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ORIGINAL ARTICLE

Renin Angiotensin System (RAS) Pathways in COVID Pathogenesis

Sampreeti Mukherjee and Minu Bajpai*
Departments of Paediatric Surgery, All India Institute of Medical Sciences, New Delhi - 110029, India

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Abstract

Background – Covid-19 pandemic has posed some rare diagnostic & therapeutic challenges. Recurrent waves of varying severity are caused by ongoing mutations in the virus. It is vital to understand the fundamentals of Renin Angiotensin System (RAS) pathway which has been incriminated in the Covid-19 pathogenesis.

Aim – We aim to understand the basic pathological and molecular basis of the disease and thereby understanding the basis of treatment options and possible outcomes of the disease.

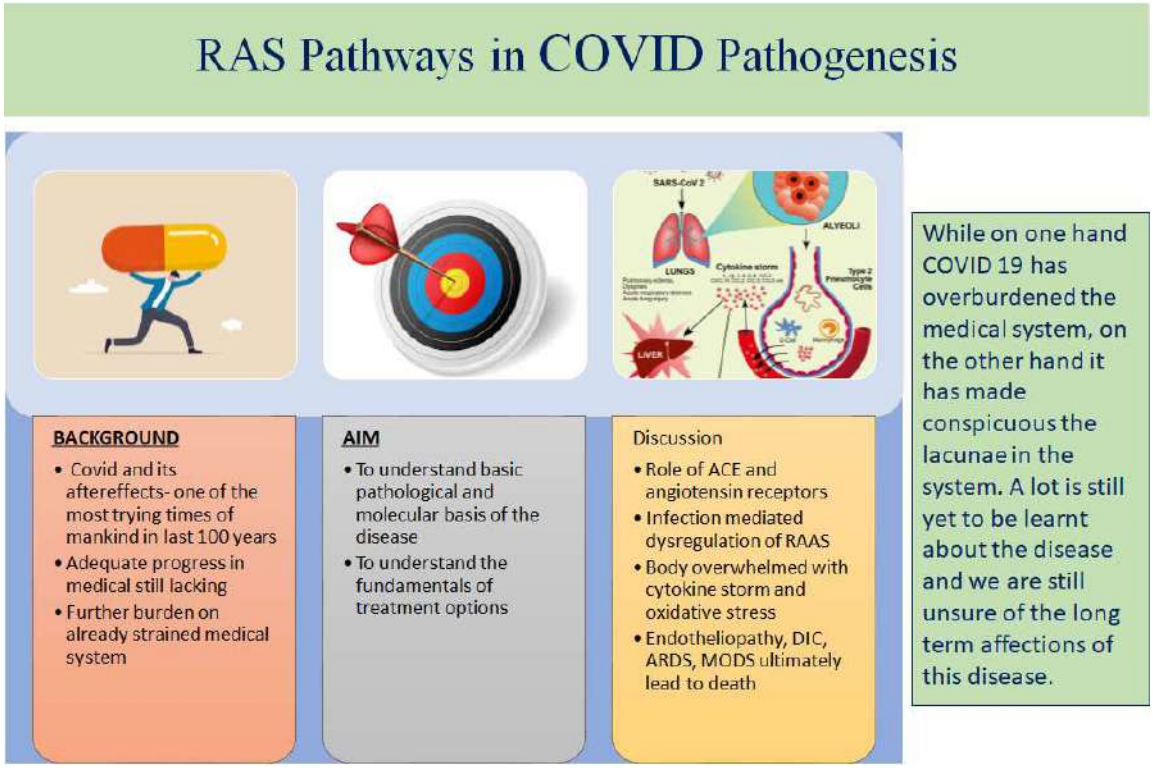
Discussion- The role of ACE and angiotensin receptors take the center stage in COVID pathogenesis. The crux of the disease process lies in the infection mediated dysregulation of the renin angiotensin aldosterone system which further leads to an oxidative stress that overwhelms the body's protective mechanisms. Children, on account of having a more robust immune system, tend to get less affected by the disease process. Various therapeutic options can be explained by understanding the pathogenesis and biology of the disease.

Conclusion- Children have an abundance of AT 2 receptors which have a predominantly anti-inflammatory effect and less of AT1 receptors which are proinflammatory. Furthermore, children tend to have a more robust and active innate immunity due to repeated viral and bacterial infections in the childhood. Ongoing research on RAS pathways may unravel the, hitherto, unsurmountable challenges in the understanding of COVID-19 pathogenesis.

