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The role of renin-angiotensin system activated phagocytes in the SARS-CoV-2 coronavirus infection

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ABSTRACT

Objective: Management of the pandemic caused by the novel coronavirus SARS-CoV-2 challenges both scientists and physicians to rapidly develop, and urgently assess, effective diagnostic tests and therapeutic interventions. The initial presentation of the disease in symptomatic patients is invariably respiratory, with dry cough being the main symptom, but an increasing number of reports reveal multiple-organ involvement. The aim of this review is to summarize the potential role of the renin-angiotensin system activated phagocytes in the pathogenesis of COVID-19 disease.

Methods: Data for this review were identified by searches of PubMed and references from relevant articles using the search terms "SARS," "COVID-19," "renin-angiotensin-system," "phagocyte," "reactive free radical," "antioxidant," "ARDS," "thrombosis," "myocardial," "ischaemia," "reperfusion," "microvascular," and "ACE2." Abstracts and reports from meetings were not included in this work. Only articles published in English between 1976 and 2020 were reviewed.

Results: The cellular target of SARS viruses is the angiotensin-converting enzyme 2, a critical regulating protein in the renin-angiotensin system. The elimination of this enzyme by the viral spike protein results in excessive activation of phagocytes, migration into the tissues via the high endothelial venules, and an oxidative burst. In the case of an over-stimulated host immune response, not only devastating respiratory symptoms but even systemic or multiorgan involvement may be observed.

Conclusions: Early-stage medical interventions may assist in returning the exaggerated immune response to a normal range; however, some therapeutic delay might result in excessive tissue damages, occasionally mimicking a systemic disease with a detrimental outcome. (J Vasc Surg 2021;73:1889-97.)

Keywords: Renin-angiotensin system; SARS-CoV-2; Activated phagocytes; Microvascular disease; Free radical

The novel coronavirus (SARS-CoV-2) emerging from the city of Wuhan in late Autumn 2019 has dominated both global health and economic management throughout the year 2020. Although the majority of cases are asymptomatic, a relatively smaller proportion of patients develop severe disease characterized by pneumonitis,[1] such that the overall mortality rate of known symptomatic cases measures 6.1% at the end of July 2020.[2] The mortality rate for patients who do require mechanical ventilation is consistently reported as over 50% in some series, and the recovery is extended.[3] The extent of recovery is not entirely known yet, albeit some recent data demonstrate, especially in patients with concomitant viral myocarditis, that complete restitution of health is not always achievable.[4] With some reports suggesting extrapulmonary, specific organ involvement such as renal, hepatic, and central nervous system manifestations, indeed when considered with a prothrombotic tendency, suggests a microvascular origin of these conditions. The same pathophysiologic background may explain the Kawasaki-like disease in some SARS-CoV-2 infected children. Our review aims to analyze a possible pathophysiologic route on which the coronavirus disease 19 (COVID-19) may interfere with the human body's normal function and regulatory pathways, resulting in a maladaptive systemic response, and leading to multiorgan dysfunction.

SEARCH STRATEGY AND SELECTION CRITERIA

Data for this review were identified by searches of PubMed and references from relevant articles using the

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search terms "SARS," "COVID-19," "renin-angiotensin-system," "phagocyte," "reactive free radical," "antioxidant," "ARDS," "thrombosis," "myocardial," "ischaemia," "reperfusion," "microvascular," and "ACE2." Abstracts and reports from meetings were not included in this work. Only articles published in English between 1976 and 2020 were reviewed.

THE ROLE OF THE ANGIOTENSIN-CONVERTING ENZYME 2 IN THE COVID-19 PATHOMECHANISM

The angiotensin-converting enzyme 2 (ACE2) was discovered in 2000 as a transmembrane peptidase, having the main role to inhibit the renin-angiotensin system (RAS). In addition, it facilitates intestinal absorption of certain amino acids and also acts as a receptor for the severe acute respiratory syndrome (SARS) virus, a coronavirus that has caused an epidemic mainly in South China and Canada in 2003.[5] The ACE2 protein is represented in several organs including the heart, kidneys, intestinal epithelium, and central nervous system, and has a high density on the microvascular endothelium. There is a significant ACE2 representation measured on the surface of type I and II alveolar pneumocytes and also expressed on the surface of alveolar macrophages and lymphocytes.[6]

