Current Hypertension Reports (2021) 23: 12
https://doi.org/10.1007/s11906-021-01130-z

INFLAMMATION AND CARDIOVASCULAR DISEASES (A KIRABO, SECTION EDITOR)

To Curb the Progression of Fatal COVID-19 Course—Dream or Reality

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Accepted: 26 January 2021 / Published online: 27 February 2021

Abstract

Purpose of Review To analyze the impact of sodium retention states on the course of COVID-19 and propose possible interventions to curb disease progression.

Recent Findings Numerous data confirm a positive association of non-communicable diseases, aging, and other sodium-retaining states, including iatrogenic ones, with more severe sometimes fatal clinical course of COVID-19. Reasons for this effect could include increased angiotensin signaling via the AT1R receptor. The endothelial glycocalyx also plays an important role in infection, leading to a vicious cycle of inflammation and tissue sodium retention when damaged. RAS inhibitors may help restore glycocalyx function and prevent severe organ damage. Anticoagulants, especially heparin, may also have therapeutic applications due to antithrombotic, anti-inflammatory, glycocalyx-repairing, and antialdosteronic properties. The ambiguous influence of some diuretics on sodium balance was also discussed.

Summary Abnormal sodium storage and increased angiotensin-converting enzyme activity are related to the severity of COVID-19. Inducing sodium removal and reducing intake might improve outcomes.

Keywords ACEI/ARB · Glycocalyx · Heparin · Spironolactone · COVID-19

Introduction

Zhou et al. [1] showed that hypertension, diabetes, coronary artery disease (CAD), and advanced age significantly worsen the prognosis in COVID-19. Chronic heart failure, chronic kidney disease, and obesity are other risk factors for severity of infection [2]. The common denominator of all these clinical entities and of aging is abnormal sodium retention [3]. Kirabo [4] recently demonstrated that clinical conditions associated with excessive sodium accumulation lead to tissue inflammation with local production of angiotensin II (ANG II). There are also experimental and clinical data supporting hypothesis that sterile sodium-induced inflammation might lead to glycocalyx dysfunction and locally increased ANG II and aldosterone production. Sodium-induced inflammation changes the balance between pressor arm comprising angiotensin-converting enzyme (ACE) and depressor arm with decreased activity of angiotensin-converting enzyme 2 (ACE2) that leads to persistent neutrophil extracellular trap formation (NETosis) via activation of factor XII (fXII) with final microvascular damage [5]. The abnormal sodium retention is due to excessive sodium intake and hyperaldosteronism, but the impact of drugs on sodium accumulation has not been fully appreciated yet. Recently, PATHWAY-2 studies have shown that recent guidelines advised treatment comprising three drug therapies in a large population of resistant hypertension lead to significant distributional differences in water and sodium retention [6]. Spironolactone turned out to be an effective antihypertensive drug, especially in the low-renin hyperaldosteronism subpopulation. Its administration reduced pulmonary congestion, body weight, stroke volume, and cardiac index. In turn, mechanisms substudies of PATHWAY-2 [7] revealed that the effective antihypertensive agent-doxazosin is paradoxically associated with sodium retention. Moreover, data from long-term follow-up ALLHAT studies showed a higher

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This article is part of the Topical Collection on *Inflammation and Cardiovascular Diseases*

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rate of heart failure in the amlodipine group, which allows us to speculate that sodium retention may be of iatrogenic origin [8]. Laffer et al. [9] demonstrated that excessive sodium loading in salt-sensitive healthy volunteers is responsible for brisk hemodynamic consequences with an increase in peripheral resistance and impairment of diastolic heart function. Other sodium-induced effects on the renin-angiotensin-aldosterone system (RAAS) include immunological, coagulation, and microcirculation system changes that may also be of particular importance in face of COVID-19 infection.

The aim of this review is to analyze the mechanisms of action of cardiovascular drugs, taking into account their effect on positive sodium balance. We highlighted the potential of exacerbated inflammation induced by both sodium storage and superimposed SARS-CoV-2 infection.