Keywords: COVID, ACE, Angiotensin, Paediatrics

*Corresponding author: Minu Bajpai
E-mail address: bajpai2b@gmail.com

Graphical Abstract



Introduction

After having witnessed one of the most horrifying events of the century, those of us who came out safely to the other side of the tunnel are still reeling from the effects and aftereffects of the COVID Pandemic. Each person across the globe has lost something or someone to this disease. The disease acted as a mirror in ways, where all the inadequacies and defects of the medical system were suddenly exposed and made very conspicuous to the entire world. Thus, it becomes imperative to thoroughly understand the core and functioning of the disease so that we are prepared to tackle any future shock waves and long term or delayed complications or repercussions of COVID 19. This we will do by going back to the basics and understanding the molecular and cellular working of COVID 19, which is the main aim of this article.

The basic biology of Angiotensin converting enzyme (ACE) and Angiotensin receptors (AT)

The role of ACE2 and AT receptors came to center force in the pathogenesis of COVID 19, interestingly the same ACE 2 receptor and RAS pathway is also a key player in CAKUT pathogenesis in children. Thus, this article will mainly focus on RAS pathways and ACE in COVID pathogenesis.

Angiotensin converting enzyme (ACE) converts angiotensin I to angiotensin II (AT II). AT II is further acted upon by ACE 2 into Angiotensin 1-7 (Ang 1-7). Furthermore, AT II acts via AT1 receptors and Ang 1-7 act via AT2 receptors. The human body maintains homeostasis by a fine coordination and regulation between ACE and ACE 2, which have counter regulatory effects. Disturbance of this delicately balanced relationship is the cornerstone in pathogenesis of COVID.

In the mid-1950s, ACE was discovered after an observation that dialysis of plasma and kidney extract with saline and water before incubation had produced two distinct pressor substances namely Angiotensin 1 and 2. ACE was rediscovered in 1966 when a bradykinin

degrading enzyme was found in the kidney namely ACE [1]. The ACE 2 enzyme was discovered much later in 2000, when homologous ACE was cloned by two independent research groups, which would convert Angiotensin I to Ang 1-9, but also was captopril insensitive [2].

The ACE gene and ACE 2 genes are located on chromosome 17q22 and Xp22. The somatic ACE contains N and C domains which as two catalytic domains and a C- terminal transmembrane stalk. Both the catalytic domains are zinc metallopeptidases wherein the zinc ion coordinates with two histidine residues. The transmembrane stalk has a dual function. It anchors the enzyme on the membrane and also helps in its release into plasma after cleavage by shedding enzymes. The ACE 2 is a chimera protein with only one catalytic domain and a C terminal resembling collectrin, which acts to deliver other proteins to brush border membrane like a chaperone protein. Ace 2 is regulated at multiple levels including transcriptional, post transcriptional (miRNA and epigenetic) and post translational levels. While the ACE via (angiotensin II) AT1 receptors acts via Gi 2/3 mechanism, the ACE2 via (ang 1-7) AT2 receptor acts via Go/11, Gi/o mechanism [3-4].

ACE 2 receptors are widely distributed in the body in endothelial cells, smooth muscle cells, podocytes, cardiomyocytes, proximal tubules of kidneys, hepatocytes, lymphatic system, goblet and ciliary cells of upper airway and type II alveolar epithelial cells to name a few. There are wide variations in ACE2 expression both in the body and in the population.(3)(5) The expression of this ACE2 receptor is hypothesized to be induced by cellular or environmental stimuli, in the intestinal epithelial cells and apical zone of respiratory epithelium. Thus forms an integral part of the innate immune system [5].

Likewise, the AT 1 receptors are located in heart, blood vessels, kidney, adrenal cortex, lung, basal ganglia and brain stem. It is stimulated by Angiotensin II and acts via G protein mediated decrease in cyclic AMP (cAMP), which causes vascular smooth muscle contraction due to increased calcium inside the cells. It also increases aldosterone thereby increasing proximal and distal tubule sodium reabsorption. It also causes vasoconstriction by stimulating endothelin production. It is overall effective in increasing blood pressure, anti-natriuresis, stimulating cyclooxygenase release, inhibiting renin release, anti-apoptotic, and pro-growth and proliferation. It is also known to stimulate renal growth in fetuses [6,7].

