COVID-19 and the renin-angiotensin system (RAS): A spark that sets the forest alight?

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A B S T R A C T

The coronavirus disease 2019 (COVID-19) pandemic has increased exponentially in numbers with more than 20 million people infected around the globe. It is clear that COVID-19 is not a simple viral pneumonia, but presents with unusual pathophysiological effects. Of special interest is that SARS-CoV-2 utilises the angiotensin-converting enzyme-2 (ACE2) for cell entry and therefore has a direct effect on the renin angiotensin system (RAS). The RAS is primarily responsible for blood pressure control via the classic pathway. Recently numerous other pathological processes have been described due to stimulation of this classic pathway. There is also a protective RAS pathway medicated by ACE2 which may be suppressed in COVID-19. This leads to overstimulation of the classic pathway with adverse cardiovascular and respiratory effects, hypercoagulation, endothelial dysfunction, inflammation and insulin resistance. We hypothesize that overreaction of the renin-angiotensin-aldosterone may account for the myriad of unusual biochemical and clinical abnormalities noted in patients infected with SARS-CoV-2.

Background

The World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19), caused by a novel coronavirus SARS-CoV-2, a pandemic in early March 2020. The world was placed under lockdown and now, months after this intervention, the harsh reality of the social, economic and health impact of the disease is evident.

It is clear that COVID-19 is not a simple viral pneumonia. A myriad of unusual pathophysiological, biochemical and haematological effects are being described. Of particular interest is the interaction of SARS-CoV-2 and the renin angiotensin system (RAS) via angiotensin converting enzyme 2 (ACE2), the receptor used by the SARS-CoV-2 to gain access to cells. In the context of virally infected cells, this interaction could trigger and explain a number of the novel findings observed, including a fulminant immune response and coagulation abnormalities, which ultimately leads to multi organ failure and death in some individuals.

The intricate RAS comprises a carefully balanced and controlled cascade of hormones and receptors involving multiple organ systems. The system is primarily responsible for blood pressure control by maintaining fluid and electrolyte balance and preserving systemic vascular resistance [1]. Numerous factors regulate the system, including an increase in the sodium concentration in the distal tubule of the nephron, a decrease in the glomerular afferent arteriole pressure, and the release of cardiac natriuretic peptide which plays an important role in the counter regulation of the system [1,2].

Angiotensinogen, continuously released from the liver into the circulation, is cleaved to angiotensin I (AngI) by renin which is released from the kidney. The cascaded RAS ultimately results in the formation of angiotensin II (AngII) from AngI catalyzed by angiotensin converting enzyme (ACE) located on vascular endothelium, and most abundantly found in lung tissue [1,2]. AngII is the most active end product of the classic arm of the RAS system and acts mainly via angiotensin 1 (AT1) receptors located in the heart, vasculature, kidney, adrenal cortex, basal ganglia and the brainstem where it mediates vasoconstriction (See figure). This is the so-called "classical arm" in the RAS.

Earlier in the pathway, AngI is also converted to Ang (1–9) and AngII to Ang (1–7) by ACE2. Ang (1–7) primarily exerts effects on the MAS receptor and to a lesser degree also on AT2. When Ang (1–7) binds to MAS receptors, it causes vasodilation, natriuresis, diuresis, and also exerts anti-proliferative and anti-inflammatory effects. This arm of the pathway constitutes the so-called "protective pathway" of the RAS as the effects are believed to be physiologically favourable [2,3].

The commonly used antihypertensives namely ACE-inhibitors (ACEi) and angiotensin receptor blockers (ARB) act directly on the RAS as shown in Fig. 1.

The RAS appears to be important in a number of pathological processes. AngII/AT1 activation leads to a number of unfavorable effects, which include vasoconstriction and hypertension, cellular differentiation and growth, endothelial dysfunction, and the formation of reactive
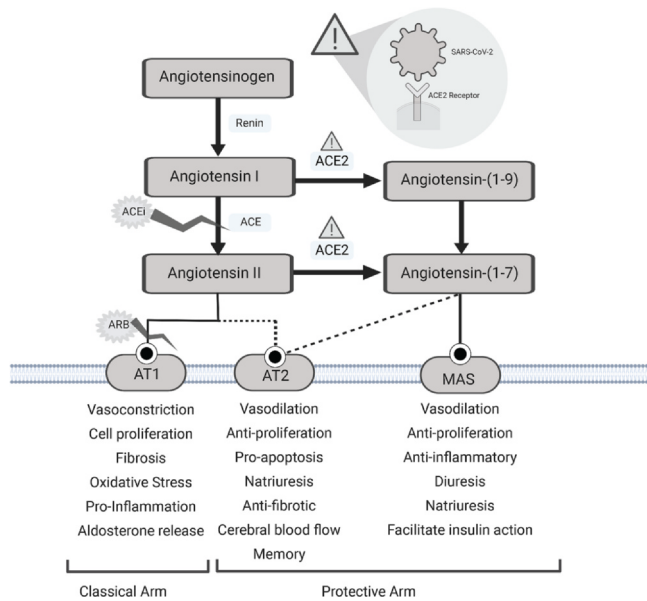