RAAS Inhibition in COVID-19 and Other Infections

Whether and how the use of renin-angiotensin-aldosterone blockers influences the course of COVID-19 has become a topic of heated debate among researchers and clinicians. ACE 2 is used by coronaviruses as a receptor for cell entry [10]. ACE inhibitors (ACEIs) which are used as a first-line antihypertensive medication, as well as for treatment of heart failure, are known to increase expression of ACE2 [11, 12], and thus, it has been hypothesized that they may facilitate SARS-CoV-2 infection or increase severity. On the other hand, some studies have shown beneficial effects of ACE inhibitors in animal models of acute lung injury, leading to hypotheses that they may protect from a severe course of COVID-19 [13••, 14–17].

Influenza A presents a similar mechanism of lung damage using ACE2 to that seen in SARS, and therefore, Chung et al. conducted a study on the electronic healthcare records of 5.6 million UK patients to establish a link between the use of ACEI or angiotensin receptor blockers (ARB) and the incidence of influenza [18••]. The observed effect depended on the duration of prescription days, ranging from no effect when prescribed between 0 and 1.5 years, to a hazard ratio of 0.29 for ACEI and as low as 0.11 for ARB when prescribed for >10 years. However, as observed by Hayward et al., most cases of influenza infection (confirmed by PCR) are asymptomatic (54% of all infections), not severe enough for patients to visit a doctor (83% of all infections), or not recorded as influenza even upon a medical visit (92% of infected patients who visited a GP) [19]. Therefore, what the authors actually reported was rather the occurrence of symptomatic influenza, with symptoms severe enough to warrant a visit to the GP and conducting an influenza test. The actual number of infections is impossible to assess in a record study and, assuming similar exposition, is probably similar in both groups. Therefore, we may conclude that long-term intake of ACEI and ARBs reduces the severity of influenza, similar to the animal studies of severe acute respiratory syndrome (SARS) [14, 15]. In fact, it may be supposed that the total mortality reduction achieved with ACEI [20] may in part be due to the enhanced immunity against severe influenza or other viral or bacterial infections [21]. This may not have been found in large randomized trials of cardiovascular drugs before due to not including deaths of infectious diseases as endpoints in antihypertensive agent studies, or due to a too short observation period. A significant and large protective effect is observable after several years, and more time would be needed for a significant number of subjects to contract an infectious disease, whereas clinical trials often only last 2–4 years. Moreover, common beliefs of the low rate of endpoints due to infectious origin in cardiovascular trials could also be influenced by diagnostic discrepancies in an infection imposed on end-stage heart failure with pulmonary congestion, or due to a subclinical infection triggering a fatal arrhythmia or other cardiovascular adverse events. However, the appearance of SARS-CoV-19, a widely spread infectious agent without any known effective or specific drug and with a reliable diagnostic test showed the real scale of life-threatening respiratory infections in heart failure and in other conditions associated with sodium retention.

Chung et al.'s study and their relevance for COVID-19 are supported by a study conducted by Zhang et al. on 1128 patients with hypertension and COVID-19, 188 of them taking ACEI or ARBs [22•]. Both the unadjusted and adjusted risks of total mortality were far lower in the ACEI/ARB group than in the group not receiving medication (3.7% vs. 9.8%, adjusted HR 0.37). Julia Hippisely-Cox et al. revealed in a cohort study of 8.3 million people that ACEIs were linked with a significantly reduced risk of COVID-19 (HR 0.71, 95% CI 0.67–0.74) [23]. A further study by Mancia et al. analyzes odds ratios (OR) of COVID-19 infection in 6292 patients using common antihypertensive agents in Italy vs. a matched control group [13••]. None of the results is statistically significant, but an interesting trend can be observed. The study included groups of patients with 1–2 prescriptions of the drug in 2019 and 3 or more consecutive prescriptions. The adjusted OR was slightly lower with more vs. fewer prescriptions of ACEI or ARB, but slightly higher with more prescriptions of calcium channel blockers (CCBs). Furthermore, the ORs for ARB and ACEI fall below 1.0, while the ORs for CCB are higher than 1.0. There may be several reasons for the lack of statistical significance in this study. As observed in the study by Chung et al. on influenza, the beneficial effect of using ACEI/ARB is significant only after several years (>2.5, but most significant >10), whereas in this study, only the previous year was taken into account. Zhang et al.'s study, which describes a significant benefit of ACEI/ARB, was conducted on inpatients, with a more severe course of COVID-19, while Mancia et al. analyzed all the confirmed cases in the region, including ones with mild or no symptoms, who were treated at home [13••, 22•]. Also, a head-to-head comparison between the

CCB and ACEI/ARB groups, as opposed to comparing both with a matched control group, might have yielded a significant difference. In non-communicable diseases and aging, abnormal sodium accumulation is accompanied by a decrease in ACE2 activity, a known Des-Arg9 bradykinin (DABK) inactivator.

