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Beta-adrenergic blocker treatment for COVID-19

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Abstract:

More than 2.5 million people were affected by COVID-19 and it had caused around 175000 deaths as on April 23, 2020. Currently, no effective treatment option is available for COVID-19 patients. Even though many drugs have been proposed, none of them showed their efficacy in clinical trials. In this article, I had focused on the Adrenergic system- RAAS relation in COVID-19 and proposed a vicious Adrenergic system-RAAS-ACE2-SARS-CoV-2 (ARAS) loop. Hyperactivation of the ARAS loop may be the underlying pathophysiological mechanism in COVID-19. I had proposed beta-adrenergic blockers as a potential treatment option for treating COVID-19. Beta-adrenergic blockers may decrease the SARS-CoV-2 cellular entry by decreasing ACE2 receptors expression, and CD147 in various cells in the body. Beta-adrenergic blockers may decrease the morbidity and mortality in COVID-19 patients by preventing or reducing the ARDS, pulmonary embolism, pulmonary edema, refractory hypoxemia, and septic shock complications. Considering potential beneficial effects of beta-adrenergic blockers in COVID-19, retrospective and prospective clinical trials need to be conducted to check the validity of the hypothesis and clarify its role in COVID-19. I had also speculated that beta2-adrenergic agonists use in the nebulizers, and norepinephrine use in the COVID-19 patients having septic shock may worsen the condition.

Keywords: SARS-CoV-2, COVID-19, ACE2, Beta-adrenergic blockers, Septic Shock, ARDS, pulmonary embolism.

Highlights:

- ❖ Adrenergic system by its action on RAAS, ACE2, and SARS-CoV-2 plays a crucial role in COVID-19.
- ❖ Hyperactivation of the vicious ARAS loop may be the mechanism behind COVID-19.
- ❖ Beta-adrenergic blockers should be used in COVID-19.
- ❖ Norepinephrine should not be given for COVID-19 patients.
- ❖ Beta-agonists in nebulizer solution should not be given for COVID-19 patients.

Introduction:

COVID-19 has affected people's lives world over, and as on 23 April 2020, 2544792 people are affected globally and caused 175694 deaths [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive-sense single-stranded RNA virus, belongs to the beta coronavirus genus. It is known that the SARS-CoV-2 spike protein binds to human angiotensin-converting enzyme 2 (ACE2), which acts as a receptor, and binding to ACE2 is crucial for the cellular entry of SARS-CoV-2 [2,3]. It has been proposed recently that CD147 also known as Basigin, maybe another receptor in the host cells that play a role in the SARS-CoV-2 entry into the cell [4-6].

Clinical features and pathogenesis in COVID-19: Clinical course of COVID-19 patients are variable – ranging from being asymptomatic to having mild problems like fever, cough, sore throat, dyspnea, muscle pain, tiredness, loss of taste or smell sensation, etc. [7,8]. Around 15% of COVID-19 patients exhibit pneumonia, and ~5% progress to acute respiratory distress syndrome (ARDS), where the patient may have tachypnoea, decrease oxygen saturation, decreased partial pressure of oxygen in arterial blood, and lung infiltrates in the X-ray and CT chest imaging [9]. Laboratory investigations in moderately or severely affected COVID-19 patients showed increased IL-6, D-dimer, CRP, LDH [8]. Severely affected COVID-19 patients had lymphopenia, and increased cytokines levels (IL-6, IL-1 β , TNF α) [9]. Macrophage and neutrophil damage of alveoli may lead to hyaline membrane formation.

Severe COVID-19 patients having complications like ARDS, respiratory failure, and septic shock have a high mortality rate [10]. Increased IL-6 is an indicator of poor outcome in patients with ARDS and Tocilizumab can be used to block the action of IL-6 [9]. It has been shown that IL-6 is increased in non-survivors [11]. Increased mucus aggregation has been noticed in the distal airways and alveoli in the postmortem study of COVID-19 patients [12].

