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

Szymon Price 1 · Radosław Targoński 2 · Janusz Sadowski 1 · Ryszard Targoński 2

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 antialdosterone 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-doazosin is paradoxically associated with sodium retention. Moreover, data from long-term follow-up ALLHAT studies showed a higher

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1 Miejski Szpital Zespolony w Olsztynie, Klinika Kardiologii i Chorób Wewnętrznych, Clinic of Cardiology and Internal Medicine, Metropolitan Hospital of Nicolaus Copernicus, University of Warmia and Mazury, Niepodległości 44, 10-045 Olsztyn, Poland
2 Department of Cardiac & Vascular Surgery, University Hospital of Gdańsk, M. Skłodowskiej-Curie 3a street, 80-210 Gdańsk, Poland

Szymon Price and Radosław Targoński contributed equally to the paper and are considered co-first authors.

This article is part of the Topical Collection on Inflammation and Cardiovascular Diseases
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 [13–17].

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 Hippisley-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 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 ω-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
damage is through its impact on the kinin system. DABK is another important way in which ACE2 protects from lung damage. ANG II–proliferative, and anti-fibrotic effects, further reducing lung risk of harmful lung edema. It also has anti-hypertrophic, anti-inflammatory, and antioxidant properties.

\[ \text{ANG II vs ANG 1–7} \]

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.

\[ \text{ACE 2 and the Kinin System} \]

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.

\[ \text{Mineralocorticoid Receptor Antagonists and Other Diuretics} \]

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 oxygenation in COVID-19 [54]. 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 co-morbidities 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/Ci 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 levels 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, glyocalyx 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 glyocalyx dysfunction. Heparin may preserve or protect the endothelial glyocalyx. In a septic shock model, Yini et al. [69] showed that treatment with crystalloids and antibiotics only partially reversed the glyocalyx degradation, whereas treatment with crystalloids, antibiotics, and unfractionated heparin normalized the endothelial glyocalyx [69]. It was suggested that heparin either had a direct protective effect on the glyocalyx or its anti-inflammatory effects caused less organ dysfunction and thereby reduced glyocalyx shedding [70]. Sulodexide is a mixture of natural porcine glycosaminoglycans serving as precursors for the synthesis of glycosaminoglycans in the endothelial glyocalyx 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 glyocalyx 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.
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.

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance
• Of major importance

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054–62. https://doi.org/10.1016/S0140-6736(20)30566-3.

2. Petrelli CM, Jones SA, Yang J, Rajagopalan H, O’&039;Dorrell LF, Chemyak Y, Tobin K, Cerfolio RJ, Francois F, Horwitz LL. Factors associated with hospitalization and critical illness among 4,103 patients with COVID-19 disease in New York City. medRxiv 2020; : 2020.04.08.20057794. https://doi.org/10.1101/2020.04.08.20057794.

3. Kopp W. How western diet and lifestyle drive the pandemic of obesity and civilization diseases. Diabetes, Metab Syndr Obes Targets Ther. 2019;12:2221–36. https://doi.org/10.2147/DMSO.S216791.

4. Kirabo A. A new paradigm of sodium regulation in inflammation and hypertension. Am J Phys Regul Integr Comp Phys. 2017;313:R706–10. https://doi.org/10.1152/ajpregu.00250.2017.

5. Targoński R, Sadowski J, Price S, Targóński R. Sodium-induced inflammation—an invisible player in resistant hypertension. Hypertens Res e-pub ahead of print 2020; https://doi.org/10.1038/s41440-020-0428-y.

6. Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McElmes G, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet (London, England). 2015;386:2059–68. https://doi.org/10.1016/S0140-6736(15)00257-3.

7. Williams B, MacDonald TM, Morant SV, Webb DJ, Sever P, McElmes GT, et al. Endocrine and haemodynamic changes in resistant hypertension, and blood pressure responses to spironolactone or amiloride: the PATHWAY-2 mechanisms sub-studies. Lancet Diabetes Endocrinol. 2018;6:464–75. https://doi.org/10.1016/S2213-8587(18)30071-8.

8. Oparil S, Fu RH. Revisiting ASCOT 16 years later. Lancet (London, England). 2018;392:1092–4. https://doi.org/10.1016/S0140-6736(18)31943-3.

9. Laffer CL, Scott RC 3rd, Titze JM, Luft FC, Elijovich F. Hemodynamics and salt-and-water balance link sodium storage and vascular dysfunction in salt-sensitive subjects. Hypertens (Dallas, Texas 1979). 2016;68:195–203. https://doi.org/10.1161/HYPERTENSIONAHA.116.07289.

10. Zhou P, Yang X-L, Wang X-Q, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579:270–3. https://doi.org/10.1038/s41586-020-2012-7.

11. FC M, Jewell J, CM C, AD B, Bridget BK, Ann TE, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation. 2005;11:2605–10. https://doi.org/10.1161/CIRCULATIONAHA.104.510461.