Sodium Excess, Inflammation, and ACE Activity

Evidence so far shows a clear link between non-communicable diseases and COVID-19, as people with pre-existing non-communicable diseases and/or advanced age, both of which are sodium-retaining states, appear to be more vulnerable to becoming severely ill or even dying from the virus [13••, 24, 25].

It was demonstrated that tissue sodium accumulation plays an important role in peripheral inflammation, which activates immune cells, enhancing, IL-6, TNF-α, and IL-23, and IL-17 production [26]. These studies indicate that salt activates immune cells, which leads to hypertension and most likely enhances macrophage function and microbicidal activity via increased nitric oxide production [27•]. This mechanism probably developed in the course of evolution as a protective factor in case of local infection. However, in the case of excessive sodium storage, exaggerated cellular or cytokine response may be detrimental for affected individuals.

Dumanli et al. [28•] showed that hypoxemia, hypernatremia, and hypokalemia are common findings in COVID-19 with acute respiratory distress syndrome (ARDS). All these laboratory abnormalities might be related to underlying hyperaldosteronism caused by sodium storage dependent local inflammation and ANG II production. They might have an adverse impact on pulmonary infection. Therefore, aldosterone antagonists with anti-inflammatory and anti-fibrotic properties, widely used in cardiac diseases, should be also considered in COVID-19 ARDS patients [29]. SARS-CoV-2 can enter ACE2-expressing cells. Not only is ACE2 is expressed in lung alveolar type 2 cell but it can also be found in the digestive system. In a retrospective study of 1141 patients with COVID-19 in China, 16% presented with gastrointestinal symptoms only [30]. A recent US study reported that 14.2% of patients with COVID-19 had digestive symptoms as their main presenting complaint. The severity of disease in this group of patients did not correlate with comorbidities or age, indicating that exclusively the pulmonary mechanisms triggered by SARS-CoV-2 infection are exaggerated by sodium accumulation and lead to a dramatic and sometimes fatal disease course [31–33]. The ACE plays a key role in generating ANG II and increasing the activity of the pressor arm. This enzyme is located mainly in the capillaries of the lungs [34]. It is an open question whether this selective location explains why a pulmonary infection is associated with a more severe course of COVID-19 than the gastrointestinal one [35]. ACE activity is increased in the presence of chloride ions while sulfhydryl compounds and chelating agents are inhibitory [36].

Sodium Excess, Oxidative Stress, and Immune Response

High sodium concentrations have a pro-inflammatory effect, causing oxidative stress, tissue damage, and eGCX damage, leading to resistant hypertension [5].

Kirabo et al. [37] described a pathway in elevated sodium concentrations that promote dendritic cell (DC) activation of T cells, ultimately leading to hypertension. Using multiple murine models of hypertension, the authors determined that proteins oxidatively modified by highly reactive γ-ketoaldehydes (isoketals) are formed in hypertension and accumulate in DCs. Isoketal accumulation was associated with DC production of IL-6, IL-1β, and IL-23 and an increase in co-stimulatory proteins CD80 and CD86. These activated DCs promoted T cell, particularly CD8+ T cell, proliferation, production of IFN-γ, and IL-17A, and hypertension.