It is known that IL-6 plays a key role in the activation of MUC5AC and MUC5B gene expression and increases the mucus secretion [13]. It has been suggested that Tocilizumab by the inhibition of IL-6R may help decrease the mucus secretion in COVID-19[14]. Postmortem study had also shown the presence of hyperplasia of type II alveolar epithelial cells, diffuse alveolar damage, macrophage and neutrophil infiltration, fibrosis, hyaline membrane formation [15].

It is known that cytokine storm occurs in COVID-19, as the levels of IL-1 β , IL-6, TNF α are increased and this cytokine storm may lead to multiple organ dysfunction and septic shock [9]. Inflammatory responses like macrophage and neutrophil infiltration may lead to alveolar damage, pulmonary capillary endothelial dysfunction, and the pulmonary capillary leak that may lead to pulmonary edema. Since type II pulmonary alveolar epithelial cells are the main cells that express ACE2 receptors, their damage might cause problems in surfactant secretion by these cells. Decreased surfactant leads to increased surface tension in the alveoli, which along with the damage in the alveolar epithelium and pulmonary capillary endothelium, may lead to pulmonary edema. Respiratory dysfunction as a result of this leads to decreased P_aO₂, decreased oxygen saturation, and severe cases were put on mechanical ventilation. If refractory hypoxemia develops irrespective of mechanical ventilation, then extracorporeal membrane oxygenation (ECMO) can be tried as per WHO interim guidance [16].

Around 30% of the severely affected COVID-19 patients developed pulmonary embolism in COVID-19 and d-dimer level is found higher in these patients [17-19]. Around 5% of the COVID-19 patients have severe complications like ARDS, septic shock [20]. Septic shock occurs in severely affected COVID-19 patients. In septic shock state, mean arterial pressure is low (<65mmHg) irrespective of fluid management, and plasma lactate concentration will be >2mM/L. Septic shock state carries a high mortality rate. The primary drug used in septic shock is Norepinephrine [21].

In COVID-19, cytokine storm and hyper-inflammation occur irrespective of lymphopenia [22,23]. Considering the cytokine storm and potential activation of the NLRP3 inflammasome, it is likely that immune hyperactivation occurs in COVID-19. Nucleocapsid protein of SARS-CoV has been shown to increase IL-6 via the activation of NFkB [24]. Since the nucleocapsid protein of SARS-CoV-2 shares 89.6% homology with SARS-CoV nucleocapsid [25], it is likely that the increase in IL-6 found in severely affected COVID-19 patients also may have a similar underlying mechanism. IL-6 level has been shown to positively correlate with the SARS-CoV-2 viral load [26]. Nucleotide-binding domain (NOD)-like receptor protein 3 (NLRP3) inflammasome has been suggested to be activated by SARS-CoV-2. It is known that Colchicine inhibits NLRP3 inflammasome, and clinical trials have been already registered to test whether colchicine treatment in COVID-19 improves the clinical condition by inhibiting NLRP3 [27]. It is known that the SARS-COV orf3a protein activates the NLRP3 [28]. SARS-CoV viroporin 3a has also been shown to activate NLRP3 [29]. SARS-CoV-2 may also activate NLRP3 by a similar mechanism. NLRP3 downstream effectors are caspase 1, IL-1 β , IL-18 [30]. It is known that the decrease in surfactant protein D in ARDS patients associated with mortality [31]. Surfactant protein D has been shown to inhibit NLRP3 [32]. Since the type 2 alveolar epithelial cells which secrete the surfactant are one of the main cells affected by SARS-CoV-2, surfactant secretion may likely be decreased. Reduction in surfactant D may result in loss of its inhibitory role on NLRP3. Activation of the NLRP3 inflammasome pathway may produce an inflammatory response in COVID-19, and as said earlier few trials targeting NLRP3 have been already started.

