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COVID, ACE inhibitors/ARBs, and cardiovascular diseases

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Abstract

Angiotensin Converting Enzyme Inhibitors (ACE-I) and Angiotensin Receptor Blockers (ARBs) reduce morbidity, mortality and hospitalisations from hypertension and heart failure. There are no convincing clinical data to support adverse or beneficial effects in COVID19 patients in the face of theoretical arguments in both directions. Most authoritative national and international bodies have released statements to the effect that the beneficial effects of ACE-I and ARBs are proven, the adverse effects in COVID-19 patients are not and have advise people to continue these drugs pending evidence to the contrary.

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Manuscript

Cardiovascular disease during a pandemic- the big picture

As the world watches COVID-19 spread affecting the health of millions of people and the lives of everyone on the planet common health conditions including heart disease, stroke, cancer and other chronic disease continue. While there is no doubting the direct consequences for morbidity and mortality of COVID-19, including its direct cardiovascular effects it will be important to ensure that these are not matched by the indirect consequences. Different countries are at different stages in the natural history of the pandemic but there is a clear pattern with an overloaded health system necessitating hasty development of new protocols and pathways for common conditions that deviate from established guidelines, changes in community behaviours either imposed, or arising from fear. Unproven therapies are being tested in the field and in the absence of evidence there is the potential for theory to drive practice to an extent that is generally not seen in conditions with an established evidence base.

Emergency Department attendances fell dramatically in England with 89 584 attendances in the week after the lockdown (March 23-29), down 25% on the 120 356 seen the previous week and almost 50% down on attendances in February[1]. This has also been reported from Europe, Canada and Australia[2]. ST elevated myocardial infarction (STEMI) rates fell by about 40% in reports from Spain[3] and the US[4]. It is possible that COVID-19 is associated with plaque stabilisation and lower rates of STEMI but it seems more likely that some people with heart disease are abandoning the usual medical advice at a time when they may need it the most.

In New York a 50% decrease in emergency department visits for acute coronary syndromes has been reported at the same time as an 8-fold increase in out of hospital cardiac arrest calls in the first week of April[5]. It is not clear how many of these are COVID-19 related but there seems no doubt that people have a reluctance to attend hospital during the peak of the epidemic and this is coming at a significant cost in mortality.

The ACE-I and ARB controversy

In the midst of all this a controversy has emerged about the safety and value of angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs) commonly used for treatment of hypertension and heart failure in the context of the COVID-19 pandemic. In normal times these are considered to be amongst the safest, best tolerated and effective drugs both in the management of hypertension and for heart failure with a strong evidence base showing reduction in morbidity and mortality from these conditions[6,7].

To date there is insufficient clinical evidence that ACE-I, ARBs or other inhibitors of the renin angiotensin system are either harmful or beneficial in the acquisition of COVID-19 or its subsequent clinical course in individual patients. A number of clinical trials of losartan and of recombinant ACE-2 are underway[8]. The debate has arisen because of circumstantial arguments based on COVID-19 pathophysiology and renin- angiotensin system physiology[9,10].

On the one hand it is argued that ACE-I and ARBs may be harmful because:

- Hypertension is overrepresented amongst people who develop the most severe complications of COVID-19.
- Coronavirus (SARS-CoV-2) gains entry to a cell utilizing ACE2 and type II transmembrane serine proteases (TMPRSS2).
- ACE2 is most expressed in the cardiovascular (CV) system, gut, kidneys and lungs. In the CV system, ACE2 is expressed in cardiomyocytes, epicardial adipose tissue, cardiac fibroblasts, vascular smooth muscle and endothelial cells.
- In some experimental models ACE-I or ARBs upregulate ACE2 in heart cells
- This may lead to a greater viral load and more serious infection

Several important links in this logic chain are contested. Early reports of high rates of hypertension in those dying or suffering severely from COVID-19 did not have adjustment for age. However, it is clear that most do have comorbidities including hypertension, heart failure and diabetes, all of which are more common in an older population. Mortality in the intensive care unit in 72 regional hospitals in Lombardy, Italy was 26%. Most were male (82%) and had extensive comorbidities, especially hypertension (49% overall and 62% of deaths)[11].