AT 2 receptors are located in large numbers in fetus and neonate and found in cerebellum in adults. It has the opposite effect of AT 1 mediated actions. It gets stimulated by binding of Ang 1-7 and increases bradykinin, nitric oxide and cyclic GMP (cGMP). This leads to vasodilation, natriuresis, low blood pressure, stimulation of cytochrome P-450, pro apoptotic, anti-growth and anti-proliferative by inhibition of fibrosis and collagen deposition. It has been known to cause inhibition of cell growth and tissue development in fetuses [8,9]

AT3 and AT4 are two other receptors of angiotensin II but are very poorly characterized. AT 4 is activated by angiotensin II metabolite angiotensin IV and may play a role in central nervous system extracellular matrix regulation and modulation of oxygen release [10,11]

Thus, to summarize, ACE acts on angiotensin I and converts it into AT II which acts via AT1 receptors and has vasoconstricting, pro inflammatory, pro apoptotic, pro fibrogenic action and it increases oxidative stress, whereas, in contrast, ACE 2 via Ang 1-7 is a potent vasodilator, anti- apoptotic, anti-proliferative agent which reduces oxidative stress (as shown in Figure 1). Therefore ACE 2 functions as a negative regulator of classical ACE in the RAS pathway [9].

SARS Cov-2 infection and entry into a cell

Severe acute respiratory syndrome coronavirus 2 (SARS – Co-V-2) uses membrane bound ACE-2 to gain cell entry. The SARS – CoV-2 spike protein has structural homology to the spike protein of SARS-CoV, however, the former binds to ACE2 with much higher affinity than the latter. The membrane fusion of the virus with the cell via ACE 2 leads to down regulation of ACE2 and therefore an imbalance in ACE/ACE2 ratio which tips the body's homeostasis to pro inflammatory and apoptotic state. The spike protein for both the SARS viruses require priming by TMPRSS2 (a serine protease) for optimal entry of the virus into the cell [1]. This is utilized in the fact that camostatmesylate- an

inhibitor of TMPRSS2- can be used in treatment strategies [12].

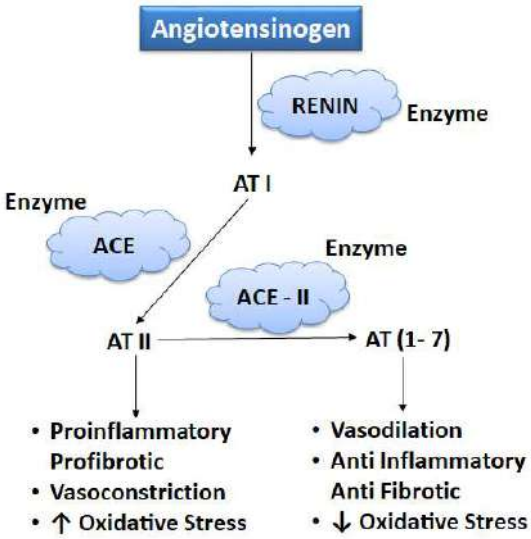


Fig. 1. Role of ACE and ACE-II in the body.

The primary target of SARS Cov2 are the epithelial cells in the tracheal and bronchial epithelium and the gastrointestinal tract. The spread of the virus into blood and alveoli is further facilitated from there on. The virus enters the epithelial cell from the apical pole in the initial stage of infection and exits the cell from basolateral pole in the late stage of infection and begets infection to subsequently more cells [13]. Endogenous serine proteases such as furin, cathepsin, human airway trypsin like protease and transmembrane serine protease (TMPRSS2 and 4) separate the S- spike of the virus into two pincers- S1 which binds to the ACE2 receptor, and S2 which anchors to the cell membrane thereby gaining cell entry. S1 and ACE binding triggers the cleavage of ACE2 by a disintegrin and metallopeptidase domain 17 (ADAM 17) and tumour necrosis factor converting enzyme (TACE) at the ectodomain sites. This process leads to shedding of host ACE2 receptor and systemic release of S1/ACE2 complex (as shown in Figures 2a, 2b, 2c, 2d, 2e). This causes inflammation, oxidative stress (direct stimulation of polymorphonuclear cells and production of superoxide dismuatase), reduced innate immunity, pulmonary endothelial vasoconstriction and microthrombi formation leading to ARDS [1].

