Mini-Review

New Horizons: Does Mineralocorticoid Receptor Activation by Cortisol Cause ATP Release and COVID-19 Complications?

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Abbreviations: 11β-HSD2, 11β-hydroxysteroid dehydrogenase type 2; ACE, angiotensin-converting enzyme; AMP, adenosine 5′-monophosphate; ARDS, acute respiratory distress syndrome; ATP, adenosine 5′-triphosphate; BAME, Black, Asian and Minority Ethnic; COVID-19, coronavirus disease 2019; CtBP, C-terminal binding protein; eNOS, endothelial nitric oxide synthase; ER, estrogen receptor; G6PD, glucose-6-phosphate dehydrogenase; GR, glucocorticoid receptor; HUVEC, human umbilical vein endothelial cell; ICU, intensive care unit; IL-6, interleukin-6; IV, intravenously; KO, knockout; MAS, angiotensin (1–7) receptor; MR, mineralocorticoid receptor; NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; O2–, superoxide; PARP, poly(ADP-ribose) polymerase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane serine protease 2; VWF, von Willebrand factor; WPB, Weibel-Palade body.

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Abstract

This paper attempts to explain how the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus causes the complications that make coronavirus disease 2019 (COVID-19) a serious disease in specific patient subgroups. It suggests that cortisol-associated activation of the mineralocorticoid receptor (MR) in epithelial and endothelial cells infected with the virus stimulates the release of adenosine 5′-triphosphate (ATP), which then acts back on purinergic receptors. In the lung this could produce the nonproductive cough via purinergic P2X3 receptors on vagal afferent nerves. In endothelial cells it could stimulate exocytosis of Weibel-Palade bodies (WPBs) that contain angiopoietin-2, which is important in the pathogenesis of acute respiratory distress syndrome (ARDS) by increasing capillary permeability and von Willebrand factor (VWF), which mediates platelet adhesion to the endothelium and hence clotting. Angiopoietin-2 and VWF levels both are markedly elevated in COVID-19–associated ARDS. This paper offers an explanation for the sex differences in SARS-CoV-2 complications and also for why these are strongly associated with age, race, diabetes, and body mass index. It also explains why individuals with blood group A have a higher risk of severe infection than those with blood group O. Dexamethasone has been shown to be of benefit in coronavirus ARDS patients and has been thought to act as an anti-inflammatory drug. This paper suggests that a major part of its effect may be due to suppression of cortisol secretion. There is...
an urgent need to trial the combination of dexamethasone and an MR antagonist such as spironolactone to more effectively block the MR and hence the exocytosis of WPBs.

**Freeform/Key Words:** mineralocorticoid receptor, COVID-19 complications, spironolactone and dexamethasone

This New Horizons paper focuses on the following hypotheses:

1. The loss of the angiotensin-converting enzyme 2 (ACE2) receptor, which is used by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus to get into endothelial and type II alveolar cells, plays a major role in the development of the complications of the infection, acute respiratory distress syndrome (ARDS) and clotting abnormalities.

2. The loss of the ACE2 receptor results in high levels of angiotensin II, which stimulate nicotinamide adenine dinucleotide phosphate (NADP) oxidase to produce reactive oxygen species (ROS). This removes a key protective mechanism for the mineralocorticoid receptor (MR), which can be activated by cortisol and is no longer aldosterone selective.

3. Activation of the MR releases adenosine 5'-triphosphate (ATP) from the cells. This then has a paracrine effect on purinergic receptors resulting in calcium entry into the cells.

4. Increased intracellular calcium results in exocytosis of Weibel-Palade bodies (WPBs) from the cells. These contain the von Willebrand factor (VWF), which spreads like a spiderweb, attracts platelets, and results in microthrombi. The bodies also contain angiopoietin-2, which markedly increases capillary permeability and hence pulmonary edema.

5. MR blockade with spironolactone has been shown in vitro to block exocytosis of WPBs.

6. This paper suggests that on the basis of these hypotheses, there should be trials of dexamethasone to suppress cortisol secretion together with an MR antagonist such as spironolactone or eplerenone.

In 2005 we found that aldosterone opened sodium channels by a novel purinergic mechanism (1). After binding to the MR, ATP is released from the cell. The time course for this suggests it is nongenomic (ie, does not require DNA transcription). The released ATP acts back on the cell and adjacent cells to stimulate purinergic receptors (P2X4) that then increase calcium entry. This results in cell contraction with opening of the sodium channel (Fig. 1). If hexokinase and glucose are added to the cell to consume ATP, the cell does not contract and the sodium channel does not open.

To understand how the virus activates the MR, it is necessary to focus on the role that ACE2 plays in the cell and the consequences of its inactivation by the virus.