The RAS inhibitory action of ACE2 is a catalytic function splitting angiotensin I into angiotensin (1-9). Furthermore, ACE2 converts angiotensin II (ATII) into angiotensin (1-7), and angiotensin binds the MAS-related G protein-coupled receptor (MAS receptor) causing vasodilation and exerting an anti-inflammatory effect.[7-10] The coronaviruses, including SARS and SARS-CoV-2, bind the ACE2 enzyme on a different location than its catalytic spot with their spike protein (S-protein), initiating virus internalization into the ACE2-carrying target cell.[7,8,11]

The pulmonary RAS pathway, including the antagonizing effect of ACE2, has been extensively investigated in both experimental models and clinical investigations, in the context of acute respiratory distress syndrome (ARDS). The potential role of ACE2 in the pathogenesis of severe lung injury has been demonstrated in experiments with ACE2 knockout mice, having initial healthy lung structure and function. In this investigation, the same dosage of toxin on the lungs of knockout mice resulted in more severe histological and functional changes compared with those seen in wild-type control specimens. The wild-type mice after infection with SARS virus, or treated just with its S-protein, behaved similar to the ACE2 knockout mice; and an increase in serum ATII levels was detected. Furthermore, the administration of an ATII type 1 (AT1) receptor blocker successfully limited the extent of pulmonary damage in the ACE2 depleted cohort.[7] In another animal experiment, following exposure to a lipopolysaccharide toxin, administration of recombinant ACE2 protein significantly improved the partial oxygen pressure with the same ventilation settings, and this was associated with a reduction the extent of lung damage.[7,12] The preventive effect of ACE2 against ARDS has been demonstrated in infants suffering from meconium aspiration, where the lung aspirates revealed excessive ACE2 breakdown by proteases in cases developing ARDS. This effect was shown to be reversed with the aid of protease inhibitors in experimental settings.[13] In SARS and middle east respiratory syndrome, mortality results not from the direct cytopathic effect of the coronavirus load, but from the emerging ARDS, in a framework of excessive and maladaptive immune response orchestrated by the host immune system,[14,15] coming from an imbalance in the RAS function.

THE IMBALANCE IN THE RAS RESULTING FROM ACE2 LOSS AND THE "CYTOKINE STORM"

Considering the above data from the medical literature, the SARS-CoV-2 infection downregulates the ACE2 enzyme, leading to an imbalance in the inhibitory function of the ACE2 on the RAS cascade. As a result of this shift in the RAS balance (angiotensin I-angiotensin 1-7), the increased ATII level activates a pathologic inflammatory response via the AT1 receptor (Fig 1). The AT1 receptor initiates the nuclear factor kappa-light-chain-enhancer of activated B-cell (NFkB) signaling pathway, leading to an interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-α surge activating the circulating neutrophil (PMN) cells and monocytes/macrophages (MPH). This activation results in adhesion and tissue migration of the phagocytes by promoting the expression of intercellular adhesion molecule, vascular adhesion molecule-1, and monocyte chemoattractant protein-1.[16-20] The vascular marginalization, endothelial rolling, diapedesis, and tissue migration of phagocytes are associated with an oxidative burst, an excessive reactive oxygen species (ROS) production.

Furthermore, after internalization of a coronavirus, the freshly synthesized viral proteins (eg, ORF3b, ORF6, nsp1, PLP) heavily influence the innate immunity on numerous target points. In SARS infection, delayed production of the critical antiviral IFNs was observed in human cell cultures and murine models, whereas increased production of cytokines (IL-6, IL-8) produced by NFkB signaling has been detected. The latter may play an essential role in the pathogenesis of ARDS,[21-23] and it has to be noted that the AT1 receptor effect is mostly related to the NFkB signaling pathway.[17]

NEUTROPHIL GRANULOCYTE AND MACROPHAGE INVOLVEMENT IN THE TISSUE DAMAGE

Emerging data from the current COVID-19 pandemic suggest that mainly the lower respiratory tract and occasionally the gastrointestinal passage represent the gate of entry for the coronavirus, but it may affect other organs either directly, or secondarily, including the heart, brain, and kidneys. This phenomenon can be understood using the above-described RAS-ACE2-proinflammatory pathway.

