COVID's Razor: RAS Imbalance, the Common Denominator Across Disparate, Unexpected Aspects of COVID-19

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Abstract: A modern iteration of Occam's Razor posits that "the simplest explanation is usually correct." Coronavirus Disease 2019 involves widespread organ damage and uneven mortality demographics, deemed unexpected from what was originally thought to be "a straightforward respiratory virus." The simplest explanation is that both the expected and unexpected aspects of COVID-19 share a common mechanism. Silent hypoxia, atypical acute respiratory distress syndrome (ARDS), stroke, olfactory loss, myocarditis, and increased mortality rates in the elderly, in men, in African-Americans, and in patients with obesity, diabetes, and cancer—all bear the fingerprints of the renin-angiotensin system (RAS) imbalance, suggesting that RAS is the common culprit. This article examines what RAS is and how it works, then from that baseline, the article presents the evidence suggesting RAS involvement in the disparate manifestations of COVID-19. Understanding the deeper workings of RAS helps one make sense of severe COVID-19. In addition, recognizing the role of RAS imbalance suggests potential routes to mitigate COVID-19 severity.

Keywords: ACE, ACE2, silent hypoxia, atypical ARDS, stroke, myocarditis

Introduction: Full of Bad Surprises

Medieval English theologian William of Occam is widely credited with the eponymous principle known as Occam's Razor: "Entities should not be multiplied without necessity." Or, in modern terms, "the simplest explanation is usually correct."

In late winter/early spring of 2020, as novel coronavirus case numbers exploded in Europe and parts of the United States, prominent newspapers and online news-media outlets reported with alarm a broad array of Coronavirus Disease 2019 (COVID-19) demographic and clinical outcomes deemed to be surprising and unexpected, even by some of the physicians interviewed. As one Washington Post headline exclaimed: "Once thought a relatively straightforward respiratory virus, COVID-19 is proving to be much more frightening."¹

Outcomes that initially jolted both the press and the medical community include cases of severe COVID-19 in young, apparently healthy adults,² mortality rates among African-Americans and Latinos doubled compared to Caucasians,^{3,4} similarly doubled mortality among men compared to women,⁵ and a tripled death rate among certain cancer patients.⁶ In the UK, government epidemiologic data suggested that Blacks there are four times more likely to die of COVID-19 compared to

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Whites, with UK residents of Indian/Pakistani/Bangladeshi ancestry also showing increased mortality rates.⁷

Journalists warned as COVID-19 patients developed renal failure requiring dialysis,⁸ and obesity was linked to higher mortality.⁹ Subsequent reports revealed occurrences of fatal COVID-19 myocarditis,¹⁰ strokes in young patients,^{1,11,12} “silent hypoxia,”¹³ a mortality rate among ventilated COVID-19 patients approaching 90%,¹⁴ and a Kawasaki-like syndrome in children.^{15,16}

In the early days of the pandemic, the clear association of pre-existing hypertension with more severe COVID-19 outcomes triggered consternation among physicians,¹⁷ as did cases of the virus presenting with seemingly incongruent hyperglycemia,¹⁸ and loss of taste and smell sensation.⁸

The widespread organ involvement and demographic perplexities do at first seem to be a bewildering pathophysiologic maelstrom. But Occam’s Razor posits that the most likely explanation is that a common underlying mechanism unites them all. When viewed through the lens of the renin-angiotensin system (RAS), the COVID-19 disarray slips into crystal clear focus. In addition to its better-known circulatory volume/pressure regulatory role, RAS is also a cellular-level system, present in the tissues of practically every organ of the body, and mediating a broad array of inflammatory, metabolic, osmotic, growth, and repair functions.¹⁹

The hallmarks of RAS imbalance, either pre-existing or COVID-19-mediated, are a common thread interwoven through wide-ranging COVID-19 symptomatology and disparate sub-population outcomes. The commonality of RAS dysregulation does not prove that RAS is the sole mediator of COVID-19 pathophysiology; there may be multiple factors that synergize to worsen COVID-19 severity (Table 1). Yet the underlying presence of RAS imbalance in so many aspects of COVID-19 does suggest that RAS may be the key to understanding and potentially mitigating COVID-19. Only after taking a deeper look at what RAS is and how it works, does severe COVID-19 itself begin to make sense.