High sodium intake also increases oxidative stress in the kidneys, promoting organ damage [38]. High salt intake also promotes a pro-inflammatory activation of macrophages, leading to increased expression of pro-inflammatory cytokines and oxidative stress [39]. A high salt diet aggravated lipopolysaccharide-induced pulmonary macrophage activation and inflammation in lungs in a mouse model of acute lung injury [39]. There is also a hypothesis that sodium-induced inflammation activates ANG II–producing dendritic cells. These findings are consistent with animal studies, proving that a high sodium diet in SS subjects led to ANG II–related kidney injury with inflammation, macrophage infiltration, elevated aldosterone, and exacerbation of hypertension [4]. Activated myeloid cells may also synthesize aldosterone and thus increase local tissue damage [40]. Summarizing, the tissue sodium accumulation in salt-sensitive individuals due to endothelial glycocalyx dysfunction causes macrophage infiltration, vascular inflammation, and local angiotensin-2 and aldosterone synthesis. This inflammatory cascade leads to factor XII-related coagulation disorders with NETosis [5]. NETosis has also been shown to increase coagulation via the intrinsic pathway [41]. This pattern is apparent in COVID-19 patients. Schönrich et al. suggest that the overwhelming production of reactive oxygen species (ROS) resulting in oxidative stress is a major cause of local or systemic tissue damage that leads to severe COVID-19 [42•]. It increases NETosis and suppresses the adaptive arm of the immune system, i.e., T cells that are necessary to kill virus-infected cells. This creates a vicious cycle that prevents a specific immune response against SARS-CoV-2. Merad and Martin write that a dysregulated

macrophage and monocyte response is largely responsible for the severe course of COVID-19, including ARDS [43].

ANG II and the AT1R Receptor

The reduction of ANG II levels in acute infection is of great prognostic importance. Huang et al. demonstrated that plasma levels of ANG II are strongly associated with disease progression and mortality in H7N9 flu [44]. In fact, it is a stronger predictor of a fatal outcome than that of C-reactive protein and some clinical parameters such as the PaO2/FiO2 ratio [44]. High levels of ANG II exert their effects through the AT1R receptor, which include vasoconstriction, fibrosis, cell proliferation, increased oxidative stress damage, sodium retention, aldosterone secretion, and kidney injury [45, 46]. Reducing the activity of the ACE-ANG II-AT1 pathway could prevent acute lung injury and therefore a severe course of coronavirus disease [14, 15].

ANG II vs ANG 1–7

ACE2 is mainly attached to the cell membrane of lung type II alveolar cells, enterocytes of the small intestine, arterial and venous endothelial cells, and arterial vascular smooth muscle in most organs. The reason for the beneficial effect of ACEI is probably in a large part due to the activity of ACE 2 in the lung. ACE 2 deactivates ANG II to angiotensin 1–7 (ANG 1–7), thus antagonizing the action of ACE. ANG 1–7 exerts its effect via the mass oncogene product receptor (MAS). The effects of MAS stimulation include diuresis and natriuresis, which reduce salt and fluid retention in the body, reducing the risk of harmful lung edema. It also has anti-hypertrophic, anti-proliferative, and anti-fibrotic effects, further reducing lung damage. ANG 1–7 also binds with the AT2 receptor, which has anti-inflammatory and anti-oxidative stress properties. Furthermore, ACE 2, ANG 1–7 has been demonstrated to increase renal atrial natriuretic peptide (ANP) production, protecting the system from salt and water overload [47••]. Thus, as described by Iwai and Horiuchi, the classic ACE-ANG II-AT1 pathway plays the role of the "devil," while the ACE2– ANG 1–7–Mas axis acts as the "angel" in natriuresis and tissue protection [48]. This may be especially important in an acute viral infection, where high levels of oxidative stress are present and ACE2 levels are reduced [49]. Natriuresis is also crucial for all sodium-retaining states.

ACE 2 and the Kinin System

Another important way in which ACE2 protects from lung damage is through its impact on the kinin system. DABK is a biological substrate of ACE2 in airway epithelia. A virus-/bacteria-triggered reduction in ACE2 function leads to impaired inactivation of DABK and increased activation of the bradykinin B1 receptor (BKB1R) signaling cascade, which enhances the production of neutrophil-recruiting chemokines in airway epithelial cells [50]. Following exposure to infectious or inflammatory stimuli, as in the case of COVID-19 disease, ACE2 activity is impaired, resulting in increased activity of the DABK/BKB1R axis. This promotes the production and release of chemokines such as C-X-C motif chemokine 5 (CXCL5) from airway epithelial cells and neutrophil infiltration of the lung, which in turn contributes to the pathogenesis of acute lung inflammation with fluid extravasation, increasing the risk of ARDS [50]. An increased level of ACE2 by ACEI use may perhaps protect the lungs from this effect.