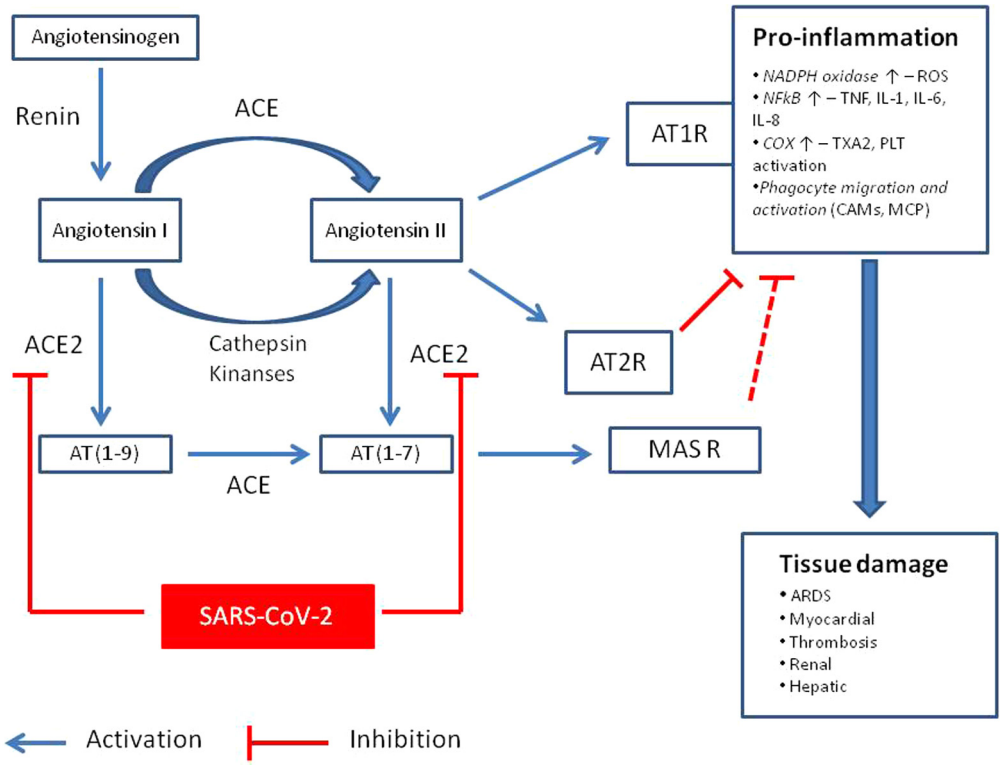

Fig 1. The interaction of the severe acute respiratory syndrome-coronavirus-2 (*SARS-CoV-2*) virus with the renin-angiotensin system and phagocyte activation cascade. *ACE*, Angiotensin-converting enzyme; *ARDS*, acute respiratory distress syndrome; *AT(1-7)*, angiotensin (1-7); *AT(1-9)*, angiotensin (1-9); *AT1R*, angiotensin II receptor type 1; *AT2R*, angiotensin II receptor type 2; *CAMs*, cellular adhesion molecules; *COX*, cyclooxygenase; *IL*, interleukin; *MAS R*, MAS-related G protein-coupled receptor; *MCP*, monocyte chemoattractant protein; *NADPH*, nicotinamide adenine dinucleotide phosphate; *NFkB*, nuclear factor kappa-light-chain-enhancer of activated B-cell signaling pathway; *PLT*, platelet; *ROS*, reactive oxygen species; *TNF*, tumor necrosis factor; *TXA2*, thromboxane A2.

The circulating PMNs defend the body against invasive microbes and foreign materials by their toxic defense substances, especially reinforced with the ROS.[24] These defensive mechanisms have a double-edged sword characteristic; hence a disproportional response to a noxa, oxidative, or enzymatic injury of the own tissues may be the result.[25] After their release from the bone marrow, the PMNs travel to the postcapillary high endothelial venules (HEV) and on reaching the intercellular junctions start their diapedesis. They migrate within the tissues during a 5- to 6-day life cycle and aim to eliminate all foreign particles with the aid of degranulation.[26] If activated by any trigger mechanisms, including the AT1 pathway, the nicotinamide-adenine-dinucleotide-phosphate oxidase initiates the oxidative burst by producing extremely reactive superoxide radical from molecular oxygen (Fig 2).[27] The free radicals damage lipid membranes and the DNA, leading to activation of poly(ADP) ribose, with the end effect of depleting intracellular adenosine triphosphate storages. Because of the free radical effect, the intracellular ionized calcium and iron concentration increases, leading to destruction of multiple biomolecules. These are "hit-and-run" type damages; once the tissues are significantly affected, the eventual therapeutic efforts are less successful.