The Original Concept of RAS

RAS was first conceptualized as an exclusively endocrine effector system, activated in response to decreased arterial blood pressure, increased sympathetic nervous system tone, or decreased filtered solute delivery within the kidney tubules as, for instance, during hemorrhage or dehydration.^{20–23} RAS was depicted as a linear sequence of enzymatic activations, with substrates circulating in the bloodstream to reach both

their enzymatic activators and their target receptors. Renin, released into circulation by renal juxtaglomerular (JG) cells, cleaves hepatically produced angiotensinogen to generate angiotensin I (AI), an intermediate and inactive compound, which circulates to encounter membrane-bound angiotensin converting enzyme (ACE) on vascular endothelial cells,²⁴ primarily within the pulmonary circulation.²⁵ ACE converts AI to angiotensin II (AII), which transits to the adrenal cortex, triggering the release of aldosterone. Aldosterone subsequently stimulates increasing renal reabsorption of sodium and water, thereby augmenting blood volume.²⁶ This sequence of RAS activations has been dubbed the Renin/ACE/Angiotensin/AT1 axis or, more succinctly, the ACE axis.²⁷

AII also binds to angiotensin type-1 receptors (AT1) on vascular smooth muscle cells to mediate vasoconstriction and increase blood pressure.²⁶ AT1 dispatches a G-protein to activate phospholipase C, which splits the membrane lipid phosphatidyl inositol bisphosphate (PIP2) into two products, inositol tri-phosphate (ITP) and diacylglycerol (DAG), both of which increase intracellular calcium levels.²⁸ Calcium-bound calmodulin next activates myosin light-chain kinase (MLCK), which phosphorylates smooth muscle myosin, enabling actin binding, smooth muscle contraction, and vasoconstriction²⁸ (Figure 1).

The “Evolving” Concept of RAS

Circulating pressure/volume regulation within the vascular system is not the only function of RAS.²⁹ After much debate,^{30,31} there is now widespread agreement that local tissue-level RAS systems administer paracrine and autocrine effects in various structures including adipose tissue, the pancreas, vascular walls, and the heart, kidneys, and brain.^{19,32}

Evidence suggests that locally produced RAS components affect physiology independently of blood pressure.³³ Although this premise remains controversial, the original purpose of some RAS components may not have involved blood pressure regulation and might even pre-date the evolution of blood vessels,³⁴ for example, the modern invertebrate fruit fly, which has an open circulatory system and therefore lacks discrete blood vessels, has an ACE-like enzyme,³⁵ and a renin-like enzyme is found in the leech.²⁶

Invertebrates demonstrate the value of a synergistic proinflammatory and procoagulant injury response system. They possess a sole cell-type having both platelet-like and macrophage-like functions which speeds injury response.³⁶ In open circulatory systems, blood directly contacts cells, so

Table I This Table Lists Patient Subpopulations Reported to Have Worse COVID-19 Prognosis and Relates the Known Aspects of Renin-Angiotensin System (RAS) Imbalance in Those Populations, as Well as Potential Non-RAS Factors That May Also Be Contributing to Worse Prognosis

Factor That Portends Worse COVID-19 Prognosis	Baseline RAS Imbalance	Synergizing Factors
Diabetes	↑ MAPK Activity	Immune impairment ▪ poor glucose control
Obesity	↑ Adipose ACE, AII, AT I	Immune impairment ▪ nutritional deficiencies Ventilatory impairment
African-American	↑ D Allele and AT I polymorphisms ▪ in hypertensives ↑ tissue RAS ▪ in hypertensives	Socioeconomic ▪ nutritional deficiencies ▪ obesity ▪ overcrowded housing
Males	↓ AT2, ACE2, A1–7 vs females	↑ smoking rates vs females Immune differences vs females
Cancer	↑ ACE AT I: ▪ tumors ▪ tumor-associated macrophages ACE DD genotype associated with ↑ cancer risk	Immune impairment ▪ nutritional depletion ▪ chemotherapy
Elderly	↑ tissue AII, ACE, AT I ↓ ACE2	Immune impairment ▪ nutritional deficiencies ▪ ↓ mucociliary clearance ↑ comorbidities ▪ hypertension ▪ cardiovascular disease ▪ diabetes
Smokers	Nicotine ↓ ACE2, MAS, A1–7	Immune impairment ▪ ↓ mucociliary clearance Ventilatory impairment

Notes: ↑ Indicates increased levels; ↓ indicates decreased levels.

pathogens entering via a breach in the exoskeleton would rapidly begin cellular invasion. In the absence of blood vessels, there is no mechanism to restrict blood flow to the injury site, and this would be fatal without prompt coagulation.³⁶ With an open circulatory system, there is no time to lose.

The evolution of vertebrate closed-circulatory systems interposed the vascular wall as a barrier to shield cells from blood-borne invaders.³⁶ Coagulation and inflammation evolved along separate, specialized cell lines,³⁶ but the advantages of integration between coagulation and inflammation during injury response were preserved through cross-talk and mutual co-activation.^{37–41} Vasoconstriction to limit blood flow to injured areas is intertwined with inflammation and coagulation to establish a fully integrated injury-response mechanism. The vascular endothelium became the

pivotal regulatory interface, with the ACE axis mediating all three processes.