**Role of Angiotensin-Converting Enzyme 2**

The SARS-CoV-2 virus uses the ectodomain of ACE2 to enter nasopharyngeal, type 2 alveolar and endothelial cells. The transmembrane serine protease 2 (TMPRSS2) expressed on these cells activates the SARS-CoV-2 spike protein. The result is cleavage of the ACE2 enzyme receptor to which the virus binds and that it uses to enter the cell. ACE2 converts angiotensin II to angiotensin-(1–7) (Fig. 2). The role of angiotensin-(1–7) has been well reviewed (2) and its loss has major effects. It binds to a G-protein–coupled receptor Mas and is part of a key counterregulatory pathway within the renin-angiotensin system. It is a vasodilator and antiproliferative. Mas deletion produces hypertension, endothelial dysfunction, and thrombogenesis. Xu et al studied endothelial function in Mas gene–deleted mice (3), using thiobarbituric acid–reactive substances levels as an indicator of oxidative stress. They found that these were significantly elevated in knockout (KO) mice. Nitric oxide (NO) acts as an endogenous antioxidant by quenching superoxide (O2−) and protects against ROS. They found decreased NO. In addition, a subunit of NADPH oxidase, a key source of ROS, was significantly higher in the KO animals and 2 important antioxidant enzymes (superoxide dismutase and catalase) were reduced.

If the angiotensin-(1–7) KO results are similar to SARS-CoV-2 ACE2 enzyme damage, then it is likely the virus produces major local tissue oxidative stress with a marked increase in ROS.
Figure 1. The effect of aldosterone on adenosine 5′-triphosphate (ATP) cellular release with consequential activation of purinergic receptors (P2 = \( P_{2X} \) receptors) entry of calcium into the cell, contraction, and sodium channel opening (ENaC). P1, adenosine receptors.

Figure 2. The intracellular signaling pathway associated with angiotensin-(1–7) and its importance in counteracting angiotensin II. ACE, angiotensin-converting enzyme; \( AT_1 \), angiotensin II type 1 receptor; eNOS, endothelial nitric oxide synthase; MAS, angiotensin (1–7) receptor; NADP, nicotinamide adenine dinucleotide phosphate; NF\( \kappa \)B, nuclear factor \( \kappa \) enhancer of activated B cells; ROS, reactive oxygen species.
Studies have shown that angiotensin-(1–7) can attenuate angiotensin II–induced ROS generation in endothelial cells. In the absence of ACE2, there are higher local levels of angiotensin II and lower angiotensin-(1–7). This has profound effects on the renin-angiotensin axis. In the acid aspiration ARDS model, mice have markedly increased angiotensin II levels both in the lung and plasma (4). However, these are significantly higher in the lungs and plasma of acid-treated ACE2 KO mice. In mice recombinant ACE2 can protect from severe acute lung injury.

If the MR is important in the pathogenesis of SARS-CoV-2 infection, how does the loss of the ACE2 enzyme result in its activation?

**What Activates the Mineralocorticoid Receptor in Severe Acute Respiratory Syndrome Coronavirus 2–Infected Cells?**

In 1987 Arriza and colleagues cloned the human MR and found it was nonselective, binding aldosterone and cortisol with equal affinity (5). This was surprising given the marked molar excess of cortisol over aldosterone. We demonstrated that in aldosterone-specific tissues, such as the distal renal tubule, the MR was protected from cortisol by an enzyme, 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), that converted cortisol to inactive cortisol (6). We described a 21-year-old man with very severe hypertension and hypokalemia who was unable to convert cortisol to cortisone because of a genetic defect (7). Treatment with dexamethasone lowered his blood pressure to normal and restored normal plasma potassium. The reason for this is that dexamethasone, unlike cortisol, binds more selectively to the glucocorticoid receptor (GR). It also suppresses the secretion of adrenocorticotropic hormone and hence cortisol. The condition is called the syndrome of apparent mineralocorticoid excess. These patients have undetectable levels of aldosterone as cortisol is present in 100-fold molar excess and thus activates the MR turning off the renin-angiotensin system.

John Funder's review "Aldosterone, mineralocorticoid receptors and vascular inflammation" (8) looks at the evidence that it is not only 11β-HSD2 that protects the MR from cortisol but also the cofactor nicotinamide adenine dinucleotide (NAD). 11β-HSD2 requires NAD to convert cortisol to cortisone and in the process produces NADH. NADH then binds to a C-terminal binding protein (CtBP) that then acts as a co-repressor of DNA transcription (9). Thus, it is suggested that the majority of cortisol is inactivated by conversion to cortisone; the residue binds the MR but is inactivated by NADH-CtBP. Further work has shown that normal intracellular glucocorticoid levels can activate the MR when aldosterone levels are low and 11β-HSD2 blocked (and thus low NADH). This then stresses the importance of factors controlling the intracellular levels of NAD and hence NADH.

Nagase and colleagues looked at oxidative stress in MR activation and kidney damage in a rat model of metabolic syndrome (10). They showed that the mineralocorticoid antagonist eplerenone markedly improved salt-induced renal injury. High salt intake is known to increase oxidative stress and paradoxically to enhance MR activation, despite suppression of aldosterone secretion, and to increase urinary albumin excretion especially in overweight individuals (11). Patients infected with the SARS-CoV-2 virus and admitted to the hospital have a high incidence of renal damage, with 57% of 4963 patients having proteinuria (12).