Fig. 1. The RAS pathway showing the classical and protective arms as well as the various receptors and their downstream effects. RAS: Renin Angiotensin System. ACEi: Angiotensin Converting Enzyme inhibitor. ARB: Angiotensin Receptor Blocker. AT1: Angiotensin 1 receptor. AT2: Angiotensin 2 receptor.

oxidative species (ROS) that may ultimately lead to organ damage [2–4]. The vasodilator nitric oxide (NO) is released when Ang (1–7) binds to MAS and AT2 receptors [5]. This is part of the protective arm of the RAS and possibly counteracts the vasoconstrictive effects of the classical arm. Additionally, aldosterone secretion, mediated by AngII/ AT1 binding, also plays a central role in the establishment and development of inflammation and coagulation. More recently, AngII/AT1 activation, has been proposed as a contributor in the development of atherosclerosis, and insulin resistance in diabetic patients [6,7].

In summary, the classic pathway of the RAS, namely AngII/AT1 receptor interaction, results not only in the well-known vasoconstrictive effects, but also a host of potentially detrimental effects on the endothelium, inflammation, and coagulation. AngII/AT2 and AngII/MAS receptor interactions act as a critical "protective arm", acting as an important counter-control mechanism to balance these effects [2]. ACE2 can therefore be considered a central component of the counter-RAS system in both the development of, and protection against disease.

Studies now confirm that ACE2 is the port of entry for SARS-CoV-2, and is the same mechanism found in the original Severe Acute Respiratory Syndrome (SARS) [8–10]. To fully understand the pathophysiology of COVID-19, it is important to understand the expression and function of ACE2.

Studies are ongoing to establish the exact locations of ACE2 tissue expression, but currently it is accepted that the ACE2 receptor protein is found on the endothelium in various human organs, including the skin, lymph nodes, thymus, bone marrow, spleen, liver, kidney, and brain as well as the oral and nasal mucosa, nasopharynx, lung, stomach, small intestine, colon, while

ACE2 mRNA is found in almost every organ [11]. The most remarkable finding is the surface expression of ACE2 protein on lung alveolar epithelial cells and enterocytes of the small intestine [11]. This is especially important when considering the pathogenesis and clinical picture of COVID-19 infected patients.

Once a cell becomes infected with SARS-CoV-2, ACE2 is internalised and the expression of ACE2 is downregulated. Therefore the beneficial degradation of AngII to the counter-regulatory Ang (1–7) decreases, leading to unopposed AngII/AT1 effects [12], a theory supported by the finding of raised AngII levels in infected COVID-19 patients [12,13].

Hypothesis

Currently, there is a lack of data on how SARS-CoV-2 and the RAS interact. We hypothesize that the RAS may be involved the pathophysiology of COVID-19 via activation of the classic pathway. The ubiquitous distribution of ACE2 in the endothelium could potentially allow for widespread of effects outside the lung once viraemia is established. In the context of a viral induced inflammation, this SARS-CoV-2/ACE2 interaction with the potential loss of the RAS counter-regulatory protective arm, could theoretically result in a number of the observed clinical findings seen in COVID-19.

Evaluation of the hypothesis

High risk populations

A number of important epidemiological observations have been made in COVID-19 disease, especially in severe disease. Firstly, older people, males, hypertensives, diabetics and people who are overweight seem to be most at risk [14–16] while the pulmonary oedema, capillary leak and acute respiratory distress syndrome (ARDS) noted to develop with the infection appears to be associated with a raised Interleukin-6 and very high CRP levels [14] which is unusual for an early viral infection. Also, a hypercoagulable state is being increasingly recognised in severely ill patients [17,18]. It is hypothetically possible, that many of these effects could be explained by ACE2 receptor loss and AngII/ AT1 over activation, at least in the initial phases of the disease.