Free radicals cause changes in the endothelial cellular phospholipid metabolism, leading to increased production of lipid mediators, namely the platelet-activating factor (PAF) and leukotriene B4, both facilitating further chemotaxis of phagocytes. Furthermore, intracellular xanthine oxidase produces additional superoxide anions from xanthine; the superoxide radical activates phospholipase A2, leading to a significant amendment in arachidonic acid metabolism with a substantial effect on prostaglandin and Leukotriene production. The hypochlorite anion gets into a reaction with the free amino terminals of proteins and builds up a protein-amino-hypochlorite. The protein-amino-hypochlorite inactivates the nitrogen monoxide (NO), produced from L-arginine. NO is a potent PMN inhibitor, and the hypochlorite additionally activates the proteases secreted from the azurophil granule of the PMNs.[27] Therefore, a drop in NO levels may lead to microvascular vasoconstriction, local stasis, and a vicious circle in PMN activation. Local thrombocyte activation by PAF and stasis may explain

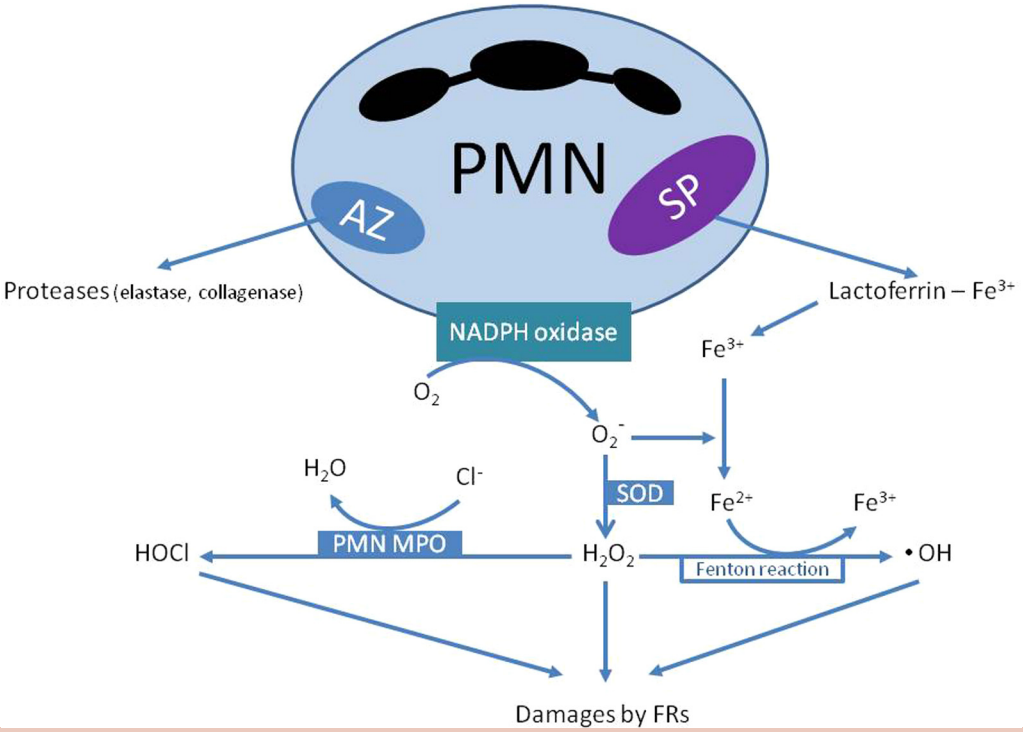

Fig 2. Free radical cascade after neutrophil granulocyte (*PMN*) activation. *•OH*, Hydroxyl radical; *AZ*, azurophil granules; *Cl^-*, chlorite; *Fe^{2+}*, ferrous ion; *Fe^{3+}*, ferric ion; *FR*, free radical; *H_2O*, water molecule; *H_2O_2*, hydrogen peroxide; *HOCl*, hypochlorite ion; *MPO*, myeloperoxidase; *NADPH*, nicotinamide adenine dinucleotide phosphate; *O_2^-*, oxygen radical; *O_2*, oxygen molecule; *SOD*, superoxide dismutase; *SP*, specific granules.