Type II lung epithelial cells and endothelial cells have MR and express 11β-HSD2 (13, 14). Because of the high affinity of cortisol for the MR, it is not surprising that these cells contain cortisol-MR complexes. Under normal circumstances these are not activated, probably because of binding of NADH-CtBP to the complex. They can be activated by ROS (8, 15, 16). As discussed earlier, ROS levels are very high in SARS-CoV-2–infected cells with ACE2 depletions.

Cells infected with SARS-CoV-2 have high intracellular and pericellular levels of angiotensin II following the loss of the ACE2 receptor. It would seem likely that these would have an effect on adjacent vascular smooth muscle cells. It has been shown that angiotensin II stimulates MR messenger RNA and protein expression in vascular smooth muscle cells (17). It is unclear what effect if any angiotensin II has on MR expression in endothelial cells. It does, however, have a very interesting effect on MR transcription, which is blocked by spironolactone (18).

If cortisol is important in activating the MR in type II alveolar cells and endothelial cells, then circulating and tissue levels of this corticosteroid may be important. Tan and colleagues looked at this in patients who had a single baseline plasma cortisol taken within 48 hours of hospital admission for COVID-19 (19). Patients with confirmed COVID-19 had significantly higher plasma cortisol levels than those who did not have a positive test. Of particular interest was their observation that patients with a baseline plasma cortisol of less than 744 nmol/L (27 µg/dL) (67%: 268 patients) had a median survival of 36 days. Those with cortisol greater than 744 nmol/L (27 µg/dL) (33%: 135 patients) had a median survival of 15 days (P < .001).

A key enzyme controlling local cortisol levels is 11β-HSD1. This interconverts cortisol and cortisone. The
enzyme is present both in type II alveolar cells and in endothelial cells. There is extensive evidence suggesting that this enzyme plays an important role in acute and chronic inflammatory states (20). There are as yet no publications on the role that this enzyme might play in COVID-19 infections.

The previously described research strongly suggests that cortisol could play a role in activating the MR in COVID-19 patients.

**What Are the Consequences of Activation of the Mineralocorticoid Receptor in Infected Cells?**

**Unproductive cough**

After nasopharyngeal cells, the virus infects type II alveolar epithelial cells. These contain the MR and 11β-HSD2. What would be the consequences of activation of the MR in these cells? If they release ATP, then this could have a paracrine effect on adjacent cells with purinergic receptors. The lung has neuroepithelial bodies that consist of clusters of pulmonary neuroendocrine cells. These are normal components of the epithelium of the intrapulmonary airways. They have an extensive innervation by myelinated vagus nerve fibers. Purinergic P2X3 receptors are abundantly expressed on the terminal arborizations of these sensory fibers (21, 22) (Fig. 3).

One of the most common early symptoms of infection with SARS-CoV-2 is a nonproductive cough. Recent studies have shown that blockade of P2X3 receptors markedly inhibits chronic cough (23). In addition, Fowles et al (23) have shown that inhalation of ATP as compared to adenosine 5’-monophosphate (AMP) has a marked tussive effect. This work suggests the possibility that the cough of COVID-19 could be the first indicator of its activation of the purinergic system.

**Acute respiratory distress syndrome and excessive clotting**

In 2009 Jeong et al (24) showed that the purinergic mechanism that we had described for epithelial cells also stimulated exocytosis of WPBs from endothelial cells (Fig. 4). They measured the VWF levels after incubating the cells with aldosterone and used this as

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**Figure 3.** Purinergic innervation of pulmonary neuroepithelial bodies (NEBs) and proposed role of adenosine 5’-triphosphate (ATP) released from type 2 alveolar cells in the genesis of cough in coronavirus disease 2019 patients.
a measure of the exocytosis of WPBs. This could be inhibited by the MR antagonist spironolactone (Fig. 5). They demonstrated that low-dose cortisol did not stimulate exocytosis, suggesting that in normal cells the MR is aldosterone selective.

Weibel-Palade bodies

WPBs are unique organelles that contain hemostatic, inflammatory, and angiogenic mediators that are released into the vascular lumen by exocytosis. The main cargo of WPBs is VWF. Exocytic release of WPBs from the endothelial cell results in local accumulation of ultra-large VWF multimers that assemble into strings on the apical side of the endothelium (25). These lead to a spiderweb that functions as a platform for platelet adhesion and hence microthrombi.

Another key molecule in WPBs is angiopoietin-2. Kümpers and Lukasz reviewed the potential importance of this (“The curse of angiopoietin-2 in ARDS”) (26). Angiopoietin-1 is an antipermeability factor that protects the vasculature from plasma leakage. One source is alveolar type II cells that are damaged by SARS-CoV-2. Angiopoietin-2 release from WPBs in endothelial cells prevents angiopoietin-1 from binding to its receptor, thus promoting inflammation and vascular permeability. The plasma levels of angiopoietin-2 are proportional to ARDS severity, and rising levels predict a poor ARDS outcome (27).