Hypercoagulation state in COVID-19: As mentioned earlier, severely affected COVID-19 patients developed pulmonary embolism and d-dimer levels were shown to be high [17-19]. But so far, it is not known what causes pulmonary embolism or deep vein thrombosis (DVT) in COVID-19. I hypothesize that the hypercoagulation state in COVID-19 may be due to a

sympathetic storm. Increased catecholamine levels may hyperactivate the vicious ARAS loop, which will be explained in a later section. It has been known that beta2-adrenergic agonist nebulization increases the plasma catecholamine level [33]. Sympathetic hyperactivation has been shown to be related to hypercoagulation state [34]. Inhalation of beta2-adrenergic agonists has been shown to increase factor VIII, vWF, d-Dimer, and lead to hypercoagulation state [35]. I suggest that use of catecholamines in COVID-19 patients may lead to hypercoagulation state, and use of beta2-adrenergic agonists nebulization for respiratory illness and intravenous administration of Norepinephrine for treating septic shock should be avoided in COVID-19, as it may lead to hypercoagulation state and may induce complications like deep vein thrombosis and pulmonary embolism.

Other organ damage in COVID-19 is not discussed in this article due to space constraints.

Current treatment recommendations and controversies:

At present, there is no effective drug available against the present coronavirus disease 2019 (COVID-19) pandemic [8,36,37]. Many potential treatments were proposed and some are on clinical trials. Many were focusing on drugs that interrupt the binding of spike protein with the ACE2 receptor, which will be useful in the treatment of COVID-19. Remdesivir, Hydroxychloroquine, Azithromycin, Tozulisumab are used in COVID-19 condition all over the world, irrespective of the lack of evidence for efficacy so far. Remdesivir by its inhibitory action on RNA dependent RNA polymerase restricts the viral replication is thought to work, but so far its efficacy has not been shown in clinical trials [36]. Hydroxychloroquine may restrict the SARS-CoV-2 cellular entry but its efficacy has not been shown in clinical trials so far. Tozulisumab by its action on the IL-6 receptor blocks the inflammatory actions due to IL-6, again its efficacy has not been in clinical trials so far. As mentioned earlier, Tocilizumab

may help decrease the mucus secretion in COVID-19 [14]. Currently, NIH did not recommend the Hydroxychloroquine, Remdesivir, Azithromycin, Tozulisumab treatment [37].

Other treatment options on the trial are convalescent plasma therapy. Supportive measures are used depending on the clinical condition, such as the use of mechanical ventilation, ECMO, etc. WHO suggests that if refractory hypoxemia persists irrespective of mechanical ventilation then ECMO can be opted for in selected cases [16]. As said earlier none of them has been effective in COVID-19 so far. Many had raised concerns about the use of ECMO in COVID-19, as some studies showed increased mortality in patients who suffered from ARDS and were on ECMO support [38-40].

In summary, the underlying pathophysiology of the COVID-19 is not known and no effective treatment is available at present. In this article, I speculate the dangerous relationship between the adrenergic system, RAAS, ACE2, and SARS-CoV-2 in the COVID-19 condition may be the underlying pathological mechanism behind COVID-19. I propose the existence of a vicious Adrenergic system-RAAS-ACE2-SARS-CoV-2 (ARAS) loop in COVID-19 condition. Any drugs like norepinephrine, beta2 agonist, that increase the activity of ARAS loop, may worsen the condition in COVID-19 patients. Adrenergic blockers may inhibit this vicious ARAS loop. I propose beta-adrenergic blockers may be a potential drug option for the treatment of COVID-19.