12. Soler MJ, Barrios C, Oliva R, Batlle D. Pharmacologic modulation of ACE2 expression. Curr Hypertens Rep. 2008;10:410–4. https://doi.org/10.1007/s11906-008-0076-0.

13. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-angiotensin-aldosterone system blockers and the risk of Covid-19. N Engl J Med. 2020;1–10. https://doi.org/10.1056/NEJMoa2006923 This paper evaluated the risk of COVID-19 in patients on various antihypertensive agents.

14. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med. 2005;11:875–9. https://doi.org/10.1038/nm1267.

15. Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature. 2005;436:112–6. https://doi.org/10.1038/nature03712.

16. Esler M, Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? J Hypertens. 2020.38. https://journals.lww.com/jhypertension/Fulltext/2020/05000/Can-angiotensin_receptor_blocking_drugs_perhaps_be.aspx:781–2.

17. Jan DAH, Murray E, Daniel B. Renin-angiotensin system blockers and the COVID-19 pandemic. Hypertension. 2020;75:1382–5. https://doi.org/10.1161/HYPERTENSIONAHA.120.15082.

18. Chung S-C, Providencia R, Sofat R. Association between angiotensin blockade and incidence of influenza in the United Kingdom. N Engl J Med e-pub ahead of print 8 May 2020; https://doi.org/10.1056/NEJMoa2005396. This paper studied a British database to evaluate the incidence of influenza in a very large population of patients on various antihypertensive medications.

19. Hayward AC, Fragaesy EB, Bermingham A, Wang L, Copas A, Edmunds WJ, et al. Comparative community burden and severity of seasonal and pandemic influenza: results of the Flu Watch cohort study. Lancet Respir Med. 2014;2:445–54. https://doi.org/10.1016/S2213-2600(14)70034-7.

20. van Vark LC, Bertrand M, Akkerhuis KM, Brugs JJ, Fox K, Mourad J-J, et al. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158,998 patients. Eur Heart J. 2012;33:2088–97. https://doi.org/10.1038/eurheartj.eds075.

21. Mortensen EM, Nakashima B, Cornell J, Copeland LA, Pugh MJ, Anzueto A, et al. Population-based study of statins, angiotensin II receptor blockers, and angiotensin-converting enzyme inhibitors on pneumonia-related outcomes. Clin Infect Dis. 2012;55:1466–73. https://doi.org/10.1093/cid/cis337.

22. Zhang P, Zhu L, Cai J, Lei F, Qin J-J, Xie J, et al. Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ Res, 2020;126:1671–81. https://doi.org/10.1161/CIRCRESAHA.120.317134 This study demonstrated a protective effect of ACEI in hospitalized patients with COVID 19.
23. Hippisley-Cox J, Young D, Coupland C, Channon KM, Tan PS, Harrison DA, et al. Risk of severe COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: cohort study including 8.3 million people. Heart. 2020;106:1505–1511. https://doi.org/10.1136/heartjnl-2020-317393.

24. Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Itrurrate E, Johnson SB, et al. Renin–angiotensin–aldosterone system inhibitors and risk of covid-19. N Engl J Med. 2020;382:2441–8. https://doi.org/10.1056/NEJMoa2008975.

25. Mehra MR, Desai SS, Kuy SR, Henry TD, Patel AN. J Clin Med. 2020;9:2172. https://doi.org/10.3390/jcm9052172.

26. Yi B, Titze J, Rykova M, Feuerecker M, Vassilieva G, Nichiporuk EW, et al. JACC Heart Fail. 2020;8:1486–1495. https://doi.org/10.1016/j.jchf.2020.04.017.

27. Vitti P, Filocamo M, Di Nardo G, Morreale ML, Capuano P, Fabris M, et al. Use of spironolactone in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol. 2020;20:355–62. https://doi.org/10.1038/s41577-020-0331-4.

28. Yartas Dumanli G, Dilken O, Urkmez S. Spironolactone use in SARS-CoV-2 ARDS patients. J Clin Med. 2020;9:2173. https://doi.org/10.3390/jcm9052173.

29. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. J Med Microbiol. 2012;61:1194–203. https://doi.org/10.1099/jmm.0.0331-4.

30. Zhao Y, Cao Y, Wang S, Cai K, Xu K. COVID-19 and gastrointestinal symptoms. Br J Surg. 2020;107:e382. https://doi.org/10.1002/bjs.11821.

31. Nobel YR, Phipps M, Zucker J, Lebwohl B, Wang TC, Sobieszczuk ME, et al. Gastrointestinal symptoms and coronavirus disease 2019: a case-control study from the United States. Gastroenterology. 2020;158:1181–94. https://doi.org/10.1053/j.gastro.2020.04.017.

32. Studdy PR, Lapworth R, Bird R. Angiotensin-converting enzyme and its clinical significance—a review. J Clin Pathol. 1983;36:938–47. https://doi.org/10.1136/jcp.36.8.938.