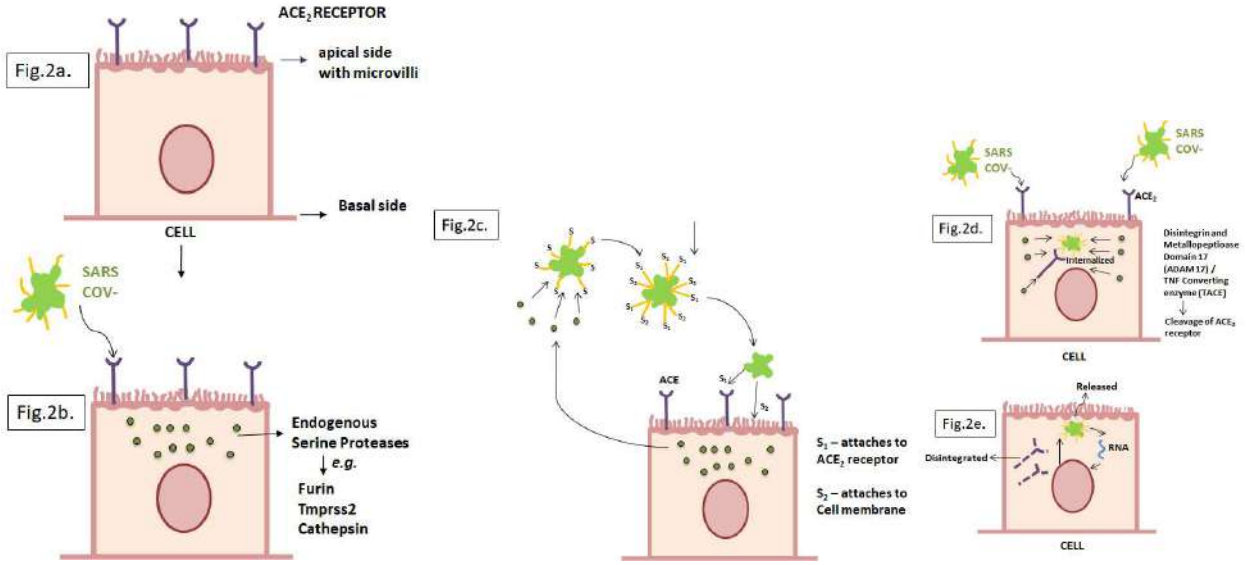
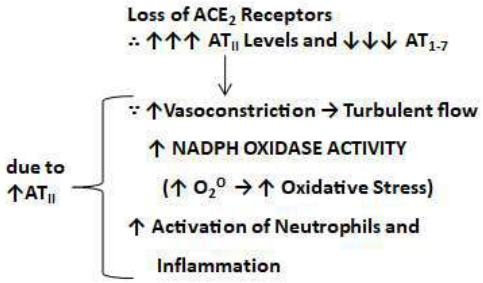


Fig. 2: Pathogenesis of SARS Cov 2 entry in cells: 2a- Normal cell. 2b- Infection with SARS Cov-2. 2c- attachment of SARS Cov virus to ACE receptor. 2d, 2e- Cleavage of ACE 2 receptor.

Systemic involvement of SARS Cov-2 virus

The vasoconstriction caused by ACE 2 inhibition causing turbulent blood flow in addition to the oxidative stress causes extensive and widespread endothelial damage. This is called endotheliopathy [14] Damage of endothelium exposed the subendothelial von Willebrand factor inside the blood vessels to factor VIII which is freely present in blood [15] (as shown in Figure 3a, 3b, 3c).

Fig.3a.



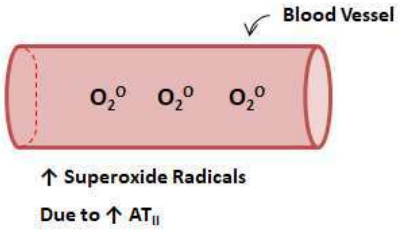


Fig.3b.