Mineralocorticoid Receptor Antagonists and Other Diuretics

ANG II, the central mediator of inflammation, is also the strongest stimulator of aldosterone release. Chander et al. demonstrated in an experimental study that aldosterone, but not ANG II, in the presence of excessive salt loading and severe hypertension, induces more severe microvascular dysfunction [51]. Many studies revealed that aldosterone promotes inflammation, leading to damage of the vasculature, heart, and kidneys [51, 52]. Aldosterone antagonists promote tissue sodium elimination and eGCX restoration, reducing thoracic fluid indices, but they have not been evaluated in the major new studies mentioned earlier in this article [5]. Furthermore, spironolactone, a common aldosterone antagonist, has also been shown to raise ACE 2 activity and mRNA expression levels by 300% and 654%, respectively [53]. Dumanli et al. reported improved oxygenation in patients with COVID-19 in ICU receiving spironolactone, supporting the hypothesis of the beneficial effect of spironolactone in COVID-19 [28•]. They have recently registered a trial to evaluate the effect of 100 mg oral spironolactone vs placebo on COVID-19 induced ARDS in patients admitted to ICU (ClinicalTrials.gov Identifier: NCT04345887). The results, which were due in October 2020, may shed more light on the issue but are not available yet (as of writing, November 2020). It is however possible that long-term spironolactone regimes before the onset of COVID-19 could be more beneficial, as restoring eGCX homeostasis may take time. Thus, a comparison of the outcomes of COVID-19 patients with comorbidities on spironolactone vs no drugs/other drugs could also be of significant clinical use. Cadegiani wrote about the potential benefits and drawbacks of spironolactone therapy in COVID-19, concluding that with current evidence, they could be used in those patients without major ethical concern [54].

All diuretics are commonly used medications for sodium-retaining conditions. The PATHWAY- 2 study showed that long-term administration of hydrochlorothiazide with natriuretic ACEIs or ARBs did not lead to a satisfactory sodium removal effect in patients with resistant hypertension. Almost all populations benefited from the administration of another diuretic, such as a mineralocorticoid receptor blocker or amiloride [6, 7]. Inhibition of the neutral Na/Cl cotransporter (NCC) in the diluting segment of the nephron by thiazide diuretics increases NaCl and volume delivery to more distal sites. Thiazides and loop diuretics decrease extracellular fluid volume (ECF), increase renin, angiotensin II, and aldosterone levels, generating a state of secondary hyperaldosteronism with metabolic alkalosis [55].

During periods of diuretic activity, urine sodium and chloride are both high. However, diuretic action is generally intermittent, consisting of periods of diuretic activity cycle with periods of inactivity and recovery. During the "off-diuretic" phases, avid kidney salt reabsorption markedly reduces distal NaCl delivery. Thus, the urine chloride and sodium cycle increases and decreases depending on the level of diuretic activity, but the total sodium balance is not necessarily negative [56]. In patients with heart failure, the administration of captopril led to a significantly higher increase in renin concentration compared to the combination of amiloride and furosemide, but it was associated with a significantly lower concentration of aldosterone, which increased on diuretics [57]. The lack of a similar relationship between the nonsignificant increase in plasma renin activity and rising aldosterone level on diuretics indicates another aldosterone secretion mechanism not related to systemic renin activity but rather to local inflammation. To stop the diuretic-related spillover of RAA activity manifested by hypokalemia and metabolic alkalosis, the administration of potassium-sparing diuretics, acetazolamide, or an inhibitor of the sodium-glucose co-transporter-2 can be helpful.

Calcium Channel Blockers

Some suggest that alternative treatment using CCBs may be preferable, e.g., in the summary of a recently registered RCT of alternative treatments to ACEI/ARB to be conducted by McEvoy and colleagues (ClinicalTrials.gov Identifier: NCT04330300).

On the other hand, recently, Reynolds et al. [58] found that calcium channel blockers (CCBs) significantly increased the likelihood of severe COVID-19 in patients with hypertension. CCBs were found to be related to an increase in intracapillary pressure leading to exuding fluid into the interstitium [59]. The demonstrated beneficial effect of ACE treatment on the frequency of edema and its severity after CCBs indicates their relationship with excessive activity of the RAA system [60]. These findings suggestive of CCB's impact on increased sodium storage [8] related inflammation as well as CCB's association with a more severe course of COVID-19 requires further investigation [58].