33. Luo S, Zhang X, Xu H. Don’t overlook digestive symptoms in patients with 2019 novel coronavirus disease (COVID-19). Clin Gastroenterol Hepatol. 2020;18:1636–7. https://doi.org/10.1016/j.cgh.2020.03.043.

34. Studdy PR, Lapworth R, Bird R. Angiotensin-converting enzyme and its clinical significance—a review. J Clin Pathol. 1983;36:938–47. https://doi.org/10.1136/jcp.36.8.938.

35. Kirabo A, Barbaro N, Foss JD, Montaniel KR, Chen W, Harrison DG. High salt activates human monocytes and promotes their conversion into dendritic cells via formation of immunogenic isoketal-adducts. FASEB J. 2016;30:1216.4–4. https://doi.org/10.1096/fasebj.30.1_supplement.1216.4.

36. Kityakara C, Chaioayavilvich T, Chen Y, Blau J, Karber A, Aslamin S, et al. Salt intake, oxidative stress, and renal expression of NADPH oxidase and superoxide dismutase. J Am Soc Nephrol. 2003;14:2775–82. https://doi.org/10.1097/01.asn.0000092145.90389.65.
55. Emmett M. Metabolic alkalosis: a brief pathophysiological review. Clin J Am Soc Nephrol. 2020;1–9. https://doi.org/10.2215/CJN.16041219.

56. Hasselgren B, Johansson P. Natriuretic and diuretic effects of feldopine and hydrochlorothiazide after single and repeated doses. Eur J Clin Pharmacol. 1995;47:395–400. https://doi.org/10.1007/BF00196851.

57. Richardson A, Scriven AJ, Poole-Wilson PA, Bayliss J, Parameshwar J, Sutton GC. Double-blind comparison of captopril alone against frusemide plus amiloride in mild heart failure. Lancet. 1987;330:709–11. https://doi.org/10.1016/S0140-6736(87)91074-9.

58. Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Iturrate E, et al. Influence of factor XII deficiency on activated partial thromboplastin time (aPTT) in critically ill patients. J Thromb Haemost. 2019. https://doi.org/10.1111/jth.14647.

59. Messeri FH. Vasodilatory edema: a common side effect of antihypertensive therapy. Am J Hypertens. 2001;14:978–9.

60. Messeri FH, Oparil S, Feng Z. Comparison of efficacy and side effects of combination therapy of angiotensin-converting enzyme inhibitor (benazepril) with calcium antagonist (either nifedipine or amlopidine) versus high-dose calcium antagonist monotherapy for systemic hypertension. Am J Cardiol. 2000;86:1182–7. https://doi.org/10.1016/S0002-9149(00)01199-1.

61. Puerta-Guardo H, Glasner DR, Harris E. Dengue virus NS1 disrupts the endothelial glycocalyx, leading to hyperpermeability. PLoS Pathog. 2016;12:e1005738. https://doi.org/10.1371/journal.ppat.1005738.

62. Benatti MN, Borges MDC, Miranda CH. Endothelial glycocalyx damage in the early phase of acute respiratory distress syndrome secondary to respiratory virus infection. 2016; 18: 6736.

63. Weidenfeld S, Kuebler WM. Shedding first light on the alveolar epithelial glycocalyx. Am J Respir Cell Mol Biol. 2018;59:283–4. https://doi.org/10.1165/rcmb.2018-0108ED.

64. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203:631–7. https://doi.org/10.1002/path.1570.

65. Yilmaz O, Afsar B, Ortız A, Kanbay M. The role of endothelial glycocalyx in health and disease. Clin Kidney J. 2019;12:611–9. https://doi.org/10.1093/ckj/szj042.

66. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020;323:2052–9. https://doi.org/10.1001/jama.2020.6777.

67. Wilck N, Balogh A, Markó L, Bartolomaeus H, Müller DN. The role of sodium in modulating immune cell function. Nat Rev Pharmacol. 2020;20:474–482. https://doi.org/10.1038/s41573-020-0114-2.

68. Bachler M, Niederwanger C, Hell T, Höfer J, Gerstmeyr D, Schenk B, et al. Influence of factor XII deficiency on activated partial thromboplastin time (aPTT) in critically ill patients. J Thromb Thrombolysis. 2019;48:466–74. https://doi.org/10.1007/s11239-019-01879-w.

69. Yini S, Heng Z, Xin A, Xiaochun M. Effect of unfractionated heparin on endothelial glycocalyx in a septic shock model. Acta Anaesthesiol Scand. 2015;59:160–9. https://doi.org/10.1111/aas.12418.

70. Pillinger NL, Kam PCA. Endothelial glycocalyx: basic science and clinical implications. Anaesth Intensive Care. 2017;45:295–307. https://doi.org/10.1117/0310057x1704500305.

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