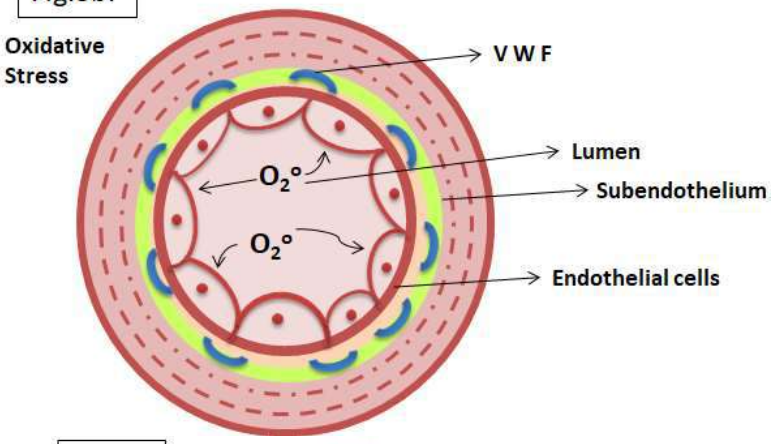


Fig.3c.

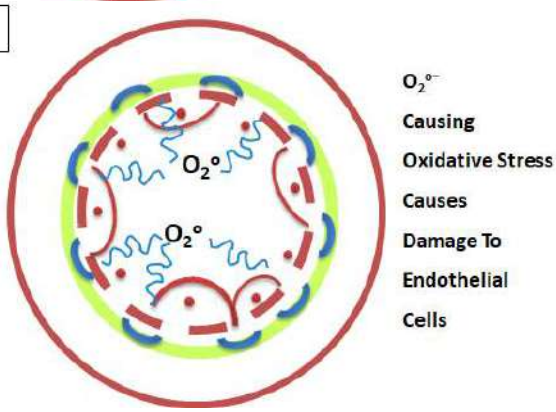
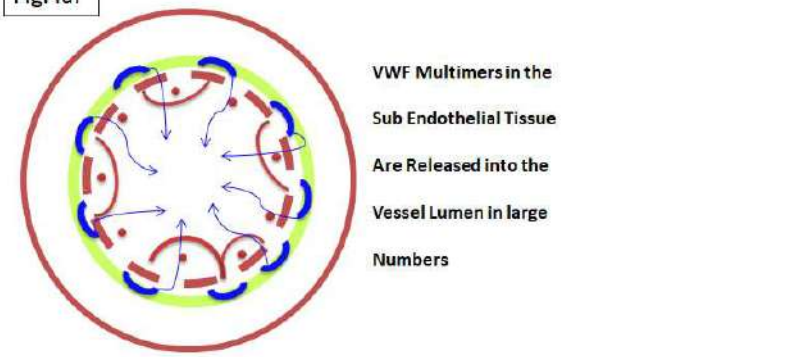


Fig. 3a, b, c: Oxidative stress, endothelial damage and release of Von Willebrand factor from subendothelial layer.

Binding of these two factors causes platelet activation, aggregation, and activation of the coagulation cascade thus production thrombosis (as shown in Figure 4a, 4b). Higher levels of serum vWF indicate a more extensive thrombosis and associated with a worse outcome [15].

Fig.4a.



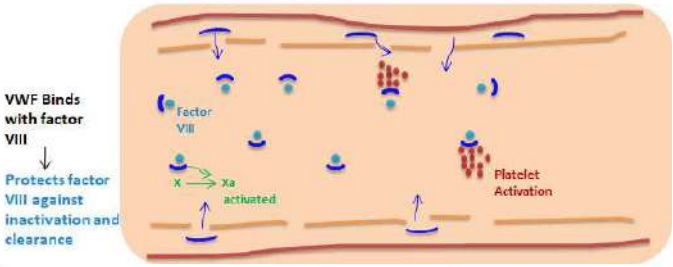


Fig.4b.

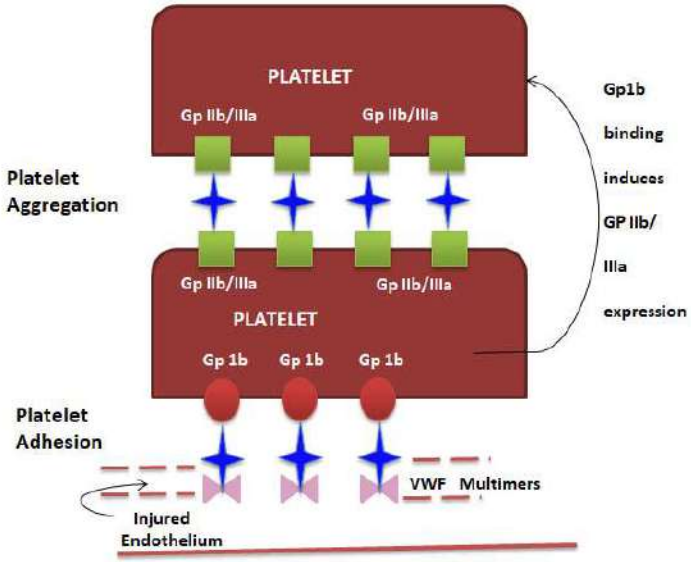


Fig. 4: 4a: Release of subendothelial von Willebrand factor. 4b. Platelet adhesion by attachment of Gp 1b with vWF multimers and platelet aggregation by interlinking of Gp IIB/IIIA between platelets. This further leads to formation of widespread microthombi and DIC.