The Darker Side of RAS: Endothelial Dysfunction, Hypertrophy, Fibrosis, Cell Death

RAS is a critical survival mechanism, yet when dysregulated, it poses a significant danger. Under normal conditions, the healthy vascular endothelium promotes vasodilation and inhibits coagulation and inflammation.^{42,43} However, when injury occurs, AII, together with proinflammatory cytokines from innate immune cells, transforms endothelium into an “activated” state that promotes vasoconstriction, inflammation, and coagulation.^{37,42,43} Endothelial activation is intended to be temporary; failure to recover a vasodilatory,

nervous system function.⁴⁸ Acting again via MAP Kinase, AT1 upregulates cytokines, such as transforming growth factor (TGF) beta, that drive fibrotic collagen deposition by myofibroblasts.^{48,49} Fibrosis and hypertrophy can at first be reversible repair responses, but when dysregulated they progressively damage vascular smooth muscle, myocardium, and kidneys.^{48,50}

In addition, some cellular damage may be too extensive for recovery, in which case the ACE axis contributes to activating cell death pathways.^{48,51,52} ROS derived from AT1 activation can inhibit anti-apoptotic BCL-2 and activate pro-apoptotic Bax pathways, triggering programmed cell death.⁵² AII can also impair mitochondrial function and increase protein misfolding, causing pathological protein aggregation.⁴⁸ And AII enhances autophagic catabolism of damaged organelles and protein aggregates, necessary for homeostasis, but capable of inciting cell death when dysregulated.⁵¹

Reining in RAS: AT2 and ACE2

It is evident that a system as powerful and far-reaching as RAS must be tightly regulated, to prevent potentially lethal misapplication of vasoconstriction, inflammation, and coagulation.

The AT2 receptor is generally described as a protective arm of RAS, opposing the actions of the AT1 receptor.^{53,54} The functional roles of AT2 have been challenging to tease out, in part because of low adult AT2 expression levels compared to AT1, whose effects may overwhelm the more subtle alterations prompted by AT2.⁵⁴ AT2 has extensive expression during fetal development, but comparatively low-level expression in adults in select sites: heart, kidney, adrenal, brain, uterus, pancreas, retina, endothelium, and vascular smooth muscle.⁵⁵

AII also binds to AT2, and in doing so, it counteracts AT1 effects, promoting instead natriuresis, which can slightly lower blood pressure, as well as stimulating anti-inflammatory, antithrombotic, and antifibrotic effects.⁵⁴ AT2 activates superoxide dismutase (SOD), which neutralizes ROS and defends against oxidative stress created by AT1.⁵² AT2 knockout mice have increased vascular hypertrophy, indicating that AT2 has protective anti-hypertrophy functions,⁵⁵ congruent with AT2 upregulation in the heart during disease states including heart failure, cardiac ischemia, and dilated cardiomyopathy.⁵⁵ Some of the benefits of angiotensin receptor blockers (ARBs), such as reducing vascular and cardiac hypertrophy, appear to be AT2-mediated, by shunting AII away from AT1.⁵⁵

The principal AT2 second messenger pathway involves production of nitric oxide (NO), cyclic GMP (cGMP), and bradykinin, all of which promote vasodilation and oppose inflammation.⁵⁵ Endothelial NO upregulates AT2 which then decreases ACE activity.⁵⁴ cGMP also deactivates RhoA, an AT1 second messenger, thereby antagonizing AT1-mediated vasoconstriction.⁵⁵

ACE has a counterbalancing “younger brother” enzyme known as ACE2.^{56,57} ACE2 converts AII into angiotensin 1–7 (A1–7), so named because it possesses only seven of AII’s original eight amino acids. A1–7 binds to Mas receptors, yielding vasodilatory, anti-inflammatory, and antifibrotic effects.^{27,32,33} In sum, ACE2 depletes AII levels by converting it to A1–7, which binds to Mas receptors, thereby counteracting AT1 actions.^{56–58}

Through a side-pathway, ACE2 can also convert AI into angiotensin 1–9 (A1–9),⁵⁵ which possesses nine of AI’s original ten amino acids. Interestingly, ACE then converts A1–9 into A1–7; therefore, ACE plays a role in producing AII, but also in decreasing AII levels by shunting substrates toward A1–7 instead of AII. Rather than being a linear cascade of enzymatic reactions, RAS is now understood as a web of counterbalancing activations and deactivations^{26,55} (Figure 2).

SARS, SARS2: Runaway RAS

The original SARS coronavirus (SARS-CoV or SARS), which caused severe acute respiratory syndrome, (also called SARS) hitchhiked inside cells using cell-surface ACE2.⁵⁶ The new, closely related coronavirus SARS-CoV-2 or SARS2 (which is responsible for COVID-19) uses the same method.⁵⁹ Once inside the host cell, original SARS virus dramatically reduces cellular expression of ACE2.⁶⁰ SARS2 virus evidently functions the same way.⁶¹ Because ACE2 is critical for regulating the balance between the effects of AII and A1–7,⁶² reduced ACE2 expression leaves the “big brother” enzyme ACE, unchecked, enabling unopposed oxidative, inflammatory and procoagulant effects⁶¹ (Figure 3).