Figure 4. von Willebrand factor immunofluorescent staining of human umbilical vein endothelial cells showing the typical Weibel-Palade body distribution. Courtesy of Dr Tom McKinnon and Prof Anna Randi, Imperial College, London.

Figure 5. Aldosterone stimulated the release of von Willebrand factor (VWF) from human aortic endothelial cells. This could be blocked by the mineralocorticoid-receptor antagonist spironolactone. In contrast, thrombin also released the VWF but was not blocked by spironolactone (24).
If the contents of the WPBs play a key role in the pathogenesis of SARS-CoV-2 infection, then understanding the secretory pathway is important. Exocytosis can be triggered by many physiological or pathological signals that use Ca\(^{++}\) or 3',5'-cyclic AMP as second messengers. Ca\(^{++}\)-mediated secretagogues such as histamine and thrombin are part of an integrated response to vascular injury and promote a prothrombotic, pro-inflammatory state by rapidly releasing large amounts of VWF, angiopoietin-2, and other WPB contents while increasing endothelial permeability and vascular tone. It has recently become clear that sustained elevation of intracellular Ca\(^{++}\) is sufficient to drive WPB fusion independently from additional receptor-triggered signaling (28). This paper suggests that the SARS-CoV-2 virus infection of endothelial cells activates the MR in the cells with consequent increase in intracellular Ca\(^{++}\) and exocytosis of WPBs.

Ackermann and colleagues compared lung pathology obtained at autopsy from patients with influenza-associated ARDS and that from patients with COVID-19 (29). In patients who died with COVID-19 as compared to influenza, there was 9 times the capillary microthrombi \( (P < .001) \) and 2.7 times higher angiogenesis \( (P < .001) \). Both features would be expected with high levels of VWF and angiopoietin-2. The current explanation for the difference between the pathogenesis of COVID-19–associated ARDS and that of influenza is the cytokine storm. It is suggested that this produces a hyperactive immune response and that high levels of released cytokines are responsible for tissue damage. This has led to the use of monoclonal antibodies targeting interleukin-6 (IL-6), but trials have not shown benefit from this approach. The cytokine storm has been critically analyzed by Sinha et al (30), who concluded that there were few data to support it. IL-6 levels, for example, in 5 large cohorts of patients with COVID-19 were lower than the median value typically reported in ARDS. They suggested that the linkage of a cytokine storm to COVID-19 might be nothing more than a tempest in a teapot!

In contrast to this, Goshua et al studied coagulation in 68 patients with COVID-19, of whom 48 were in the intensive care unit (ICU) and 20 were non-ICU (31). VWF antigen and activity were elevated in 80\% and 75\% of non-ICU patients. These levels were significantly higher in the ICU patients \( (P < .001 \) both for antigen and activity). VWF levels were significantly correlated with mortality. They suggest that COVID-19–associated coagulopathy is an endotheliopathy that results in augmented VWF release and platelet activation with subsequent thrombus formation.

Starke et al have demonstrated a key role for VWF in regulating angiogenesis (32). Inhibition of VWF expression caused increased angiogenesis and increased vascular endothelial growth factor receptor-2–dependent proliferation. This was associated with increased angiopoietin-2 release. Because VWF is essential for the formation of WPBs in endothelial cells, they speculated that the loss of VWF may result in the inability of endothelial cells to store angiopoietin-2. This raises the question—does the loss of VWF by excessive exocytosis result in depletion of intracellular VWF and hence excess local release of angiopoietin-2?

If Activation by Cortisol of the Mineralocorticoid Receptor in Endothelial Cells Plays a Key Role in the Pathogenesis of Infection by the Severe Acute Respiratory Syndrome Coronavirus 2 Virus, what Is Responsible for the Very Variable Clinical Pattern of the Disease?

**Hypertension, cardiovascular disease, and obesity**

It has been recognized for many years that the MR plays an important role in the genesis of vascular disease (33). This has been extensively explored in mice in which the endothelial MR has been knocked out. Mice were given desoxycorticosterone acetate and salt (34). The loss of the MR prevented macrophage infiltration and expression of proinflammatory genes. There has also been a major focus on oxidative stress following MR activation leading to cardiac fibrosis and dysfunction. It is thought that these processes underpin the development of heart failure. One of the most famous and influential papers was the RALES study by Bertram Pitt and colleagues (35). They gave low-dose spironolactone (25 mg/day) to patients with end-stage heart failure. The effects were astonishing (30\% reduction in mortality, 35\% lower hospital admissions). These patients had plasma aldosterone concentrations in the low-normal range. It is suggested that the MR in these patients was being activated by normal circulating levels of cortisol and that this was then blocked by spironolactone (36).

It is well known that patients with hypertension and primary aldosteronism have a higher cardiovascular risk profile in comparison with age-, sex-, and blood pressure–matched hypertensive individuals (37), suggesting that activation of the MR has adverse effects over and above salt retention and hypertension.