Endothelial Glycocalyx—the Key to Homeostasis

The endothelial glycocalyx is an apical endothelial layer composed of transmembrane proteoglycans such as syndecan-1 and thrombomodulin, covalently attached to glycosaminoglycans (GAG) that project into the vascular lumen. The glycocalyx plays a key role in regulating permeability of the endothelial barrier. Viral infection or sepsis was found to disrupt the glycocalyx on human pulmonary microvascular endothelial cells, inducing degradation of sialic acid and shedding of heparin sulfate proteoglycans [61]. Recently, an elevation of biomarkers of the glycocalyx endothelial damage was observed in the early phase of ARDS secondary to respiratory virus infection [62].

Weidenfeld and Kuebler [63] proposed that shedding of the glycocalyx may present an evolutionarily preserved protection mechanism, given that some bacteria and viruses use heparin sulfate as a receptor. However, for other pathogens that infect cells through specific receptors, for example, the SARS virus via ACE2 receptors [64], an intact glycocalyx may act as a shield preventing host infection. Conversely, pathogens and toxins may degrade the glycocalyx, thus increasing permeability, providing access for subsequent infections [64], and facilitating their progression.

The endothelial glycocalyx (eGCX) plays an important role in health and various diseases. The mortality in COVID-19 is especially high in patients with hypertension, diabetes, cardiovascular disease, or older age, which are usually accompanied by various degrees of eGCX dysfunction [65, 66]. Damaged eGCX promotes inflammation via increased vascular permeability and the recruitment of leukocytes and platelets, leading to fluid extravasation, edema, and end-organ damage [5, 65]. RAAS inhibitors act to promote natriuresis, effectively lowering tissue sodium concentration and in the long term helping to break the vicious cycle and restore homeostasis. Increased sodium concentrations in the tissues promote pro-inflammatory macrophage activation and subsequent pro-inflammatory cytokine release [67]. Salt also promotes a pathogenic Th17 phenotype which produces IL-17A and/or IL-17F, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-2, and tumor necrosis factor (TNF), further promoting inflammation [67]. This shift towards a more pro-inflammatory immune response in salt retention leads to vasodilation and edema and may account for a more severe course of COVID-19 in hypertension, which involves elevated tissue sodium levels. This may be another reason for the beneficial effect of ACEI in COVID-19 and influenza infections. The size and composition of the glycocalyx may adversely change during

intravenous fluid administration or mechanical ventilation [64]. Mechanical ventilation could in turn increase pathogen adhesion and invasion in the context of ventilator-associated pneumonia [68]. In resistant hypertension and in salt-sensitive individuals, glycocalyx dysfunction is closely related to impairment of microvascular perfusion [5]. The highest mortality of COVID-19 is observed in patients with arterial hypertension or heart disease and other states associated with glycocalyx dysfunction. Heparin may preserve or protect the endothelial glycocalyx. In a septic shock model, Yini et al. [69] showed that treatment with crystalloids and antibiotics only partially reversed the glycocalyx degradation, whereas treatment with crystalloids, antibiotics, and unfractionated heparin normalized the endothelial glycocalyx [69]. It was suggested that heparin either had a direct protective effect on the glycocalyx or its anti-inflammatory effects caused less organ dysfunction and thereby reduced glycocalyx shedding [70]. Sulodexide is a mixture of natural porcine glycosaminoglycans serving as precursors for the synthesis of glycosaminoglycans in the endothelial glycocalyx or prevention of heparin sulfate degradation. A recent breakthrough trial by the RECOVERY group demonstrated a beneficial effect of dexamethasone in COVID-19 patients requiring oxygen or mechanical ventilation, but not in those with a more mild course [71]. This supports the hypothesis that the severe course of the disease is related to a pathological immune system response [71]. COVID-19 is significantly more fatal in hypertensive patients [72]. When viewing all this evidence together, we may hypothesize that a pathological pro-inflammatory response driven by salt overload may be responsible for the high mortality rate in hypertensive patients and that agents reducing sodium retention may act protectively.

Nowadays, alternative strategies in critical care medicine are desperately needed and the glycocalyx should be considered as a new therapeutic target in COVID-19.