Adrenergic system-RAAS-SARS-CoV-2 (ARAS) loop may be the underlying mechanism behind COVID-19:

It is important to study whether a sympathetic storm occurs in COVID-19. Considering all the above evidence and clinical features of pulmonary edema, pulmonary embolism, deep vein thrombosis, septic shock it looks like the COVID 19 critical illness may exhibit a sympathetic storm condition in the body and maybe the basis for all the problem occurring in COVID-19

condition. Increased catecholamine levels in the COVID-19 patients may trigger a hypothetical ARAS loop. Adrenergic system regulation of RAAS is crucial in the COVID-19 condition. Increased plasma catecholamine level will activate the adrenergic system, which in turn lead to the activation of RAAS, and increase in ACE2 as a result of this will increase the SARS-CoV-2 entry which produces complications in COVID patients, in response to the critical illness, the endogenous catecholamines will be increased and the vicious cycle goes on. I would like to call this as Adrenergic system-RAAS-ACE2-SARS-CoV-2 (ARAS) loop (Figure 1).

Critical illness conditions will increase the plasma catecholamine level [41]. It is interesting to note that adenoviral respiratory illness caused increased plasma catecholamine levels. SARS-CoV-2 infection may also lead to increased catecholamine levels [42]. I speculate that in the severely affected COVID-19 patients with complications like ARDS, Septic shock, it is likely that endogenous catecholamine levels may be high and it may trigger the ARAS loop. Apart from the increased endogenous catecholamine level in these complicated COVID-19 patients, giving exogenous catecholamines like beta-agonists in the nebulizer solution for treating dyspnea or norepinephrine given intravenously for the patients having septic shock, may further increase the catecholamine level, and hyperactivate the vicious ARAS loop and worsen the condition. I speculate that any drug that augments the activation of the ARAS loop will worsen the COVID-19 condition and increase the mortality. The potential dangers of using norepinephrine, beta2-agonists, and ARBs in COVID-19 are discussed in a later section.

ARB problem and RAAS inhibitors: It is known that the Renin-Angiotensin-Aldosterone System (RAAS) plays a crucial role in the regulation of blood pressure, sodium level, extracellular fluid volume, etc. RAAS system has two opposing arms, the classic Renin-Angiotensin I- Angiotensin-converting-enzyme (ACE)–Angiotensin II(ATII)-Aldosterone and Renin-ATII-Angiotensin-converting-enzyme2(ACE2)-Angiotensin-(1-7)-Mas-receptor (MasR). Along with the classic pathway which produces effects like vasoconstriction and

inflammation, one more pathway with opposing actions to classic pathway exist which produces effects like vasorelaxation and it is anti-inflammatory. Unlike the classic RAAS pathway which uses ACE, the vasorelaxation arm uses ACE2 [43]. Recently concerns were raised regarding the use of angiotensin receptor blocker (ARB) drugs as it may increase the ACE2 expression, which in turn may increase the SARS-CoV-2 entry [44,45]. It has been suggested that other antihypertensive drugs like beta-adrenergic blockers and calcium channel blockers can be used in COVID-19 cases with hypertension comorbidity instead of ARBs [44]. On the contrary, many opined that without sufficient evidence there is no need to change the drugs like ARBs in the COVID-19 patients who are already taking it, and many cardiovascular societies had issued a notice regarding this issue [46,47]. Withdrawal of angiotensin receptor-blockers (ARBs) and angiotensin-converting-enzyme inhibitors (ACEIs) in COVID-19 patients with hypertension comorbidity was suggested not to be done without sufficient evidence [48]. I suggest that beta-adrenergic blockers decrease the renin level by its inhibitory action on the sympathetic system and decrease ATII. Unlike ARBs and ACEIs, beta-adrenergic blockers have an advantage by its action on upstream protein renin, which may decrease the activity of both arms. Thereby, beta-adrenergic blockers not only decrease ATII levels but also reduce the ACE2 receptors, which will be useful in regulating the blood pressure and at the same time decreases the SARS-CoV-2 cellular entry. I suggest that beta-adrenergic blockers can be considered as an alternative to ARBs in the COVID-19 patients having hypertension co-morbidity and ARBs should be avoided in COVID-19 patients. Since ARBs by blocking the angiotensin II receptor will increase the ATII level, it may trigger the ARAS loop and complicate the COVID-19 condition. It has been already shown that angiotensin II induces pulmonary edema in the animal model study [49], which supports the view that increased ATII may be detrimental in COVID-19.