Davel et al (38) suggest that the endothelial MR is the key mediator of the switch from vascular health to disease. They propose that in the presence of cardiovascular risk factors the endothelium becomes proinflammatory and prothrombotic and is characterized by impaired endothelium-dependent relaxation. They suggest that in
healthy individuals the MR plays a role in vascular relaxation and is antithrombotic and anti-inflammatory. This compares with individuals with risk factors such as obesity, diabetes, and hypertension, in whom MR activation is responsible for endothelial dysfunction, vasoconstriction, vascular stiffness, and inflammation. These are remarkably similar to the risk factors for COVID-19 complications.

Obesity appears to be a risk factor for patients with COVID-19. Those who are morbidly obese (BMI ≥ 40) have a greater risk of death and are more likely to require intubation (39). Obesity, especially associated with metabolic syndrome, is a chronic inflammatory disease. To what extent this plays a role or whether it is associated comorbidities such as hypertension or diabetes is unclear.

Sex

One of the striking differences in the clinical presentation of COVID-19 is the male-to-female ratio with regard to complications. A review of 1591 patients with COVID-19 admitted to the ICU in Lombardy found that 82% were male (40). In 5700 patients hospitalized with COVID-19 in New York, 60% were male and male mortality exceeded female in every adult age group (41).

In a study investigating the relative protection of women from cardiovascular disease, Barrett Mueller et al looked at the interaction between the estrogen receptor (ER) and the MR (42). They found that the ER and the MR associate as part of a common protein complex in cells and that ERα in the presence of estrogen prevents aldosterone stimulation of MR transcriptional activity. It is unclear whether the ERα binds directly to the MR or via other proteins. They looked at the effect of this interaction on transcription. It would seem likely that the interaction would also affect the release of ATP from the cell induced by activation of the MR. If this is so, then it could be a factor in the male-to-female ratio in susceptibility to SARS-CoV-2 infection.

Race

The racial differences in patients infected with SARS-CoV-2 have been of concern, with Black, Asian and Minority Ethnic (BAME) groups having significantly higher mortality than Whites. In the United States, the age-related mortality among Blacks is 3.8, Hispanics 2.5, and Asians 1.5 times higher than Whites. In the United Kingdom, the figures are Blacks 2.9, Pakistani and Bangladeshi 2.2, and South Indians 2.5 times Whites.

These figures have been attributed to the higher rates of comorbidities in Blacks (43). BAME patients are more likely to have diabetes but this has a hazard ratio of 1.11 for mortality. In addition, young age does not seem to be a protective factor in BAME patients with COVID-19. Karan and colleagues suggest that glucocorticoid resistance could be responsible for the more aggressive disease among minorities (43). One of the ways of testing for glucocorticoid resistance is the skin vasoconstrictor assay, which uses skin blanching after topical application of glucocorticoids as an index of potency (44). Whereas only about 10% of Whites fail to get a vasoconstrictor response, this is much higher in Africans and South Asians. The authors have an interesting model in which patients with metabolic syndrome and acanthosis nigricans have severe insulin and glucocorticoid resistance (45).

Karan et al suggest impaired glucocorticoid responsiveness may result in BAME patients being less able to suppress inflammation triggered by SARS-CoV-2. An alternative explanation is that glucocorticoid resistance results in activation of the MR. This is well known in familial glucocorticoid resistance syndromes that present with hypertension and hypokalemia (46). Thus, patients with glucocorticoid resistance would be at a disadvantage if infected with SARS-CoV-2.

A serine protease TMPRSS2 on nasal and bronchial epithelium is important in coronavirus infection (47). Bunyavanich and colleagues showed that TMPRSS2 expression was significantly higher in Black compared to Asian, Latino, mixed race, and White individuals (48).

Kalinowski et al (49) looked at race-specific differences in endothelial function given the high prevalence of endothelial-impaired function disorders such as hypertension and diabetes and the severity of their complications in Black individuals as compared to Whites. They tested human umbilical vein endothelial cells (HUVECs) isolated from Blacks and Whites. Compared with those from Whites, HUVECs from Blacks had reduced release of bioactive NO and increased release of O2−. There was increased NO degradation by excess O2− that was produced primarily by NADPH-oxidase and uncoupled endothelial NO synthase. It is thus not surprising that infection of the cell with SARS-CoV-2 with the loss of the ACE2 enzyme is likely to be more damaging in Black rather than White individuals, because this will further increase local ROS production.

Glutathione is the main defense mechanism against ROS. Glucose-6-phosphate dehydrogenase (G6PD) in the pentose phosphate pathway converts glucose-6-phosphate to 6-phosphogluconolactone and NADP to NADPH. NADPH then maintains the reduced glutathione to mop up free radicals. X-linked G6PD deficiency affects about 400 million people globally and is especially common in the BAME population. In the United States, males of African descent have the highest prevalence of G6PD deficiency, approaching 10%. Studies have shown that G6PD...
deficiency activates endothelial cells by increasing levels of ROS, NOX-4, and intercellular adhesion molecule 1, while reducing NO (50). Thus the loss of the ACE2 receptor in G6PD-deficient endothelial cells would likely have a markedly adverse effect on endothelial cell function with activation of cortisol-MR complexes (8).