This article focuses primarily on COVID-19 due to the current pandemic and the urgent need for research on this topic. However, many of the mechanisms revealed in relation to COVID-19 are likely to be true for various viral and non-viral infectious diseases. The immune modulation and eGCX modifications caused by excess sodium storage are most likely universal mechanisms present in many diseases. Further studies are urgently required to evaluate the effects described in this article, observed primarily in influenza and COVID-19, also in other diseases.

An example of complex interplay between viral infections and sodium sensitivity may be observed in the case of people living with the human immunodeficiency virus (PLH) who contract COVID-19. A recent study revealed that PLH had a higher risk of mortality at 30 days (RR 1.55, 95% CI: 1.01−2.39) and were more likely to need inpatient services (RR 1.83, 95% CI: 1.496−2.24) [73]. After matching for BMI, diabetes, hypertension, chronic lung diseases, chronic kidney disease, race, history of nicotine dependence, and sex, the risk ratios of hospitalization and mortality were lower. This is likely due to human immunodeficiency virus (HIV) causing chronic immune system dysregulation with increased inflammation, which leads to eGCX damage and sodium sensitivity, sodium overload, hypertension, renal impairment, and lung disease, which were all found to be more likely in PLH [73]. The association of sodium retention on HIV comorbidities is currently speculative, but Masenga et al. published a paper reviewing the supporting evidence and have planned a trial to evaluate this effect [74].

Thrombosis and the Immune System

Another point of action of ACEI in COVID-19 patients could be vascular thrombosis. Ackermann and colleagues recently performed histologic analysis of pulmonary vessels of patients who died from COVID-19. Histologic analysis of pulmonary vessels in patients with COVID-19 showed widespread thrombosis with microangiopathy. Alveolar capillary microthrombi were 9 times as prevalent in patients with COVID-19 as in patients with influenza ($P<0.001$). In the lungs of patients with COVID-19, the amount of new vessel growth—predominantly through a mechanism of intussusceptive angiogenesis—was 2.7 times as high as that in the lungs from patients with influenza ($P<0.001$) [75]. It has been demonstrated that ANG II may promote arterial thrombosis, whereas ACE 2 promotes antithrombotic activity [76, 77]. ACEI also influences the kallikrein-kinin system, thereby promoting fibrinolysis [78]. A retrospective study proved that patients taking RAS inhibitors had a lower risk of thromboembolism [79]. These findings show a potential application of anticoagulant treatment in COVID-19 patients. The findings of Paranjpe et al. suggest that systemic anticoagulation may be associated with improved outcomes among patients hospitalized with COVID-19 [80]. Heparin may be especially useful. Heparin interacts nonspecifically with cytokines, growth factors, adhesion molecules, and proteases, associated with inflammation processes, which are attenuated upon its administration [81]. Experimental studies suggest that heparin, due to its interaction with the eGCX, may be found useful in antiviral therapy [82]. Heparin's usefulness is most likely due to its simultaneous activities involving interrelated processes of inflammation, atherogenesis, cell proliferation, and thrombogenesis [83, 84].

Potential Implications for Therapy

ACEIs help reduce the impact of the angiotensin II-AT1 pressor arm, improve natriuresis, and modulate ACE2 expression. ACEIs have been linked to lower risk of COVID-19 and severe course of COVID-19 in large-scale clinical studies.