Beta2-adrenergic agonist nebulizer solution problem: Clinicians used to treat dyspnoeic patients routinely with beta2-adrenergic agonists like salbutamol, anticholinergics, and corticosteroids either alone or in combinations. Beta2-adrenergic agonists are one of the primary drugs used in nebulizers, considering its role in sympathetic activation and renin release, beta2-adrenergic agonists may increase ACE2 expression in the alveolar epithelial cells which may help the SARS-CoV-2 and worsen the condition. It has been already suggested that beta-2 agonists should be avoided in ARDS, as it worsens the condition [50]. Irrespective of it, still beta2-adrenergic agonists are given by many for ARDS. As mentioned earlier, beta2-adrenergic agonists like salbutamol used in the nebulizer solutions, increased the plasma catecholamine level, and produced hypercoagulable state [33-35]. Considering the vicious ARAS loop, I suggest beta2-adrenergic agonists should be avoided in the nebulizer solutions, as it will worsen the clinical condition in COVID-19 patients and may produce complications like pulmonary embolism.

Norepinephrine problem in COVID-19: Adrenergic system hyperactivation occurs in critical conditions, which increases the catecholamine level. Critically ill COVID-19 patients may also have sympathetic storm condition i.e. increased catecholamine level in the body. So far whether increased catecholamine level occurs in COVID-19 patients is not known, but since any critical condition may increase the adrenergic system, it is likely that in severe COVID-19 patients catecholamine levels may increase. Increased catecholamine levels will lead to increase renin release, which increases the activity of its both arm including an increase in ACE2 expression, which may help the SARS-Cov-2 cellular entry and worsen the condition. Some of the severe COVID-19 patients may end up in septic shock, where the mean arterial pressure (MAP) will be lower than 65mmHg irrespective of fluid resuscitation, and plasma lactate will be more than 2mM/L. The primary drug used in septic shock is Norepinephrine [21]. As mentioned earlier, in the critical COVID-19 patients, endogenous catecholamine levels may be increased, and

giving the norepinephrine exogenously will further worsen the condition. Many had raised concerns about the use of norepinephrine in septic shock, as norepinephrine may worsen the condition and increase the mortality rate in septic shock [51-54]. Not only increased catecholamine but increased RAAS activation also is detrimental in sepsis patients, it has been shown that increased AT II, plasma renin activity worsens the sepsis condition [55]. Recent studies showed that beta-adrenergic blockers may be beneficial in septic shock [56,57]. I suggest that Norepinephrine should not be used in the treatment of COVID-19 patients having septic shock, instead beta-adrenergic blockers should be used in the treatment of septic shock in COVID-19 patients.

Adrenergic hyperactivation may produce pulmonary edema: As mentioned earlier, increased catecholamine levels may trigger the ARAS loop and worsen the COVID-19. It is well known that increased catecholamine induces pulmonary edema. Studies had shown that both alpha- and beta-adrenergic receptors may be involved in this. Both alpha1 and beta-adrenergic blockers have shown to relieve pulmonary edema in many animal models studies. Due to adrenergic receptor involvement in the etiology of pulmonary edema, it has been suggested that beta-2 agonists should not be used routinely in the mechanically ventilated patients [58]. As mentioned earlier, increased catecholamine levels may induce pulmonary edema and it can be prevented by adrenergic receptor blockers. I suggest beta-adrenergic blockers like Propranolol or alpha1 adrenergic blockers like Prazosin should be used to reduce or prevent pulmonary edema in COVID-19 patients.