microthrombotic tendencies in coronavirus infections. The catecholamine and histamine receptors of the phagocytes reveal an additional neuroendocrine effect pathway on this system. In contrast, the glucocorticoids have a significant suppressive effect on both the phagocytosis and the concomitant destructive biosynthetic processes.[27]

Neutrophil extracellular traps (NETs) consist of extracellular fibers, mainly composed of PMN DNA, which bind pathogens, primarily bacteria, and yeasts.[28] NETs eliminate germs with antimicrobial proteins, for example, cathepsin, elastase, and histones; maintain a high local concentration of antimicrobial elements; and destroy microbes extracellularly independent of phagocyte uptake. NETs also serve as a physical barrier that prevents further spread of the pathogens.[29] NETs facilitate immune-mediated fibrin formation and microvascular clotting by various mechanisms including recruitment and activation of platelets; therefore, they probably contribute to several facets of COVID-19.[30]

THE ANTIOXIDANT SYSTEM

The tissue-related antioxidants defend against adverse effects of free radicals. The primary antioxidants mitigate the production of derived free radicals from initial radicals by modification into less harmful molecules. This group of antioxidants consists of superoxide dismutase, the enzyme breaking down the superoxide radical into hydrogen peroxide; the glutathione peroxidase amending the hydrogen peroxide and lipid peroxides to harmless substances; and the metal-binding proteins, such as ferritin and coeruloplasmin, that limit the hydroxyl free radical production by eliminating the ferro ion availability.

The secondary antioxidants, for example, α-tocopherol, β-carotin, uric acid, bilirubin, and albumin, entrap free radicals to hinder chain reactions, and the tertiary line of antioxidants repair the biomolecules damaged by free radicals, that is, DNA repair enzymes, methionine-sulfoxide reductase, and so on.[27]

THE ROLE OF HEV IN THE IMMUNE CASCADE

The site for phagocyte extravasation is the postcapillary HEV. The distribution of HEV in time and location is dynamic, depending on the place of immune system activation, concomitant inflammatory response, and this process is functionally regulated and reversible. The endothelium on HEV expresses adhesion molecules to coordinate the leukocyte homing; the adhesion molecules are regulated by soluble factors, mainly cytokines IL-1, INFγ, and tumor necrosis factor-α.[26]

The HEV activation is further facilitated by the local vascular smooth muscle cell production of NO, IL-1, and IL-6; the expression of P-selectin and PAF increases on

the endothelial surface within minutes. After the cellular bond with the PMNs, the endothelium produces IL-8 and expresses E-selectin after several hours or days.[31,32] The experimental blockage of selectins by a polysaccharide has reduced the myocardial reperfusion injury in an animal model, well demonstrating the destructive nature of immune cell overreaction on the affected organ tissue.[33]

The P-selectin molecules are not available on "resting" endothelium, but highly expressed in diseased organs, facilitating the homing and migration of phagocytes.[31] The activated granulocytes can damage the endothelial surface, leading to initiation of the coagulation cascade.[34-37] The free radicals are known to have a prothrombotic effect, facilitating platelet aggregation by inhibiting antithrombin III[38] and modifying the prostacyclin synthase effect.[39] Thrombin is a potent P-selectin activator, so a vicious circle of phagocyte attraction, endothelial damages, local coagulation, and facilitated coagulation by PAF on the HEV endothelial surface[33,40,41] may explain the microthrombotic tendencies observed in COVID-19-affected organs in severe infection.

FOCUS ON ESTABLISHED ISCHEMIC HEART DISEASE IN CORONAVIRUS INFECTION

The role of the phagocyte system and free radical load in ischemic heart disease, especially reperfusion tissue injury and arrhythmias, is a well-researched field. The effect of SARS-CoV-2 infection on the heart is not completely established yet, but there are signs that the coronavirus may also cause myocarditis and might interfere with pre-existing coronary disease.

