ACE2 in SARS-CoV-2 entry to cells, cardiovascular illnesses or cardiovascular drugs which increase ACE2 expression, and there are several important instances of this[4-7], could possibly increase human SARS-CoV-2 infectivity and illness severity. Perhaps in the COVID-19 pandemic a new infection risk was arising from special properties of some antihypertensive drugs? Pretty much simultaneously four research groups, including our own, published the suggestion that drugs blocking the renin-angiotensin system may be implicated[5,8-10], by increasing ACE2 expression, which they commonly do ([6,7]). This idea does have plausibility. Several types of experiment in animals give credence to the idea that the level of ACE2 expression may perhaps be important in COVID-19 infection. Knockout mice genetically modified to have no ACE2 are totally resistant to coronavirus infections[11]. And the converse; transgenic mice bred to over-express human ACE2 exhibit markedly increased infectivity and lethality when exposed to SARS coronavirus[12,13]. A general principle might apply, using an analogy drawn from chemical transporter kinetics, where the rate of reaction is determined by:

- (i) Affinity of the transporter for the substrate (in this case of ACE2 for the SARS-CoV-2 virus)
- (ii) The number of transporter active sites (here, amount of ACE2 protein in cell membranes)
- (iii) The substrate concentration (in this case coronavirus load).

The obvious difference is that the active site and substrate are not in kinetic equilibrium, as the ACE2 and coronavirus are internalized after binding.

How might the hypothetical RAS-blockers adverse effect on COVID-19 be tested? One method would be to administer RAS-blockers to COVID-19 sufferers and evaluate the effects. This is actually being done (see, ClinicalTrials.gov Identifier: NCT04312009) for another reason, to test whether RAS-blockade is actually beneficial in the severe illness, with the logic for this described below. Possibly the most immediate and direct clinical testing should come from interrogating the pandemic data bases of China, Italy, France, Spain United Kingdom or United States. From these populations, presence of COVID-19 illness, illness severity and death could be matched against, age, pre-existing medical diagnoses and drugs prescribed at the onset of COVID-19 illness. Perhaps the most convincing analysis of this type was performed by Mancia and colleagues in Lombardy[2], who found in a large case-control analysis an unadjusted apparently adverse effect of all antihypertensives, but this disappeared with multivariate analysis which cancelled out the effect of higher prevalence of cardiovascular disease in RAS-blocker users. *There was no evidence that ACE-inhibitors or angiotensin receptor-blockers specifically affects the risk of COVID-19.* Importantly, if the studies testing whether dosing initiated with ACE-inhibitors or ARBs given during COVID-19, hoping for benefit, actually cause harm this conclusion will need revision.

What remained after multivariate analysis in the Lombardy population was substantially greater use of loop diuretics and spironolactone in COVID-19 patients. This might provide an important lead, suggesting COVID-19 risk from these drug classes, this being consistent with the finding that reduction in body sodium, quite independent of ACE-inhibitors and ARBs, increases ACE2 expression. Mineralocorticoid block with spironolactone and loop diuretics increases ACE2 expression[14]; conversely aldosterone and dietary sodium loading reduce ACE2 expression[15,16].

## Pulmonary ACE2 in severe lung injury: A potential therapeutic target ?

The case was first presented in relation to the SARS epidemic[11] that in severe lung injury pulmonary ACE2 is depleted. A special form of this pulmonary ACE2 depletion is seen with coronavirus infections, where after the virus binds to the ACE2 protein both are internalized, depleting membrane ACE2[11].

Depletion of ACE2 is accompanied by accumulation of angiotensin, its substrate, in the lung, with adverse effects. Renin-angiotensin block, through repleting ACE2, is beneficial in non-coronavirus acute respiratory disease caused by influenza viruses, acid inhalation and other noxious influences[17]. Could this benefit extend to COVID-19 infection ?