Thus, Virchow's triad of thrombus formations is favored i.e., altered blood flow, endothelial damage, and hypercoagulable state. In addition, extensive endotheliopathy causes widespread thrombus production in the body which overwhelms the plasmin mediated

thrombolytic system thus leading to the formation of widespread microthrombi which eventually leads to cytokine storm- DIC (disseminated intravascular coagulopathy)- MODS (multiorgan dysfunction) and ARDS finally leading to death. The factors favoring this extensive endotheliopathy is directly related to the load of viral infection, collateral; damage to tissues because of immune infiltration and activation, compliment activation and release of large number of inflammatory cytokines all at once [16]. It is also higher in patients with preexisting oxidative stress. This sudden load of cytokines on the body also known as the cytokine storm is way too much to tackle especially in adults who are already dealing with an ongoing oxidative stress and have a dysregulated renin angiotensin system to start with such as in people with obesity, diabetes, hypertension or any cardiovascular or any other such morbid disease [16].

Pathogenesis of COVID pneumonia

Inhalation of the SARS virus leads to primary assault of the respiratory system which is essentially the principal target of the virus. As discussed, the virus enters the cell from the apical surface and the virions exit the cell from the basal surface of the alveoli. Inactivation of ACE2 and endotheliopathy leads to pulmonary endothelial vasoconstriction and microthrombi which causes ARDS. This results in high elastance of the lung and a right to left shunt due to pulmonary vasoconstriction. Increased exodus of fluid into the alveoli from the high-pressure vessels cause increase in lung weight and increase in recruitment of lung alveoli to counter hypoxia (type H lung problem). Patients present with gradual onset progressive dyspnea, bilateral lung infiltrates and co2 retention, eventually requiring mechanical ventilation. The picture is that of a full-blown ARDS. Prone positioning and low tidal volume and high PEEP ventilation may help tide over this state. However, this process takes some time and occurs slowly [17, 18].

The virions after release from alveoli also enter the systemic circulation. It then causes widespread endotheliopathy, vasoconstriction and microthrombi which leads to occlusion of blood supply to all the organs in the body leading to sudden acute multi organ failure. This type causes a L type of lung with low ventilation: perfusion ratio, low elastance and low recruitability. Such patients present early on in the disease process. Vasoplegia due to modest local subpleural interstitial edema contributes to severe hypoxemia [17-19]. However, some recent studies postulate that both these types describe the early and late stages of COVID pneumonia and both benefit from the same type of treatment [20].

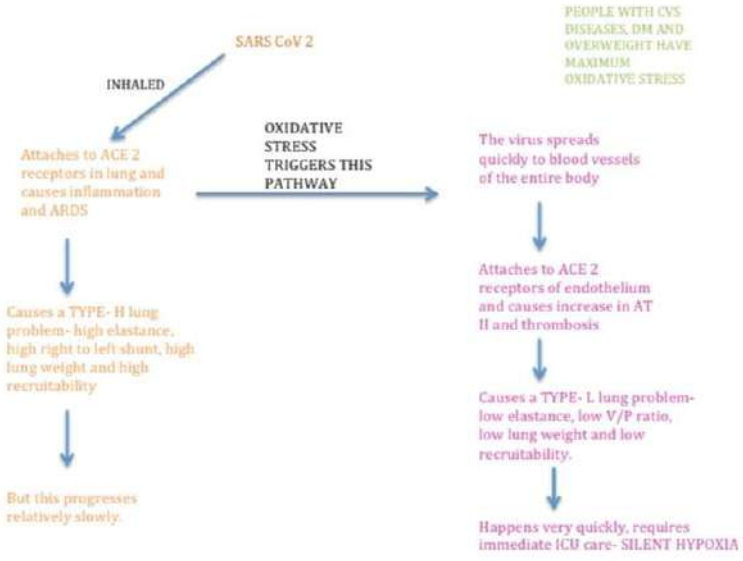


Fig. 5: Flowchart depicting an overview of the SARS CoV 2 pathogenesis.