In addition to the X-linked disorder G6PD deficiency can result from activation of the MR. Leopold et al (51) showed that bovine aortic and human coronary endothelial cells exposed to aldosterone for 24 hours had a concentration-dependent decrease in G6PD protein expression associated with decreased activity and NADPH levels. Aldosterone also increased ROS and decreased eNOS activity. In vivo experiments in mice infused with aldosterone showed that these had impaired endothelium-dependent vasodilation and that this was the same as seen in G6PD-deficient mice.

Age

Age-related depletion of the 11β-HSD2 cofactor NAD could play a major role in the susceptibility of older patients to SARS-CoV-2. Massudi et al found major changes in age-related NAD+ metabolism in human skin (52). Oxidative DNA damage is an important factor associated with age-related diseases. This activates a DNA repair mechanism, poly(ADP-ribose) polymerase (PARP). Essential to this enzyme is NAD+. Overactivity of this system can lead to severe NAD+ depletion.

Massudi and colleagues showed a striking fall in tissue NAD+ levels with increasing age (0-1 years 8.54 ng NAD+ per mg protein; 30-50 years 2.74; 51-70 years 1.08, and > 71 years 1.06). This was inversely correlated with the progressive increase in PARP activity. There were also sex-related differences in NAD+ levels with aging. These were negatively correlated with age for males age 0 to 77 years (P < .001). The age-related decline in females was less obvious but in those age 37 to 76 was significant. The authors make the point that females may have a greater capacity to recycle NAD+ from the PARP metabolite nicotinamide.

Krug et al have shown that the MR plays a role in vascular ageing (17). They found that MR expression and signaling increased with age in rat blood vessels, especially in smooth muscle cells.

Factors controlling von Willebrand factor plasma levels

If the excessive release of VWF plays a role in the pathogenesis of COVID-19 complications, then factors controlling VWF plasma levels could be important. In the Atherosclerosis Risk in Communities (ARIC) study, Conlan et al looked at the associations of factor 8 and VWF with age, race, sex, and risk factors for atherosclerosis (53). The strongest associations observed were of factor 8 and VWF with race and diabetes. In a multivariate analysis, Blacks had factor 8 and VWF levels 15% to 18% higher than Whites, and diabetics had factor 8 and VWF levels 11% to 18% higher than nondiabetics. Factor 8 and VWF levels were positively associated with body mass index, waist-hip ratio, serum insulin, and age. All of these are known to be risk factors for severe SARS-CoV-2 infection.

There is a 5-fold range of VWF levels in healthy populations. This depends on genetic and environmental factors. A Norwegian identical twin study suggested that heritability accounted for 66%, with 30% of this being attributable to ABO blood groups (54). They looked at 2 patient groups, one age 33 to 39 years and the other 57 to 62 years. The VWF and factor 8 were higher in the older age group. The heritability of VWF levels has been reported as being as high as 75% in the United Kingdom and as low as 32% in Spain (55).

Blood group

The blood group linkage is of particular interest in relation to this hypothesis for COVID-19 complications. Zhao et al (56) reported that blood group A individuals in Wuhan were more likely to get severe COVID-19 and to die of it than patients with blood group O. Thus, the proportion of blood group A among patients with COVID-19 was significantly higher than the control group (37.8% in the former and 32.2% in the latter—P < .001). This was in contrast to blood group O (25.8% in COVID-19 patients vs 33.8% in the control group (P < .001). The same difference applied to mortality. In the 206 patients who died, the blood group A patients had an odds ratio of 1.482 as compared to non-A blood groups (P < .008), whereas blood group O had an odds ratio of 0.66 compared to non-O blood groups (P < .001). A small study of SARS patients with ARDS in Hong Kong suggested a similar risk pattern (57).

In non-Chinese patients the blood group association is conflicting. A genome-wide association study looked at the genomes of Italian and Spanish patients who were SARS-CoV-2 positive and had severe disease (58). They found an association that coincided with the ABO locus. Analysis of the patient population showed that those with blood group A were at a significantly higher risk than those with blood group O. This was in contrast to the study by Latz et al (59), who found no association between blood group and outcome. They looked at a multiracial group admitted to the hospital with COVID-19 in the United States. There were major differences in the distribution of blood groups. White patients, for example, had 50% blood group A,
whereas Black patients had only 19%. The authors make the point that there is certainly a racial element to blood group typing and they hoped that their multivariable model had taken this into account. However, they suggested that the full effects of ethnicity on COVID-19 susceptibility and severity warranted further investigation.

The reason for these associations was unclear. The authors suggested that it might relate to natural anti–blood group antibodies. This paper suggests an alternative explanation.