A trial of the ARB losartan in severe COVID-19 infections, based on this line of thinking mentioned above, has commenced (ClinicalTrials.gov Identifier: NCT04312009). But is it possible that such a trial could carry risks of worsening the infection? Benefit from renin-angiotensin system block in acute severe lung disease has not been shown experimentally in coronavirus infections. Augmenting pulmonary ACE2 expression might increase coronavirus uptake and viral load. The classic study of Kuba et al[11] is often misquoted as providing evidence of ARBs and ACE-inhibitors benefiting coronavirus pneumonia. Kuba et al[11] actually administered coronavirus fragments, spike protein, not replicable entire virus. The spike fragments depleted pulmonary ACE2 after binding, aggravating the existing experimental pneumonia, which was improved by pharmacological renin-angiotensin system block. Neither this study, or any others to our knowledge, have demonstrated benefit or renin-angiotensin block in coronavirus infection. Augmentation of virus uptake and replication might overwhelm any specific pulmonary benefits. The empirical results of the RAS-blocker dosing trials in COVID-19 will inform what has become a theoretical impasse.

## Antiviral drugs

The pro-drug Remdesivir, which targets the SARS-CoV-2 virus RNA dependent RNA polymerase, is the antiviral drug holding most promise. Remdesivir is an adenosine C-nucleoside, which it is hoped will have a beneficial action in COVID-19, similar in type to that of sofosbuvir in hepatitis C, achieved by antagonizing RNA synthesis by the virus. Observational results to-date with remdesivir are promising, but of course these do not provide a firm path for future action. The same applies to observational results with hydroxychloroquine, on which discussion now is unfortunately highly politicized. Preliminary results from the *Active COVID-19 Treatment Trial*, a randomized controlled trial of remdesivir sponsored by the US National Institute of Allergy and Infectious Diseases (NIAID) in 1063 patients, showed significantly shortened recovery time and a non-significant trend towards improved survival. The results from additional, ongoing controlled trials of remdesivir are pending.

## "Herd Immunity"

Testing for antibodies to SARS-CoV-2, conducted by governments and municipalities in US, Sweden and the United Kingdom, has disclosed unpublished seropositivity rates reported as 4% (Los Angeles), 7.5% (Stockholm) and 17% London (5% elsewhere in United Kingdom). These values fall far short of the community immunity needed to materially counter the spread of COVID-19. Achieving community immunity will require a safe and effective vaccine. A number of vaccine candidates are progressing, however the ultimate success of these and the timeframe for release remains in question.

Returning to RAS-blocker prescribing in hypertension, our earlier recommendation[5] was to not discontinue these drugs prior to confirmation of the hypothesis remains, can in fact now be strengthened. Analysis of ACE-inhibitor and ARB use in clinical data bases from regions hard-hit by the pandemic has led to the conclusion that the hypothesis that RAS-blocker prescribing for hypertension, heart failure and diabetes during the COVID-19 pandemic is adverse can be discounted[2]. Importantly, it should be remembered, however, that patient dosing compliance in hypertension is surprisingly low, perhaps 50%, which is a confounder, potentially undermining the validity of the conclusion. *In addition, the conclusion will need to be revised if the ongoing studies in which RAS-blockade is initiated during the infection show harm.* Despite these caveats, treatment changes should not be made in hypertension "just in case". Any resulting destabilizing of blood pressure control in hypertension would carry risks of strokes and heart attacks which are not just hypothetical. Simply discontinuing antihypertensives is strongly discouraged and is not an option[5].

Moving forward, the co-morbidity profile of those most likely to have a severe outcome with SARS-CoV-2 warrants further investigation, as do the morbidity and mortality outcomes of infection in different countries. Broad questions into the role of ACE2 in COVID-19 and implications of changed ACE2 expression as a consequence of medications do remain unanswered, including the status of loop diuretics and aldosterone antagonists in COVID-19 infection. Cardiovascular and hypertension doctors and scientists have an ongoing contribution to make in the understanding of and fight against COVID-19.

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