Treatment options

The possible treatment modalities include usage of ACE inhibitors or ACE receptor blockers (ARBs) which downregulate the ACE pathway by putting a block to this vicious cycle at an early stage and preventing an uncontrolled oxidative stress and cytokine storm (as shown in Figure 6). There are a multitude of other treatment modalities that have been tried with some successs including use of N- acetly cystine(NAC), eculizumab, tocilizumab, dipyridamole, defibrotide, zinc, vitamin D etc. NAC in addition of being an antioxidant also works by cleaving vWF multimers inside occlusive thrombi, thus, causing recanalization of vessels [21]. Eculizumab and Tocilizumab are monoclonal antibodies against C5 complement and IL6 respectively thereby regulating cytokine storm [22,23]. Dypyridamole is under clinical trials for usage in severe covid infection. It is an antiplatelet agent that prevents platelet aggregation and thus, prevents formation of microthrombi [24]. Similarly, defibrotide is an antithrombotic agent that is under trials for uasge in severe pneumonia in COVID [25] Zinc has been widely studied for their prophylactic and preventive role in COVID infection. It enhances antiviral immunity of the body by a multitude of actions on the innate and humoral immunity [26]. Vitamin D has a conflicting role, while correct body levels of vitamin D favours a milder disease course; vitamin D itself as a does not act as a treament modality for COVID [27,28]. Other possible drugs that can be used in treatment and act as possible area of future research include TMPSSR inhibitor- camostar mesylate- which works by inhibiting viral entry into the cell.

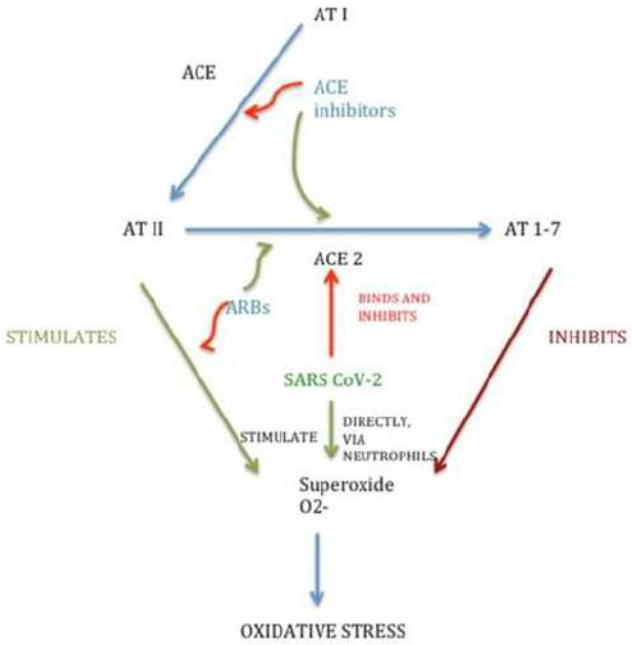


Fig. 6: Role of ACE inhibitors and ARBs in COVID.

COVID infection in paediatrics

It is now well understood that children and infants have some sort of inherent immunity against COVID infection and older people are increasingly susceptible to the infection. Children even after being infected tend to show milder symptoms with very quick recovery. This may be explained by a physiological elevation of lymphocytes and reduction in pro inflammatory cytokines and higher production of anti-inflammatory in children as compared to adults. Also, children have and abundance of AT 2 receptors which have a predominantly anti-inflammatory effect and less of AT1 receptors which are proinflammatory. Furthermore, children tend to have a more robust and active innate immunity due to repeated viral and bacterial infections in the childhood. In addition, the endothelium is less pre- damaged in children on account of less age [29].

Conclusion

COVID pathogenesis is still not fully understood. Children have an abundance of AT 2 receptors which have a predominantly anti-inflammatory effect and less of AT1 receptors which are proinflammatory. Furthermore, children tend to have a more robust and active innate immunity due to repeated viral and bacterial infections in the childhood. Ongoing research on RAS pathways may unravel the, hitherto, unsurmountable challenges in the understanding of COVID-19 pathogenesis. Ongoing studies on Renin Angiotensin System pathways have the potential to unravel the pathogenesis of COVID-19.

Conflicts of interest

The authors have no competing interests to declare that are relevant to the content of this article

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