In animal models and human cases of acute respiratory distress syndrome (ARDS), ACE2 levels are severely decreased,⁶³ and ACE/ACE2 balance is lost.⁵⁷ Overactive AII/AT1 contributes to severe oxidative and inflammatory lung injury,⁶³ which in mouse models is blunted by ACE2.⁶⁴ ACE inhibitors (ACEIs) and ARBs lessen pulmonary damage in mice injected with the original SARS surface spike-protein,^{65,66} suggesting that unbalanced ACE axis activity, after ACE2 is downregulated, is the root of original SARS lung pathophysiology.

Figure 3 ACE, ACE2 expression, action in alveolar units. Pulmonary vasculature has the highest levels of ACE expression in the body. In contrast, ACE2 expression is more restricted in the lungs, largely to type II pneumocytes,⁶¹ although there is evidence of some expression in pulmonary capillary endothelium.²⁴⁰ ACE2 deactivates AII, by converting it to A1-7, thereby blunting the pro-inflammatory, pro-fibrotic effects of the ACE axis. In COVID-19, novel coronavirus SARS-CoV-2 can enter type II pneumocytes utilizing ACE2 and then downregulate ACE2 expression,⁶¹ leaving the lungs vulnerable to damaging, unbalanced proinflammatory effects of ACE/AII.⁶¹ Type II pneumocytes have multiple protective functions, including producing surfactant, and serving as stem cells to replenish damaged Type I pneumocytes (which function in gas exchange).⁶¹ Viral impairment of Type II pneumocytes, coupled with AII inflammatory damage to Type I pneumocytes, would thus severely damage multiple aspects of alveolar function in COVID-19, including oxygen exchange and capacity for repair. Figure property of the authors.

Abbreviations: ACE, Angiotensin Converting Enzyme; ACE2, Angiotensin Converting Enzyme 2; AI, Angiotensin I; AII, Angiotensin II; A1-7, Angiotensin 1-7; I, Type I pneumocytes; II, Type II pneumocytes.

routes. First, AII overactivation could drive infected glomus cells into programmed cell death. This would be consistent with experimental AII/AT1 apoptosis induction in rat and human alveolar epithelial cells.^{73–75} Alternatively, glomus failure could be akin to cellular dysfunction in heart failure, in which excessive AII triggers cell volume overload and impairment of cardiac electrical function.⁷⁶ Although AII increases cell volume, A1-7 decreases it.³³ Thus, with loss

of both ACE2 and A1-7, AII overactivity would be expected to volume overload glomus cells, impairing depolarization, and blocking neurotransmitter release. Either scenario, or both acting synergistically, would result in failure of hypoxic signaling, with an absent dyspnea response despite severe hypoxemia in COVID-19 patients.

Incidentally, those same two scenarios could also be at work in loss of olfaction and taste, both of these neural

Figure 4 Cellular mechanism of glomus cell hypoxic signaling. Glomus cells, located within the carotid body, are neural crest-derived, and they exhibit voltage-dependent neurotransmitter release upon detection of hypoxemia.^{69,70} Glomus cells detect hypoxemia by an as-yet undefined sensor, which is thought to close K^+ channels, halting K^+ exit and thereby depolarizing the Glomus cell.^{69,70,241,242} Depolarization leads to opening of voltage-gated Ca^{2+} channels and neurotransmitter release, which triggers action potential firing in nearby cranial nerve IX.^{69,70,241,242} Figure property of the authors.

Abbreviations: AP, action potential; CNIX, cranial nerve IX; NTr, neurotransmitter; NTS, nucleus tractus solitarius; SVC, superior vena cava; PA pulmonary artery; PaO_2 , arterial partial pressure of oxygen.

structures requiring depolarization and neurotransmitter release to mediate their sensory functions. Both express tissue RAS components.^{77,78}

“Atypical” ARDS: RAS “Mismatched”

But why are COVID-19 patients so severely hypoxemic in the first place? Critical care anesthesiologists in the thick of the COVID-19 crisis in Italy suggested that severe COVID-19 patients may not have classical ARDS.⁷⁹ Unlike the situation in ARDS, lung compliance is preserved in COVID-19. Instead, COVID-19 patients seemingly displayed catastrophic loss of hypoxic pulmonary vasoconstriction (HPV), with resulting ventilation-perfusion (V/Q) mismatch hypoxemia.⁷⁹