The levels of VWF are approximately 30% lower in individuals with type O blood group as compared to non-O blood types. Gallinaro et al (60) found that the half-life of VWF in O individuals (10.8 ± 0.8 h) was significantly less than non-O individuals (25.5 ± 5.3 h; P < .001).

Twenty percent of the mass of circulating VWF is composed of carbohydrate side chains with ABO N-linked blood group glycans representing about 13%. The ABO enzyme is a glycotransferase that attaches N-acetylgalactosamine (A allele) or galactose (B allele) to the H antigen. The common O allele has a single nucleotide deletion that results in a nonfunctioning transferase. It is thought that these differences in structure are responsible for the shorter half-life in blood group O patients (ie, that the major effect of ABO on VWF levels is through alteration of clearance rates [60]).

Diabetes

Control of blood glucose is important in determining the outcome of SARS-CoV-2 infection. Sardu et al (61) looked at this in 59 diabetic patients hospitalized with the infection. The patients were divided into 2 groups, one in which blood glucose was greater than 7.7 mmol/L and the other with levels that were lower. IL-6 and D-dimer levels were higher in the hyperglycemic group. The hyperglycemic and normoglycemic diabetic patients had a higher risk of severe disease than those without diabetes and with normal blood glucose. Those with hyperglycemia treated with insulin had a lower risk of severe disease than those with diabetes who were not given insulin.

NADPH oxidase is an important source of ROS. Not only is this activated by angiotensin II in SARS-CoV-2 infected cells but also by insulin and advanced glycosylation end products (62). A very similar process is closely linked to the development of atherosclerosis. This mechanism could play a role in the increased risk of diabetic patients developing COVID-19 complications. In addition, patients with cardiovascular disease and those with diabetes have a change in their vascular basement membrane with collagen being replaced by fibronectin (63). Shear stress in these vessels produces marked activation of the nuclear factor kB pathway. All forms of vascular remodeling are associated with increased oxidative stress.

If Covert Mineralocorticoid Receptor Activation by Cortisol Plays a Key Role in the Pathogenesis of Severe Acute Respiratory Syndrome Coronavirus 2 and its Complications, could Inhibition Be a Novel Way to Treat the Disease?

Jeong et al showed that inhibition of the MR by spironolactone blocked the release of WPBs and hence VWF (24). There have been no published studies of spironolactone in patients with the SARS-CoV-2 virus. The drug has been shown to be effective in an acid aspiration model used to produce ARDS in rats (64); spironolactone at a high dose (100 mg/kg) restored lung oxygenation. It is important to understand that if the MR is activated by cortisol in humans or corticosterone in rats, there is at least a 100-fold molar excess of the glucocorticoid as compared to aldosterone. Hence if spironolactone alone is used, high doses will be required. Thus, spironolactone needs to be given together with dexamethasone. Dexamethasone suppresses endogenous cortisol secretion and thus makes the combination much more effective.

If spironolactone is effective in blocking exocytosis of WPBs, could other MR antagonists be equally or more effective? These would include eplerenone and finerenone, a nonsteroidal selective antagonist that is thought to be less likely to cause hyperkalemia. A recent study has looked at this drug in patients with diabetes and chronic kidney disease and found that it resulted in a lower risk of disease progression and fewer cardiovascular events than placebo (65). The incidence of hyperkalemia was higher in the finerenone-treated group (2.3%) than placebo (0.9%) but not markedly so.

One unexpected effect of spironolactone therapy is its action on the ACE2 enzyme. Keidar et al (66) looked at this in patients with heart failure given spironolactone for 1 month. They found that spironolactone 25 mg/day increased macrophage ACE2 activity by 300% and messenger RNA expression by 654%.

Corticosteroids in the Treatment of Coronavirus Disease 2019 Patients

A recent meta-analysis of 7 trials of corticosteroid therapy in COVID-9 patients suggests that corticosteroids are effective and reduce 28-day mortality in critically ill patients (67). There was no evidence that high-dose corticosteroid therapy was of greater benefit than low. Two major trials have shown that dexamethasone is of benefit in patients with ARDS (68, 69). These results were in contrast to a
meta-analysis of 10 previous studies using corticosteroids for influenza pneumonia (majority of patients on methylprednisolone), in which there was evidence of increased mortality (70). A meta-analysis of 14 studies from the Chinese literature of patients treated with corticosteroids in the 2002 to 2003 SARS outbreak found that 12 were inconclusive and 2 showed possible harm (71).

In the Villar et al randomized control trial with dexamethasone in ARDS, the rationale for its use was its increased potency, prolonged duration of action, and weak mineralocorticoid effect (68). The causes of ARDS included pneumonia, sepsis, and aspiration. They found that at 60 days 21% of patients had died in the dexamethasone-treated group and 36% in the control group. The most common adverse effect of high-dose dexamethasone (20 mg intravenously [IV] daily for 5 days and then 10 mg IV daily for 5 days) was hyperglycemia (76%).