Beta-adrenergic blockers may reduce or prevent pulmonary embolism in COVID-19 patients: As mentioned earlier, severely affected COVID-19 patients developed pulmonary embolism in COVID-19 and d-dimer level were shown to be high [17-19]. This indicates that the hypercoagulation state occurs in COVID-19. As mentioned earlier, adrenergic hyperactivation is associated with the hypercoagulation state. It is known that beta-blockers

reduce the coagulation parameters and prevent complications like venous thrombosis in both animal models and patients [59,60]. I suggest that beta-adrenergic blockers should be used in COVID-19 patients to prevent or reduce the hypercoagulation state complications like pulmonary embolism complication and deep vein thrombosis.

Beta-adrenergic blockers treatment in COVID-19 (Figure 2): Considering the above details, beta-adrenergic blockers like Propranolol should be used in COVID-19 patients. In this article, I had focused mainly on the beta-adrenergic blocker's role in COVID-19. Which subtype of beta-adrenergic receptor blocker plays a crucial role in COVID-19 remains to be seen in the future. It is also possible that alpha1 adrenergic blockers like Prazosin or combination of beta- and alpha-adrenergic blockers may also be beneficial in COVID-19. I had discussed the advantages of using beta-adrenergic blockers in COVID-19 in the following section.

Twelve reasons that indicate beta-adrenergic blockers may be a good candidate for the treatment of COVID-19 patients:

1. Beta-adrenergic blockers block the entry of SARS-COV-2 via the ACE2 receptor as well as CD147.

Beta-blockers by its negative regulation on the juxtaglomerular cells in the kidney reduce the activity of both arms of the RAAS pathway, thereby it may decrease the ACE2 level. As ACE2 is the receptor for SARS-CoV-2 cellular entry, beta-adrenergic blockers may decrease the SARS-CoV-2 cellular entry. It is already known that beta-adrenergic blocker propranolol down-regulates CD147 [61]. Therefore, beta-adrenergic blockers treatment in COVID-19 will decrease the SARS-CoV-2 cellular entry by downregulation of both ACE2 and CD147.

2. It is known that activation of beta-adrenergic receptors plays a role in the IL-6 secretion [62]. It is also known that beta-adrenergic blockers decrease IL-6 in cardiac disorder patients [63,64]. I suggest beta-adrenergic blockers will reduce the IL-6 level in COVID-19 patients and reduce the inflammatory complications associated with it.
3. Beta-adrenergic blockers have been shown to decrease a variety of proinflammatory cytokines expression including IL-1 β , IL-6, TNF α , IFN γ [63-67]. The use of beta-adrenergic blockers in COVID-19 patients may reduce the expression of the proinflammatory cytokines and the inflammation associated with it.
4. Beta-adrenergic blockers may be beneficial in ARDS and respiratory failure condition: It is known that beta-adrenergic agonists counterintuitively worsen the ARDS condition and beta-adrenergic blockers have been shown to reduce the mortality in ARDS [50]. Noveanu et al had showed based on the BASEL II ICU study that beta-adrenergic blockers reduce mortality in respiratory failure cases [68]. A recent study has shown that beta-adrenergic blockers reduce mortality in ARDS [69].
5. Recent trends suggest that beta-adrenergic blockers are beneficial in Septic shock and reduce the mortality rate [56,57]. As mentioned earlier, many had raised concerns about the use of norepinephrine in septic shock [51-54]. I suggest that norepinephrine use for treating septic shock in the COVID-19 condition should be avoided. And beta-adrenergic blockers should be used for treating septic shock in COVID-19 patients.
6. Beta-adrenergic blockers may reduce the pulmonary edema: As mentioned earlier, increased catecholamine levels resulted in pulmonary edema in the animal model studies. And both alpha1-adrenergic blockers and beta-adrenergic blockers are shown to reduce pulmonary edema and improve the condition [58]. I suggest that beta-adrenergic blockers may prevent or reduce the pulmonary edema complication in

COVID-19 condition and alpha-1 adrenergic blockers like Prazosin may also be beneficial in reducing pulmonary edema in COVID-19 patients.