In ARDS, lung compliance is poor because of decreased alveolar elasticity from noncardiogenic pulmonary edema.^{80,81} This decreased alveolar elasticity impairs gas entry into

alveoli, lowering the alveolar partial pressure (PAO_2), the top end of the gradient which drives the transfer of oxygen into pulmonary blood. Oxygenation in ARDS patients often improves with ventilation using low tidal volumes and high positive end-expiratory pressure (PEEP) which increases PAO_2 .^{80,81} But severe COVID-19 patients have not shown a similar benefit with this ventilation strategy.⁸²

Even under normal physiologic conditions, PAO_2 is not equal in all alveoli throughout the lungs.⁸³ Because of postural differences in fluid hydrostatic pressures across the lung fields, alveolar expansion is not uniform and some alveoli inevitably have higher PAO_2 than others. HPV is a protective physiologic mechanism that optimizes arterial oxygenation by regionally vasoconstricting within the pulmonary vascular bed, thereby diverting pulmonary blood flow away from alveoli with lower PAO_2 , and vasodilating in other regions to increase blood flow to alveoli with higher PAO_2 .⁸⁴ (Figure 5) Optimal V/Q

matching yields a PaO_2 of approximately 100 mm Hg, when breathing air at atmospheric pressure. However, if the HPV response is impaired, blood flows through the lungs in an unregulated fashion, and poorly oxygenated blood with low PaO_2 , enters the systemic circulation⁸⁵ (Figure 5).

RAS plays a role in HPV that is still not precisely defined but may involve hypoxic activation of NADPH oxidase, generating ROS that close potassium channels, depolarizing pulmonary vascular smooth muscle, which in turn opens voltage-gated L-type calcium channels, activating the smooth muscle contractile apparatus.^{84,86} Mice lacking cytosolic NADPH oxidase had a 25% decrease in initial phase HPV.⁸⁷ AII has been shown to activate pulmonary vasoconstriction in hypoxic humans,⁸⁸ and ACEIs and ARBs have been shown to inhibit HPV.^{89,90} Recombinant ACE2 blunts pulmonary vasoconstriction in hypoxic pigs.⁹¹ Therefore, the loss of ACE2 due to SARS2 coronavirus together with the resultant ACE imbalance⁶¹ would be expected to dysregulate HPV and lead to hypoxemia.

Extreme Mortality Rates in Ventilated COVID Patients: The Final Straw

Mortality rates in ARDS hover around 45%.⁷⁵ By contrast, a COVID-19 case series of 5700 patients in and around New York City reported mortality rates of 88.1% in ventilated patients, essentially doubling the ARDS rate,⁹² and providing further support that COVID-19 is not traditional ARDS.⁸²

Lung tissue locally expresses almost all components of RAS.⁷⁵ ACE is heavily expressed across the entire alveolar capillary network, and the lungs are the dominant site of circulating AII production.⁷⁵ In contrast, ACE's anti-inflammatory counterpart, ACE2 is more restricted within the lungs, principally to alveolar type II pneumocytes⁷⁵ (Figure 3). In addition, in healthy adults, pulmonary expression of anti-inflammatory AT2 is low.⁷⁵ With such broad expression of the ACE axis, and comparatively restricted expression of the protective arms of RAS, the lung is poised for more severe ACE imbalance in the event of ACE2 downregulation by the SARS2 virus.

Without ACE2, ACE actions would be essentially unchecked,⁶¹ with no means to achieve appropriate V/Q matching, amidst significant inflammatory destruction of lung tissue.⁷⁵ In animal models, mechanical ventilation has been shown to upregulate ACE, promoting activation of

AII.^{93–95} It may be the case for many severe COVID-19 patients that initiation of mechanical ventilation, and consequent further ACE axis upregulation, becomes the final straw, especially when combined with anesthetic/sedating drugs that may further impair HPV.

The Kidneys and Heart in COVID: Sword versus Shield

Emerging data show a mixed picture of COVID-19 effects on the heart and kidneys. Preexisting cardiovascular risk factors are definitively associated with increased COVID-19 severity. In an Italian retrospective case series, 49% of 1591 patients admitted to the ICU for COVID-19 had preexisting hypertension, and 21% had cardiovascular disease.⁹⁶ Among a retrospective cohort of 191 COVID-19 cases hospitalized in Wuhan, China, 30% had hypertension, and 8% had coronary heart disease.⁹⁷ Hypertension and atherosclerosis have well-established associations with ACE axis dysregulation.^{98–102} Moreover, ACE2 levels in the heart are reported to be diminished in hypertension and in diabetes-associated cardiovascular disease.¹⁰³ Thus, it makes sense that these comorbidities would be heavily represented among more severe COVID-19 presentations. Studies suggest that myocardial injury worsens COVID-19 prognosis,¹⁰⁴ nevertheless, reported rates of cardiac as well as renal injury are lower than rates of pulmonary damage, suggesting that the heart and kidneys may possess some protection.