Increased expression of P-selectin was detected in atherectomy specimens from patients with unstable angina, mainly located on the endothelial surfaces. The pathogenetic importance of increased cellular activity is also reinforced by the expression of cellular adhesion molecules on circulating phagocytes, and even the amount of soluble P-selectin is markedly higher in unstable angina.[33] In blood samples obtained from the coronary sinus in patients with unstable angina, an increased level of MAC-1 adhesion molecule was registered on phagocytes. Further studies have demonstrated in histological samples from reperfused ischemic myocardium in a canine model that CD64-positive monocytes are present in the first hour of reperfusion in the HEV and perivascular connective tissue. The extracellular fluid extracted from the canine heart revealed increased phagocyte content in the first 4 hours after successful reperfusion. Initially, the PMN proportion was higher,[42] which was changed to MPH dominance at the fourth hour. The initial chemotactic activity was due to C5a, and then shifted to TGFβ1, which was regulated by the monocyte chemoattractant protein.[43] These mechanisms are essential in the repair of the ischemic damage, although in case of overshoot, they are likely to result in further myocardial damage. In an experimental model with induced intercellular adhesion molecule-1 cellular surface expression, the PMNs showed an increased adherence to isolated myocytes and higher free radical discharge.[44] Morita et al[45] demonstrated a higher MPH content on reperfused myocytes, in comparison with nonreperfused ones.

All these data suggest that so long as the reperfusion is well controlled and early after myocardial ischemia, the phagocyte system has an essential role in the damage repair. However, once the process overshoots, further damage on top of the initial ischemic insult occurs. In SARS-CoV-2 infection, especially with a high viral overload, the RAS is highly activated, overstimulating the phagocyte and free radical cascade, which has an adverse effect not only in ischemic heart disease but in other tissue types, even in the pulmonary vasculature as well.[1,33,46]

MICROVASCULAR DISEASE, THE POSSIBLE PRIMARY TARGET OF THE COVID DISEASE CASCADE

Emerging data regarding the SARS-CoV-2 infection suggest that an overreactive immune response—a "cytokine storm"—can be observed in severe or fatal outcomes.[22,23] This reinforces the role of phagocytes in the widespread tissue damage, attacking first on the microvasculature, and then extending damage in the specific tissue not only on the cells but also in the intercellular space. The initial 4 to 6 days of "honeymoon period" in a less symptomatic COVID-19 disease and sudden worsening in respiratory compromise matches with the tissue life cycle of phagocytes. As we have discussed before, the activated HEV expresses PAF on the endothelial surface, leading to platelet recruitment. The free radicals are also prothrombotic, plus the damaged tissues also trigger thrombocytes, and the local coagulation is initiated, resulting in microvascular thrombosis in the first stage of the process. The procoagulant activity has been reported by several groups found in SARS-CoV-2-infected lung tissue samples showing microthrombi[47]; recently, Lautenbach et al from the University of Pennsylvania published a remarkable phenomenon of "COVID toe" as a sign of infection in less symptomatic patients, especially in young.

The role of early anticoagulation becomes even more relevant in patients with elevated coagulation markers indicative of a process that does not resemble the pathognomic of acute disseminated intravascular coagulopathy. Reports from intensive care units (ICUs) have also highlighted the high cumulative incidence of venous thromboembolism in COVID-19 pneumonia in the absence of typical disseminated intravascular coagulopathy,[48,49] and even when patients received pharmacologic thromboprophylaxis. Klok et al[48] found a 31% incidence of thrombotic complications—acute

pulmonary embolism, deep venous thrombosis, ischemic stroke, myocardial infarction, and systemic arterial embolism—in ICU patients treated with standard doses of thromboprophylaxis, in their analysis of three academic hospitals in the Netherlands. Lodigiani et al[49] described a cumulative rate of 27.6% of arterial or venous thrombotic events within 24 hours of ICU admission in Lombardy.

Heparin has a potential role in binding to the viral spike proteins as well as downregulating IL-6, which would further support its early application in the infection. Mummery et al[50] demonstrated that in solution, heparin at low concentration provided marked protection of IL-6 from digestion with a protease specific for Lys residues. Second, their results showed that IL-6 binds to immobilized heparin.[50] Based on these data and theories, several proactive approaches using early therapeutic anticoagulation or intensified pharmacologic prophylaxis have been reported. Atallah et al[51] suggest that for patients at high risk of thromboembolism, that is, those with respiratory rate >24/min, O_2 saturation <90%, increased D-dimers, and elevated fibrinogen levels, intravenous heparin administration with an activated partial thromboplastin time target of 60 to 85 seconds and ultrasound screening for deep venous thrombosis should be considered. For low-risk, non-ICU patients having a D-dimer <3 mcg/mL, 40 mg of enoxaparin twice daily is recommended; at a level >3 mcg/mL, 1 mg/kg of enoxaparin twice daily is suggested.[51]