7. I suggest that beta-adrenergic blockers may reduce the hypercoagulation state and decrease the deep vein thrombosis and pulmonary embolism complications in COVID-19 patients. It is known that beta-adrenergic blockers reduce the coagulation parameters supports the above claim [59,60].
8. Beta-adrenergic blockers have been shown to improve the oxygenation level in the patients who were on ECMO [70]. This suggests the possibility that the use of beta-adrenergic blockers in COVID-19 patients who are on ECMO may improve the oxygenation level. It has been shown that beta-adrenergic blockers improved the oxygenation level in the hypoxic condition induced in an animal study [71]. It is known that beta-adrenergic blockers improve the P_aO_2 level in critically ill patients and increase the oxygenation [72,73]. Considering the above evidence, I suggest that beta-adrenergic blockers may improve the oxygenation level and reduce the hypoxemia in COVID-19 patients.
9. Beta-adrenergic blockers may reduce the mucus hypersecretion in COVID-19: Increased mucus aggregation has been noticed in the distal airways and alveoli in the postmortem study of COVID-19 patients [12]. It is known that IL-6 plays a key role in the activation of MUC5AC and MUC5B gene expression and increases the mucus secretion [13]. It has been suggested that Tocilizumab by the inhibition of IL-6 R may help decrease the mucus secretion in COVID-19 [14]. As mentioned earlier, beta-adrenergic blockers may decrease IL-6. It is interesting to note that chronic propranolol administration has been shown to decrease MUC5AC expression and mucus secretion [74]. I suggest that the use of beta-adrenergic blockers like propranolol may decrease the mucus secretion and MUC5AC expression in COVID-19 cases.

10. Wu et al using the computational method had shown some potential molecules that could be used for the treatment in COVID-19. In that article, beta-adrenergic blocker Oxprenolol has been suggested to potentially inhibit SARS-CoV-2 papain-like protease (PLpro) and Carvedilol has been suggested to potentially inhibit SARS-CoV-2 3-chymotrypsin like protease [75]. Using a network-based approach Zhou et al had shown 16 potential drugs that have the potential to be used in the COVID-19 treatment, and one of the drugs mentioned was beta-adrenergic blocker Carvedilol [25]. The above two recent computational studies also support the hypothesis that beta-adrenergic blockers may be useful in the treatment of COVID-19 patients.
11. Beta-adrenergic blockers inhibit NLRP3 inflammasome: As mentioned earlier NLRP3 has been suggested to be activated in COVID-19 and few clinical trials like using Colchicine to inhibit NLRP3 are already registered [27]. It is interesting to note that beta-adrenergic blocker carvedilol has been shown to inhibit NLRP3 inflammasome [77]. Thus, one of the many uses of beta-adrenergic blockers in the COVID-19 condition may be the inhibition of NLRP3 inflammasome and thereby reducing the inflammation by decreasing the NLRP3 downstream effectors IL-1 and IL-8.
12. Traditionally clinicians are hesitant in using beta-blockers in patients with respiratory illness. But recent studies are changing this viewpoint, for example, beta-adrenergic blockers has been shown beneficial effects in chronic obstructive pulmonary disease (COPD) patients [78]. I suggest that clinicians should not hesitate to use beta-adrenergic blockers in COVID-19 patients having respiratory dysfunction.

Considering the above evidence beta-adrenergic blockers like Propranolol may be a good candidate for treating COVID-19 patients. As mentioned earlier which subtype of beta-adrenergic receptor blocker plays a crucial role in COVID-19 needs to be clarified in the

future. It is also possible that alpha1-adrenergic blockers like Prazosin or combination of beta and alpha-adrenergic blockers may also be beneficial in COVID-19.