For example, the Wuhan cohort cited that among fatal cases, 93% had an ARDS diagnosis, but only 59% had a myocardial infarction (MI), and 50% had acute kidney injury (AKI) prior to death.⁹⁷ Among survivors, 7% had ARDS while only 1% had MI or AKI. Another study reported myocardial injury in 7% to 17% of hospitalized COVID-19 patients, and 22% to 31% of ICU cases.¹⁰⁵ In contrast, the Italian ICU cohort reported 88% requiring intubation and mechanical ventilation, indicative of dire pulmonary compromise.⁹⁶

Kidneys locally express all ACE axis components.^{29,106} Additionally, the renal glomeruli filter most circulating RAS proteins, which are then reabsorbed by the proximal tubule.¹⁰⁶ Combined resorption and local production result in renal AII levels 100 to 1000 times higher than in plasma.^{29,106} Dysregulated tissue RAS, as occurs in hypertension, results in significant renal inflammatory damage, with progressive destruction of nephrons amid RAS-mediated remodeling and fibrosis.⁴⁹ Similarly, the heart has

Figure 5 Hypoxic pulmonary vasoconstriction (HPV) and ventilation/perfusion (VQ) matching. Alveolar partial pressure of oxygen (PAO_2) is the top end of an oxygen gradient, driving transfer of oxygen from the alveolar air spaces into the pulmonary blood. Thick red arrows designate a sizable gradient driving oxygen transfer. Thin blue arrows designate smaller oxygen gradients, with less potent driving force for oxygen transfer between alveolar air spaces and pulmonary blood. Functional HPV regionally vasoconstricts (designated in the figure by small blood vessel tube) within the lungs, to divert pulmonary blood flow away from poorly oxygenated alveoli, which would have a more limited ability to transfer oxygen into the pulmonary blood. Such appropriate VQ matching ensures that adequately oxygenated blood, with normal arterial partial pressure of oxygen (PaO_2), is returned to the systemic circulation. When HPV fails, pulmonary flow is instead sent in excess to poorly oxygenated alveoli, such that larger volumes of poorly oxygenated blood, with low PaO_2 , are returned to the heart, to then enter the systemic circulation. Figure property of the authors.

significant local RAS, which mediates inflammatory remodeling in conditions such as hypertension and infarction.¹⁰⁷

However, the counterbalancing anti-inflammatory AT2 and ACE2 arms of RAS also have an important role in the heart and kidneys. ACE2 is highly expressed in the heart,⁶² in particular in the coronary arteries,³² and in endothelial cells within the kidneys,³² achieving significant production of A1–7.²⁷ Therefore, with higher baseline ACE2 levels, the heart and kidney may have a degree of shielding against the effects of ACE2 loss perpetrated by the SARS2 virus. In addition, cardiac and renal tissue RAS often bypass ACE, instead using chymase, trypsin, kallikrein, and cathepsins.³² Thus, local RAS function in these organs could potentially be less imbalanced by the loss of ACE2 due to the SARS2 virus.

Additionally, the coronary arteries⁵² and kidneys express comparatively higher levels of AT2 during adult life.⁵⁵ The heart also has a demonstrated capacity to upregulate AT2 during pathologic states such as ischemia.⁵⁵ Therefore, the effects of COVID-19-induced imbalance of RAS may be blunted somewhat by AII binding to AT2.

There are also reports of COVID-19-triggered myocarditis.¹⁰⁸ In one study, myocarditis was deemed likely

causative in 7% of COVID-19 deaths.¹⁰⁵ AT1 has been shown to promote myocarditis in experimental models, secondary to actions on T-cell function.¹⁰⁹ T-cells have an intrinsic RAS that regulates their proliferation and migration.¹⁰⁹ AT1 fosters cytoskeletal changes that promote T-cell migration and trigger T-cell production of cytokines and chemokines, thereby increasing T-cell recruitment to regions of active inflammation.¹⁰⁹ By inhibiting AT1, ARBs decrease experimental myocarditis.¹¹⁰ RAS-driven T-cell-mediated effects in the heart, coupled with T-cell-mediated skin effects, which are also well described,^{111,112} could potentially explain the pediatric Kawasaki-like condition linked to SARS2.¹⁶

Besides ischemic and inflammatory tissue destruction, another aspect of cardiac pathology in COVID-19 is the development of arrhythmias and sudden cardiac death.^{113,114} In addition to the arrhythmia-promoting effects of hypoxemia, arrhythmias in COVID-19 patients bear hallmarks of RAS dysregulation. Cardiac remodeling by the ACE axis is a known driver of arrhythmia events. In the atria, AII promotes fibrosis that facilitates reentry,¹¹⁵ and ACEIs and ARBs do provide some protection against the recurrence of atrial fibrillation after cardioversion in

patients with left ventricular dysfunction.⁴⁸ AII promotes ventricular arrhythmias by prolonging QRS duration, and by promoting reentry through both fibrosis and slowed ventricular conductance.⁴⁸ These factors are likely playing out in COVID-19 pathology, perhaps synergizing with potential arrhythmia-promoting effects of experimental drug treatments, including hydroxychloroquine,¹¹⁴ which was studied earlier in the pandemic but the use of which has now been curtailed.