Interestingly, the genes for the expression of the ACE2 receptor are located on the X-chromosome, which could account for an under-expression in males as males are hemizygous for the gene. The only copy of the gene is inherited from the mother, and will be expressed. In females, X-chromosome genes are expressed as mosaics. This means that in some tissues the ACE2 gene from one X-chromosome is expressed, and in some tissues the copy found on the other X-chromosome is expressed. Which copy of the gene is expressed, is determined early in development by X-inactivation [19]. Additionally it is plausible that ACE2 receptor numbers or function diminishes with age, placing older individuals at increased risk of "classic arm" activation in the setting of SARS-CoV-2 [20]. Individual and genetic variation in ACE2 expression may also prove to be an as yet unexplored factor in progression to severe disease [19].

ARDS and the cytokine storm

Using animal models, ACE2 was shown to be a critical receptor in the previous SARS infection even in animals, without which the virus was unable to gain entry into cells [21]. Once infected with SARS, mice showed markedly down-regulated ACE2 expression in the lungs, which appeared to be mediated by the mere binding of the virus to the receptor [21]. Rats with ACE2 genetically removed (knock-out rats), developed more severe ARDS when they were exposed to non-SARS lung damage (i.e. acid, endotoxin and peritonitis), compared to the wild type rats where ACE2 remain present [5]. The pathological findings in the knock-out rats included increased vascular permeability, lung oedema and neutrophil accumulation. Thus, ACE2 was shown to play a protective role in rat models of acute lung injury, while ACE, AngII and AT1 receptors (i.e. the "classic pathway" – refer to figure) were found to be lung injury-promoting [5,22]. Similarly, in SARS infection, ACE2 and components of the protective RAS system appear to play a role in controlling the severity of lung damage, once inflammation is initiated [21]. If ACE2 was removed in mice, SARS Co-V spike protein alone (i.e. no other viral elements) increased AngII levels and worsened ARDS, implying a pathological mechanism even in the absence of viable virus. This effect was also found to be partially reversed by AT1 receptor blockade [21]. It is plausible, that the SARS-CoV infection-induced downregulation of ACE2 may play an early triggering role, in upstream

progression to severe disease.

Critically ill COVID-19 patients admitted to intensive care unit (ICU) appear to exhibit a so-called cytokine storm. A massive overproduction of cytokines in response to exponential viral replication leads to epithelial and endothelial cell death with subsequent vascular leakage and the release of inflammatory cytokines and chemokines [23]. This leads to downregulation of pulmonary ACE2, and subsequent dysfunction of the RAS, in turn leading to worsening systemic inflammation and vascular permeability, eventually leading to ARDS, multi organ failure and mortality [23–25]. The hypersecretion of cytokines may also have direct cardiovascular effects including the reduction of coronary blood flow, the destabilization of atherosclerotic plaques and the formation of microthrombi [26].

Importantly Ang2/AT1 activation results in endothelial dysfunction, and in the context of a viral infection, increased endothelial signaling may be the catalyst for initiation of the coagulation cascade in certain individuals. The inflammatory response, with raised CRP and IL-6 levels have been shown to be hallmarks of disease in some COVID-19 patients, and these levels predict severity of disease [27]. It may be simplistic to ascribe these findings to one pathway, but as noted above, Ang2/AT1 working through the mechanism of increasing ROS and promoting inflammation, is able to increase both CRP and IL-6, thus in the context of a viral infection, ubiquitous Ang2/AT1 stimulation may have a multiplicative effect on inflammation within, or near the cell of infection.

The formation of ROS results in the production of inflammatory factors such as tumor necrosis factor alpha (TNF-a), monocyte chemoattractant protein-1 (MCP-1), tissue factor (TF), nuclear factor kappa B, Interleukin-6, C-reactive protein and plasminogen activator inhibitor-1(PAI-1), which may add to the state of overwhelming systemic inflammation, and hypercoagulability [28].

Hypercoagulability

Many critically ill COVID-19 patients appear to develop an overwhelming hypercoagulable state leading to the formation of pulmonary emboli, venous thrombi and disseminated intravascular coagulation (DIC) [29,30]. Increased aldosterone release, mediated by Ang II/AT1 may be associated with thrombotic events [31]. It is noted that AngII and aldosterone increase the expression of PAI-1, a major inhibitor of fibrinolysis in vivo, in vascular smooth muscle and endothelial cells [32]. Aldosterone release stimulated by AngII/AT1 activation, also upregulates protein-C receptors in human vascular endothelium [33], and is strongly associated with a prothrombotic state [34].

COVID-19 and the cardiovascular system

In our clinical experience, a number of critically ill COVID-19 patients exhibit significant and difficult to treat hypertension, despite severe hypoxia (Dr Brian Allwood, personal communication). There are a number of possible causes for this, but increased activation of the classical pathway of the RAS in patients infected with COVID-19 may play a significant role [35].