Evaluation of the hypothesis:

1. a. To check the presence of the hypothetical ARAS loop, I suggest measuring the following in COVID-19 patients - plasma catecholamine levels especially plasma norepinephrine levels, AT II, ACE, ACE2, Renin levels. These parameters need to be measured in all the COVID-19 patients along with the viral load measurement. If the above said ARAS loop molecules plasma concentration correlates with the viral load in the COVID-19, it will validate the existence of the ARAS loop in COVID-19.
- b. The plasma catecholamine levels in COVID-19 patients have to be measured in all the COVID-19 patients which will clarify whether a sympathetic storm occurs in this condition.
2. I suggest conducting retrospective and prospective clinical trials to clarify the following questions,
 - i. Whether beta-adrenergic blockers reduce the morbidity and mortality in COVID-19 patients?
 - ii. Whether beta-adrenergic agonists in nebulizer solutions increase the morbidity and mortality in COVID-19 patients?
 - iii. Whether Norepinephrine given for COVID-19 patients suffering from septic shock increases mortality?
 - iv. Whether the use of ARBs in COVID-19 patients having hypertension comorbidity increase morbidity and mortality?

Conclusion:

Adrenergic system relation to RAAS and SARS-CoV-2 plays a crucial role in COVID-19. A hypothetical ARAS loop has been proposed, hyperactivation of the ARAS loop may be the pathophysiological mechanism behind COVID-19. Beta-adrenergic blockers may produce beneficial effects in the COVID-19 patients in many ways ranging from decreasing the SARS-CoV-2 virus entry, inhibiting NLRP3 inflammasome, reduction of IL-6 to decreasing the complications like pulmonary embolism, ARDS, Septic shock. It is important to do a quick retrospective clinical trials on the COVID-19 patients, who were already on beta-adrenergic blocker for their previous cardiovascular illness and its effect on mortality. Similarly, it is also important to do a retrospective study on COVID19 patients, who were treated with beta-adrenergic agonists in nebulizer solutions and its effect on mortality. Both these proposed retrospective studies will test the validity of the hypothesis mentioned in this article. If the retrospective studies result come out as expected, it will help millions of people all over the world, as beta-adrenergic blockers are well-known drugs, used in the patients for a long time with good safety profile, it is a low cost, can be used orally and intravenously, easily available in all parts of the world. It is imperative to do the proposed retrospective and prospective clinical trial studies as soon as possible, which will clarify the role of beta-adrenergic blockers and beta-adrenergic agonists in COVID-19 patients in the near future.

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Figure 1. Adrenergic system-RAAS-ACE2-SARS-CoV-2 (ARAS) vicious loop

Figure Legends

Figure 1. Adrenergic system-RAAS-ACE2-SARS-CoV-2 (ARAS) loop: A hypothetical vicious loop consist of Adrenergic system-RAAS-ACE2-SARS-CoV-2 (ARAS) is predicted in COVID-19 condition. Severely affected COVID-19 patients may have sympathetic storm, increased endogenous catecholamine levels may hyperactivate this loop, increased ACE2 as a result of this will increase the SARS-CoV-2 entry and worsen the condition. Administration of catecholamines exogenously by the use of beta2-adrenergic agonists in the nebulizer solution or by intravenous administration of Norepinephrine for treating the septic shock condition in COVID-19 patients will hyperactivate the ARAS loop and worsen the condition. Beta-adrenergic blockers will inhibit this ARAS loop and may produce beneficial effects in the COVID-19 patients by preventing or reducing the complications like pulmonary embolism, ARDS, Septic shock.

Figure 2: Beta-adrenergic blockers effect on RAAS and COVID-19: A) Beta-adrenergic blockers by its inhibitory action on the sympathetic system decrease the renin release by Juxtaglomerular (JG) cells in the Kidney. A decrease in renin may reduce the activity in both arms and may decrease ACE2 receptors. B) Beta-adrenergic blockers decrease ACE2 receptors and this will affect the SARS-CoV-2 cellular entry and thereby reduce the viral infectivity. Beta-adrenergic blockers reduce the mortality in ARDS, septic shock and respiratory failure. Beta-adrenergic blocker may inhibit NLRP3 inflammasome, reduce IL-6 level, decrease the mucus secretion, reduce the pulmonary edema, DVT, pulmonary embolism, and refractory hypoxemia complications.