Hypercoagulability and Strokes in COVID: Sabotage by RAS

During the initial United States COVID-19 case escalation, stroke was reported in patients without traditional stroke risk factors.^{12,116} Although unanticipated in the context of a viral respiratory tract infection, stroke risk is known to be elevated in conditions of RAS overactivation such as diabetes and hypertension.^{117,118} RAS blockade with ACEIs and ARBs has been shown to reduce stroke rates in high-risk populations.⁵⁵ With the downregulation of ACE2, the coagulation-promoting effects of the ACE axis would drive arterial thrombosis.

Healthy vascular endothelium promotes vasodilation and inhibits coagulation and inflammation,^{42,43} through expression of natural anticoagulants, including tissue factor pathway inhibitor (TFPI), thrombomodulin (TM), tissue plasminogen activator (tPA), and the anti-inflammatory vasodilator NO.⁴² Produced in endothelial cells by nitric oxide synthase (NOS),⁴³ NO diffuses to neighboring vascular smooth muscle to activate guanylate cyclase/cyclic GMP/protein kinase G-mediated vasodilation⁴³ (Figure 1). NO also has myriad anti-inflammatory and anti-coagulant functions, including inhibiting both platelet aggregation and monocyte adhesion.¹¹⁹

During injury response, AII inhibits endothelium-mediated vasodilation and anti-coagulation.⁴² AT1 activates NADPH oxidase, generating ROS such as superoxide anion $O_2^{\cdot-}$ (Figure 1) $O_2^{\cdot-}$ quenches existing NO, in the process creating ONOO⁻, a very potent oxidant which in turn disables NOS so that it cannot manufacture new NO; hence, NO levels are severely depleted⁴³ (Figure 1).

AT1 also promotes increased expression of adhesion molecules such as VCAM-1 and E-Selectin that recruit inflammatory cells to the injury site, and inflammation synergistically promotes coagulation.^{119,120} AII prompts endothelial cells to promote coagulation, by new expression of procoagulants—tissue factor (TF) to initiate the blood

clotting cascade,^{121,122} von Willebrand factor (vWF) to enhance platelet adhesion,¹²³ and plasminogen activator inhibitor (PAI)-1 to blunt fibrinolytic degradation of blood clots.^{37,42,43,119} Activation of these processes would then be the drivers of stroke in COVID-19-induced RAS imbalance, with overactive AII sabotaging the anti-coagulant actions of otherwise healthy endothelium.

Higher COVID Mortality in Obesity and Diabetes: The Map Kinase Connection

Obesity and diabetes are reported to worsen COVID-19 severity and mortality. In the case series of 5700 hospitalized COVID-19 patients, 33.8% had diabetes as a preexisting comorbidity, and 41.7% were obese.⁹² In a meta-analysis of 30 published studies that assessed the outcomes among more than 6400 patients, diabetes was found to more than double both the risk of severe COVID-19 disease and the risk of mortality.¹²⁴ Diabetes more than quadrupled the risk of severe ARDS-like pulmonary outcomes in COVID-19.¹²⁴ A study in New York City reported that patients with body mass index (BMI) equal to or above 35 had more than triple the risk of in-hospital mortality from COVID-19, compared to leaner patients [OR: 3.78; 95% CI 1.45–9.83, $p=0.006$].¹²⁵

Multiple factors may be at work in these outcomes. Immune function has been shown to be impaired by nutritional deficiencies in obesity,^{126–128} and by poor glycemic control in diabetes.^{129–131} Obesity-compromised lung mechanics have been well described.^{132–134} However, both obesity and diabetes also bear the hallmarks of RAS dysregulation at baseline. In the developed world, nearly 90% of diabetes cases are the result of obesity,¹³⁵ and the two conditions are mechanistically intertwined via RAS overactivation,^{119,135–138} which primes for worse COVID-19 outcomes.

Adipocytes locally produce a full set of RAS components, including angiotensinogen, ACE, AII, AT1.¹³⁹ In obesity, this adipose ACE axis is highly upregulated,¹⁴⁰ but with diminished counterbalancing ACE2,⁶¹ this ACE imbalance negatively impacts insulin function.¹⁴⁰

The insulin receptor has two principal second messenger cascades.¹³⁵ The first, phosphatidylinositol-3 kinase (PI3K) promotes cell membrane localization of GLUT transporters that facilitate glucose uptake.¹³⁹ PI3K also activates NOS, which manufactures NO to mediate the anti-inflammatory, anti-coagulant effects of insulin.¹³⁹