THE IMPACT OF AGE IN THE INFECTIOUS PROCESS

In current reports, especially from Europe, most fatalities were observed in the septa- and octogenarian population. There are several debates present regarding this phenomenon; one is undoubtedly a contributor, namely that the elderly usually have chronic comorbidities, and less physiologic reserve. On the other hand, with aging, the responsiveness of the immune system is declining; therefore, age could be a protective factor against the overreaction of the immune system. The experience from the current pandemic suggests that advanced age is associated with worse clinical outcomes, including higher mortality.[52]

Some reports have mentioned a possible role of preexisting hypertension as significant comorbidity in severe COVID-19 infections requiring intensive therapeutic care involving mechanical ventilation.[53] With increasing age, the RAS axis faces a shift in the balanced proportion of ACE and antagonizing ACE2 enzymes in favor of the former.[54] In addition, the AT1 receptor density is increased in elderly,[55] especially in patients on chronic ACE inhibitor (ACEI) treatment, as the body works against with upregulation of AT1 receptors compensating the constant lower level of ATII. This also highlights the importance of chronic antihypertensive therapy, namely the ACEI vs angiotensin II receptor blocker (ARB) debate. If the ACE enzyme is blocked, approximately 40% of ATII is still produced on an ACE-independent pathway (Fig 1) by cathepsin and different kinases.[16] Therefore, ARBs may offer some degree of protection against an increased activation of the phagocyte system by directly blocking the AT1 receptors. The ATII acting on the AT2 receptor results in an additional anti-inflammatory effect; the latter receptor is not blocked by ARBs. Because of the viral ACE2 knockout, the angiotensin (1-7) levels drop; hence the MAS receptor anti-inflammatory effect is reduced with both antihypertensives. However, the protective effect might be somewhat influenced by a variable degree of chronic upregulation of AT1 receptors in individuals on long-term antihypertensive ARB treatment.

Recent observational studies suggested no harm associated with the use of ACEI/ARB antihypertensive medications in COVID-19 patients.[52,56,57] One of these large studies revealed a potential benefit with ARBs; the hazard ratio of all-cause mortality measured 0.79 (95% confidence interval [CI]: 0.72-0.86) in comparison with 0.89 with ACEI (95% CI: 0.81-0.96) and with 1.08 on other antihypertensives (95% CI: 1.00-1.18).[52] Statin administration may be advantageous in lowering the risk of in-hospital death, an effect that has also been demonstrated in some other severe viral infections.[58] The particular benefit associated with these two classes of medications may relate to the microvascular pathophysiology associated with the disease. Statin therapy is known for its pleiotropic effects including modulation of the immune response, reducing ROS and increasing antioxidants, and downregulating signaling pathways including NFkB, which are the most relevant mechanisms in this context.[59]

The utility of ACEIs in COVID-19 is more controversial in the literature.[60] Numerous publications investigate generally ACEI/ARB medication in the pandemic; hence in generic antihypertensive therapy, they are considered to represent the same medication group. The dosage variety, especially in clinical and experimental models, influences successful outcome comparability.[61] However, their different pharmacologic targets within the RAS may have an effect on the course of disease in SARS-CoV-2 infections; therefore, randomized, prospective, controlled, large-scale studies would be required to clarify this question. Studies concentrate on ACE2 levels that are elevated in both chronic ACEI and ARB treatment, although the protective anti-inflammatory action is provided mainly by ARBs on ATR1 (Fig 1). Nevertheless, abrupt cessation of ACEI administration is discouraged for fear of precipitating adverse acute cardiovascular outcomes.[60,61] In consideration of the pathophysiologic background, controlled transitioning of ACEIs to ARBs might be the therapy of choice.