In a study by Oudit et al, the effects of SARS-CoV infection on the cardiovascular system, including cardiac dysfunction, arrythmias and death, were demonstrated [10]. The authors postulated that SARS-CoV infection possibly downregulates ACE2 expression in the myocardium. Measuring tissue ACE2 levels in mice infected with SARS-CoV revealed a decrease in myocardium ACE2 expression. In the same study, the authors also examined the hearts of patients who died from SARS-CoV. SARS-CoV mRNA expression was found in 35% of the patients which was associated with a decrease in ACE2 expression. They postulated that the downregulation of ACE2 was possibly a cytokine mediated process [10].

Insulin resistance and obesity

A large number of patients with severe COVID-19 disease are overweight [15,16]. Interestingly, AngII is produced in adipose tissue [6] which may tip the balance to harm in overweight individuals Also, insulin has been shown to counteract the inflammatory effects of AngII [6]. Thus, insulin deficiency as in diabetes, may result in less opposed AngII inflammation. Further AngII itself, it said to play a role in insulin resistance [6] thus, it is possible that this could be a "chicken or the egg" situation in acute illness. This can possibly be attributed to an increase in AngII activity in tissue like skeletal muscle, adipose tissue and the pancreas where it alters glucose metabolism [6]. Furthermore, a strong relationship between aldosterone and the development of insulin resistance is described [6]. This is due to mineralocorticoid receptor activation by aldosterone, leading to an inhibitory effect on insulin signaling, increased uptake of glucose in adipocytes, skeletal muscle and vascular smooth muscle [6,7].

Opportunity for intervention

If activation of the classic arm of the RAS is an early trigger to overwhelming disease, there may be possibilities for early intervention using readily available medications, to prevent progression to severe and overwhelming COVD-19 disease.

The use of medication that may potentially block the classical pathway, or upregulate the protective arm of RAS in early disease, may be useful. Use of ACEi, ARBs and/or aldosterone blocking drugs, may assist in blocking some of these effects, especially in treatment naïve patients. However, this needs to be balanced against the risk of potential side-effects, and the theoretical risk of ACE2 upregulation which could facilitate SARS-CoV-2 cell entry [36,37].

Conversely, acutely stopping these medication in COVID-19 may pose the hypertensive patient at double risk, that of upregulated receptors with increased viral binding sites while acutely ceasing the RAS blocking effects of these drugs.

The question of whether ACE inhibitors or ARBs should be withdrawn was addressed by a joint statement issued on 17 March 2020 that clearly stated that no evidence is currently available to support the notion that ACE inhibitors or ARBs were detrimental to patient outcome [38]. For now, treatment should therefore not be discontinued if a patients becomes infected with COVID-19.

A number of the RAS components have been identified as possible treatment targets in COVID-19, especially given that AngII levels are increased in infected patients [39]. Soluble ACE2 receptors have been proposed as therapy for COVID-19 to "mop-up" virus, however may prove to be beneficial through their antagonistic effects on the RAS pathway [40]. Some studies advocate downregulation of ACE2, but the concern is that it may lead to unopposed AngII/AT1 effects [41]. AngII Showed promise as a treatment modality, but is still in experimental phase [42]. Ang (1–7) has been shown to reduce the acute inflammatory response in animal models [43,44].

Measuring ACE2, AngII and components of the RAS is unfortunately technically difficult, and analytes have short half-lives, making it impractical for routine use and are currently only available for experimental purposes. Using experimental treatments such as recombinant soluble ACE2 or, monitoring the effect ACEi and ARBs may have on the expression of ACE2 in individual patients to aid clinical decision making, is thus not possible at this stage [43].

Conclusion and caution

In summary, this hypothesis of overactivation of RAS induced by SARS-CoV-2 may account for many of the epidemiological and unusual clinical findings observed in COVD-19 disease, including the hypertensive, inflammatory, endothelial and coagulation effects. In susceptible individuals, this is likely to play its biggest role in early disease, before "the forest catches fire". Clearly, this is not the only disease mechanism at play within severe COVID-19, with a myriad of other

inflammatory cascades possibly involved. However, if correct, this hypothesis may provide a window of opportunity to prevent disease progression using readily available drugs, giving time for the natural host response to clear infection.

It is too early to definitively advocate either for, or against therapies based on this hypothesis, and urgent research and data is needed to obtain sufficient evidence before any recommendations can be made in this regard.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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