The recent RECOVERY trial of dexamethasone in patients infected with SARS-CoV-2 (72) recruited 2104 patients who were treated with dexamethasone (6 mg once daily for up to 10 days given either orally or IV) and 4321 given usual care. Overall 22.9% in the dexamethasone group died within 28 days and 25.7% who had usual care (P < .001). The effect was most striking in those receiving invasive mechanical ventilation (29.3% died in the dexamethasone-treated group vs 41.4% on usual care). There was also significant benefit to those receiving oxygen without ventilation (23.3% vs 26.2%) but not those receiving no respiratory support at random assignment (17.8% vs 14.0%). There were some potentially confounding issues. In the usual care group, 8% were treated with dexamethasone as part of their normal care. In addition, it is difficult to compare the death rate in the mechanically ventilated vs no receipt of oxygen group; the latter was on average 10 years older (69.4 ± 17.3 years vs 59.1 ± 11.4 years). The mechanism of action of dexamethasone was unclear but it was thought that it might affect the immunopathology.

In addition to its effects on the immune system and its anti-inflammatory action, dexamethasone will suppress cortisol by binding to the GR in the hypothalamus, suppressing corticotrophin-releasing hormone and hence adrenocorticotropic and cortisol secretion. If cortisol is activating the MR to stimulate the release of WPBs, then dexamethasone could potentially prevent this. This could explain why treatment of ARDS with corticosteroids such as hydrocortisone and methylprednisolone either produced no benefit or increased mortality (73, 74).

**Conclusion**

This paper details a novel hypothesis that aims to explain why infection with the SARS-Co-V2 virus produces severe complications in defined subgroups of patients. It suggests that the loss of the ACE2 receptor used by the virus to get into specific cells produces high levels of ROS within epithelial and endothelial cells. This causes a loss of the normal mechanism that protects the MR from being stimulated by cortisol. This activation results in the release of ATP from the cells. In the lung it is suggested that this acts on purinergic receptors that surround the neuroepithelial bodies in the alveoli. This activates the afferent purinergic fibers of the vagal nerve and produces the nonproductive cough that is common in COVID-19 patients. Of more serious import is the effect of the virus on endothelial cells. Using the same entry mechanism and producing the same metabolic effects, the virus stimulates ATP release from the cells. This acts on purinergic receptors on the cell and adjacent cells to open calcium channels. The rise in intracellular calcium then results in exocytosis of the WPBs. These contain VWF, angiopoietin-2, P-selectin, and IL-6. The VWF mediates platelet adhesion to the endothelium and the subendothelial matrix. When the VWF is released on the apical side of the cells, it unfurls to produce a spiderweb for platelet adhesion. Angiopoietin-2 produces a marked increase in capillary permeability. VWF and angiopoietin-2 both play a key role in angiogenesis. Studies comparing the pathology of influenza-related ARDS with COVID-19 have shown that the latter has a marked increase in microthrombi and angiogenesis. It is suggested that these relate to the release of the WPBs. Patients with severe COVID-19 ARDS have very high circulating levels of VWF and angiopoietin-2.

This paper examines why certain patients are at greater risk. It explains the age-related loss of NAD, the key cofactor for the enzyme that protects the MR. It details the interaction between the estrogen receptor and the MR that results in the major male predominance. The comorbidities that are common in severe SARS-CoV-2 infection (hypertension, metabolic syndrome, morbid obesity, and diabetes) are all associated with endothelial oxidative stress, which plays a key role in the eventual activation of the MR.

The hypothesis may be part of the explanation as to why BAME individuals are at higher risk of SARS-CoV-2 complications. It also could explain why people with blood group A are at much higher risk and those with blood group O much lower. The levels of VWF are 30% lower in normal individuals with blood group O than those with non-O blood types. The metabolic clearance of VWF is markedly faster in blood group O individuals (mean 10 hours) as compared to non-O (25 hours). It is thought that this is due to differences in the metabolic clearance of the VWF protein, which carries the ABO blood group glycans. If the virus stimulates exocytosis of the WPBs with the release of VWF, it would seem likely that this difference in the rate of metabolic clearance of the VWF could be of major importance.
Most important, if MR activation with WPB release plays a key role in the complications of COVID-19, then there is in vitro evidence that this can be blocked by spironolactone. The hypothesis suggests that the unprotected MR is activated by cortisol and not by aldosterone. If this is so, then suppression of cortisol secretion must be combined with inhibition of the MR. It may well be that the beneficial effect of dexamethasone in COVID-19 patients relates to suppression of cortisol secretion and not just to its anti-inflammatory effect.

If, as this paper suggests, the COVID cough is due to activation of purinergic receptors in the lung following ATP release from the virus-infected type II alveolar cells, this raises the question as to when treatment with dexamethasone and spironolactone should be started. VWF plasma levels are elevated before going into the ICU in 80% of patients, suggesting that the exocytosis of WPBs is occurring at this stage and thus supporting the need for a trial of early treatment.

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This paper is dedicated to the memory of Geoffrey Burnstock, the remarkable pioneer and discoverer of the purinergic system, who died June 3, 2020.

Additional Information
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