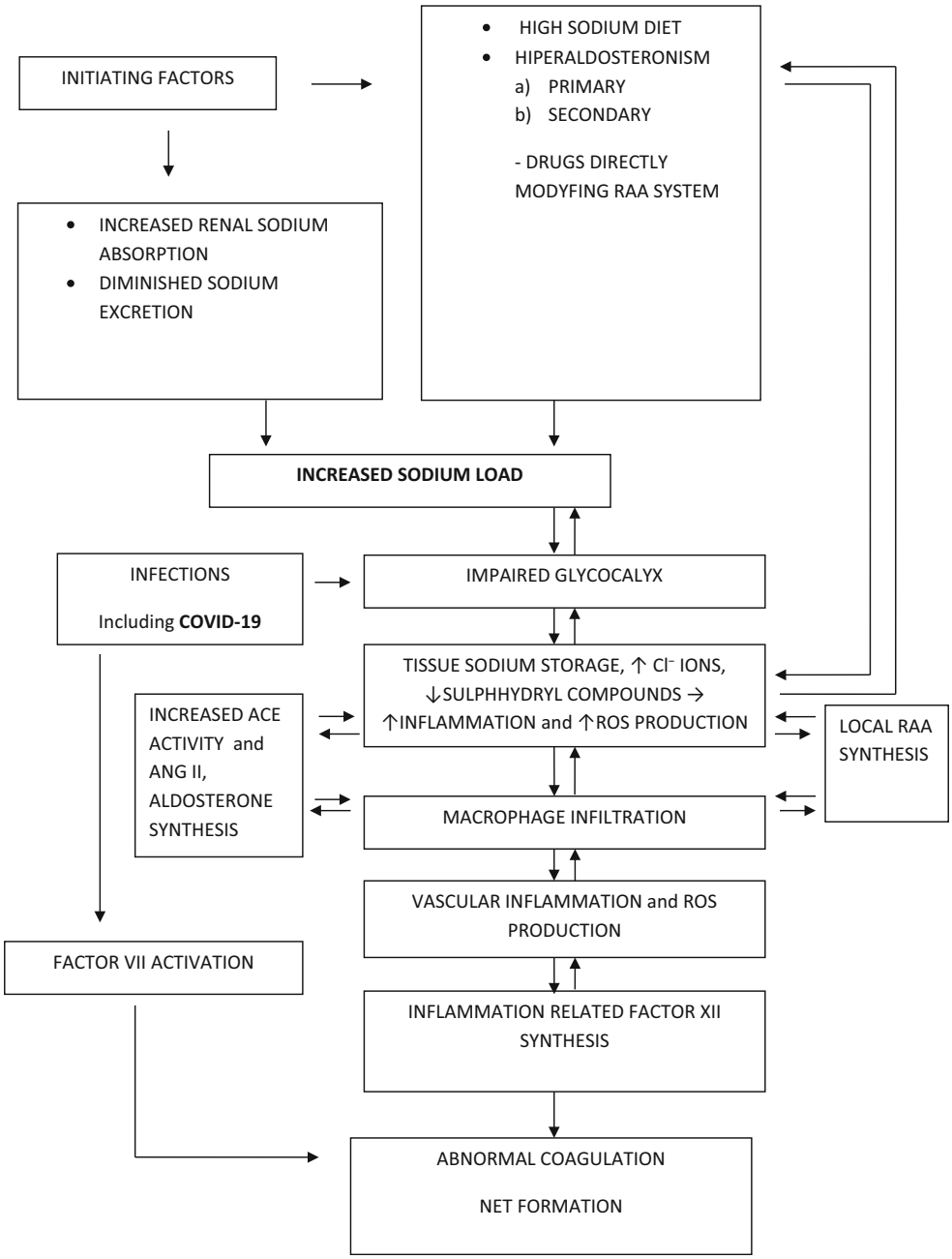

Fig. 1 The pathway leading from excessive sodium storage to a more severe course of infectious diseases. RAA, renin-angiotensin-aldosterone; ACE, angiotensin-converting enzyme; ANG II, angiotensin II; ROS, reactive oxygen species; NET, neutrophil extracellular trap

Despite the current lack of clinical evidence, spironolactone is likely to be beneficial in prevention of a severe course of COVID-19 and in early stages of disease to prevent exacerbation. This may largely be due to tissue sodium storage modulation resulting in anti-inflammatory effects in the lungs, reducing the impact of the angiotensin II-AT1 pressor arm and ACE2 expression modulation which may reduce cell entry.

Heparin may potentially be useful in due to inhibiting the cytokine storm which is associated with a severe course of the disease, reducing thrombosis, and improving natriuresis.

Sulodexide might be useful in prophylaxis in patients with eGCX damage (diabetes, hypertension) due to its impact on thickening and restoring the eGCX, the importance of which has been stressed above. Clinical evidence in COVID-19 is lacking.

CCBs require further investigation due to their potential impact on increasing sodium storage and tissue edema and should be viewed with caution in COVID-19 patients.

Conclusions

Excessive ACE activity is associated with increased severity of the pulmonary course of COVID-19 infection. Natriuretic

agents may be implemented to attenuate the negative impact of sodium retention and ACE activity. Repairing the eGCX and improving microcirculation could potentially curb disease progression. The pathways described in this review which may ultimately lead to a severe course of the disease have been presented in Fig. 1.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

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