Another component of a wide variety in COVID-19 presentation may rely on the fact that there are congenital and acquired factors in the immune response of the host also influenced by the aging process.[54] The ACE and ACE2 gene polymorphism and differences in the genetic background of immunomodulation in different populations are inevitably complicating the clinical picture.[7,8,62,63]

POSSIBLE THERAPEUTIC TARGETS OF THE "CYTOKINE STORM" AND EXCESSIVE PHAGOCYTE ACTIVATION IN SARS-CoV-2 INFECTION

Early administration of an ARB, before suffering from significant shortness of breath, as long as the patient's blood pressure asymptomatically allows (≤110 mm Hg) might show beneficial outcomes in reducing the cytokine burst, particularly in those who were previously not treated with ACEIs/ARBs, hence having no AT1 receptor upregulation to reduce the efficacy of the therapy.[52,56,57]

Microthrombotic activity, especially on the capillary level, may require minimum a low-molecular-weight heparin prophylaxis even in the early stage of the disease. As the thrombotic activity results from the phagocyte activation cascade and free radical discharge,[34,35] additional acetyl-salicylic acid therapy could be beneficial, also as an antipyretic supplement.[63] At a later stage, the tissue damage results in an additional thrombotic lesion, and the delayed treatment may not show sufficient outcomes.

Even in case of initial mild respiratory symptoms, shortness of breath, steroid inhalation (eg, budesonide) might be considered to hinder the excessive activation of phagocyte cascade at the point of viral entry.[27] There are recent trials that initiated investigating the benefits of this treatment in Japan. Systemic steroid treatment should be avoided as much as possible to keep the generic host immune response at an acceptable level against the coronavirus.

Furthermore, the application of antioxidants and scavenger molecules may reduce the extent of pulmonary damages at progressive respiratory symptoms/developing ARDS. Xanthine oxidase inhibitor administration, for example, allopurinol and oxypurinol, may reduce the free radical-caused tissue damages, as it was already proven in myocardial function preservation after ischemia-reperfusion.[64,65] A scavenger, the mercaptopropionyl-glycine has a proven beneficial effect in high-risk myocardial ischemia. This molecule is a potent hydroxyl free radical scavenger, well tolerable for long-term oral application, and penetrates into the intracellular space.[66,67] The supplementary zinc therapy was proven successful in SARS infections as the ion reduces the viral protein transcription.[68]

In emerging ARDS, the bacterial superinfection is often fatal and present in a high proportion of patients.[3] Azithromycin, a macrolide antibiotic, is carried in high concentrations by phagocytes to the site of infection and has a reasonably long half-life time, usually the life cycle of the phagocyte migrating in the tissues. The tissues damaged by both coronavirus and free radicals are prone to bacterial superinfection. Still, the phagocytes are in this exact location, where the bacterial superinfection has a gate of entry. Starting azithromycin at the initial stage of respiratory complaints may hinder bacterial colonization of the virus-infected microvascular site.

Direct targeting of the "cytokine storm" on one of its triggering components, IL-6, has demonstrated promising outcomes in Brescia, Italy. In 100 consecutive patients developing ARDS, the IL-6 receptor antagonist monoclonal antibody, tocilizumab, was administered in a dosage of 8 mg/kg by two consecutive intravenous infusions 12 hours apart, and a significant improvement in the course of pneumonitis was observed, including respiratory condition stabilization, disease regression on imaging studies, an increase in lymphocyte count, and a decrease in C-reactive protein, fibrinogen, and ferritin levels.[69] Earlier administration, at the stage of starting shortness of breath, should be considered to achieve even more beneficial outcomes, as in manifested ARDS, the lungs already have suffered from a significant, partially persistent hit by the burst of the immune response.

SUMMARY

The SARS-CoV-2 virus pandemic poses a major challenge currently to our global society. Although there are emerging data about the nature of the viral infection, we do not yet have any specific treatment with proven efficacy. In this review, we have summarized a possible major pathophysiologic pathway of the novel coronavirus infection using data from the previous SARS epidemic and emerging evidence from the COVID-19 pandemic. We believe that the excessive activation of RAS, resulting in an uncontrolled response of the phagocyte system, represents the key element of the severe respiratory system damage culminating in life-threatening ARDS. Understanding the chain reaction involving the RAS and phagocyte system may assist us better in using the therapeutic timeframe in the coronavirus therapy.

AUTHOR CONTRIBUTIONS

Conception and design: LG, IR, MH, ERS, RS, ET
Analysis and interpretation: LG, IR, BA, WA, FA, ET
Data collection: LG, IR, MH, ERS, BA, WA, FA, RS, GB
Writing the article: LG, IR, MH, ERS, BA, WA, ET
Critical revision of the article: LG, MH, ERS, BA, WA, FA, RS, GB, ET
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