ACE2 and COVID-19 pathophysiology

The relationship between COVID-19 and the renin angiotensin system has been reviewed extensively e.g.[12]. Although there is no doubt that ACE2 is a receptor for COVID-19 and that the gene is widely expressed in the body there is mixed evidence on whether it is upregulated by ACE-I or ARBs in animal models and no evidence that it is increased *de novo* in tissues that have low expression[13]. COVID-19 suppresses ACE-2. If ACE2 expression is increased by ACE-I or ARBs, it does not necessarily imply that this enhances the ability of SARS-CoV-2 to infect cells. The affinity of the virus for ACE-2 is very high and it is not clear that a small increase in expression due to renin angiotensin inhibition would increase intracellular viral load.

Another counter argument to this hypothesis that has been put is that an increase in ACE2 expression would provide a counter to the suppression due to SARS-CoV-2 and allow the beneficial effects of ACE2 including anti-inflammatory activity to manifest i.e. ACE-I or ARB could be beneficial. Furthermore, ACE2 expression is known to reduce with age but it is clear that older people are more vulnerable to COVID-19. The experience during the pandemic has included a striking sex difference in mortality and in intensive care unit admissions affecting males much more than females yet as a sex linked gene located on the X chromosome females have higher expression of ACE2 than males, again seemingly counter to the hypothesis that ACE2 levels are proportionate to the infectivity and severity of SARS-CoV-2 illness.

Trial design to resolve the matter

In considering the possibility of interactions between COVID-19 and medications it is important to take into account the different stages in the evolution of the disease in an individual. The earliest stages are characterised by mild or absent upper respiratory symptoms and lymphopenia. A minority of people infected with SARS-CoV-2 subsequently develop pneumonitis and pulmonary complications. Even fewer develop the most severe

complications with hyperinflammation, often called a cytokine storm, often with myocarditis and other major organ failures. It is quite likely that the renin angiotensin system and by implication drugs that interact with it such as ACEI or ARBs have different actions at various stages of the condition according to the tissues affected. For example, ACE2 is protective in acute lung injury, suggesting that, although it facilitates viral entry through the epithelium, the ACE2 and its product, the Ang 1–7 axis could be used to reduce tissue injury caused by SARS, a potential target for therapy[12]. This will be an important consideration in the design and setting of clinical trials.

What clinicians can do in the meantime

There are highly circumstantial arguments either way (and there are many more in the literature, as preprints and on social media). In the absence of good epidemiological and clinical trial data there is no immediate and definitive resolution to the debate. What is clear is that people with hypertension and heart failure benefit from ACE-I and ARBs where indicated and withdrawing treatment is likely to have serious consequences in some people. We are thus left with a situation where stopping ACE-I or ARBs in some people has known and potentially serious sequelae whereas continuing them in people with or vulnerable to COVID-19 has unknown consequences which depending on how the experimental evidence is interpreted may be negative, neutral or even positive. International and national authorities on cardiovascular disease including the High Blood Pressure Research Council of Australia, World Health Organisation, the American Heart Association and the European Society of Cardiology have been united in their recommendation that ACE-I or ARB medications should be continued during the present pandemic pending any hard information from clinical studies to the contrary (summarised in a review[14]).

In a number of patient groups ACE-I or ARBs are first line choices, for example those with hypertension and proteinuria, or people with heart failure. Given the clear benefits they have been shown to provide over several decades a decision to withdraw first line therapies should only be based on good reasons supported by a strong evidence base. In other groups such as those with uncomplicated essential hypertension there are alternatives such as calcium channel blockers or diuretics. However, changing over medications in patients with well controlled blood pressure requires careful monitoring and a risk in the short term that blood pressure will fall outside the optimal range. This may prove challenging during a period when telemedicine is the norm and not all households have home blood pressure equipment and training.

As this issue has been wisely canvassed in the public media health professionals will need to have a conversation with patients about the benefits or otherwise of continuing their present therapies. It is particularly important that people understand that no concerns have been raised about other medications they may be taking such as statins, anti-thrombotic or treatment for diabetes. In recommending continuation of ACE-I or ARBs physicians can draw comfort that they are backed by almost every authoritative cardiovascular health authority in the world. Nevertheless, the clinical trial results cannot come quickly enough and in the best case they will allow us to turn practice into the right theory!

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