The second cascade, utilizing MAP Kinase, is responsible for the growth-factor-like actions of insulin, including fibrosis, vascular smooth muscle proliferation, and cardiac myocyte hypertrophy.^{136,139}

Under normal circumstances, PI3K-produced NO inhibits the MAP Kinase arm.¹³⁹ In RAS upregulation, however, superoxide produced by AT1 eliminates NO, thus short-circuiting the PI3K function of the insulin receptor, so that glucose uptake fails, hence the connection between obesity and diabetes.¹⁴¹ This mechanism would also explain the correlation between COVID-19 and hyperglycemia. With ACE axis overactivity, insulin receptor function is shunted to MAP Kinase,¹³⁹ and as a result of this alteration, insulin receptors and AT1 receptors—which also use MAP Kinase as a second messenger—synergize to promote inflammatory and hypertrophic damage to the cardiovascular system which is a hallmark of diabetes. Blocking RAS overactivation with ACEIs or ARBs helps restore normal insulin receptor function, improves insulin-mediated glucose uptake, and mitigates vascular damage.¹³⁹

Higher COVID Mortality Among African-Americans: Visible Meets Invisible

As data accumulate showing elevated COVID-19 mortality rates in African-Americans, attention has focused on socioeconomic inequalities, including limited access to nutritious food, overcrowded housing conditions, and consequent health-related comorbidities, such as obesity, diabetes, and hypertension. These clearly evident factors undoubtedly play important roles, but less visible factors may also be at work. There is evidence of RAS dysregulation that drives hypertension disparities in African-Americans. This could also be contributing to the increased severity of COVID-19 among this population.

It has been firmly established that African-Americans have higher prevalence, earlier onset, and more severe complications of hypertension than Caucasians.¹⁴² Recent data from the US Department of Health and Human Services Office of Minority Health attest that African-Americans currently have higher rates of obesity than Caucasians.¹⁴³ Obesity greater than 20% above ideal body weight doubles-to-triples hypertension risk,¹⁴⁴ and obesity significantly increases ACE activity.¹⁴⁵ Yet obesity alone cannot explain the unequal prevalence of hypertension. According to National Health and Nutrition Examination Survey (NHANES) data from 1988 to 1994, African-American and

Caucasian males had almost identical obesity rates during that time frame, but African-Americans had 46% higher rates of hypertension.¹⁴⁶

Research has identified critical physiologic distinctions among many African-Americans that influence response to hypertension therapies. Most African-American hypertensives have low-renin hypertension secondary to either a mutation of aldosterone synthetase (and consequent aldosterone overproduction) or of the epithelial sodium (eNaC) channels in the kidney, both of which lead to excessive renal sodium resorption.¹⁴⁷ Although sodium retention inhibits renin release into the circulation, reduced activation of the circulating RAS does not prevent hypertension. However, in mouse experiments, renin gene deletion solely within the kidneys did confer protection against developing AII-mediated hypertension, suggesting that tissue RAS is more critical than circulating RAS for blood pressure regulation—and for the development of hypertensive nephropathy.¹⁰⁶ In chronic kidney disease, renal tissue RAS was found to be elevated, independent of circulating RAS levels.¹⁴⁶ African-American hypertensives have increased incidence of RAS-mediated organ damage, congruent with overactive tissue RAS despite low circulating renin.¹⁴² In keeping with this, African-Americans taking ACEIs and ARBs have comparatively poor blood pressure decrease, yet have significant protection against hypertensive end-organ damage.¹⁴⁶

Several gene polymorphisms have been discovered to increase RAS activity. For example, increased hypertension prevalence among African-Americans has been linked to the -535T polymorphism of AT1.¹⁴⁴ Best studied, however, is the ACE gene I/D polymorphism, distinguished by insertion (I) or deletion (D) of a nearly 300 base pair DNA segment.³⁵ The DD genotype doubles ACE activity, in both circulation and tissue, compared to the II homozygous genotype; heterozygous ACE ID is intermediate between the two.³⁵ In a population-based study, the ACE D polymorphism was slightly more common with African ancestry than with European or Japanese ancestry.¹⁴⁸ African-American hypertensives in particular have been shown to have higher prevalence of the D allele.^{149,150} It is important to stress, however, that although those of African descent may be more likely to carry the D allele, D is found among many ethnicities. For instance, it was found to occur at increased frequency among Caucasian Australians who suffered myocardial infarction compared to the general healthy population.¹⁵¹

When ACE D polymorphism occurs, it has often been linked to adverse medical conditions, including increased susceptibility to ARDS.⁷⁵ In children, the D allele was associated with worse outcomes in focal glomerulosclerosis¹⁵² and single ventricle congenital heart disease.¹⁵³ ACE D allele correlates with ventricular hypertrophy in endurance athletes.³⁵ Additionally, the Rotterdam Study showed an association of D allele with early mortality.³⁵

Despite current potentially negative consequences, ethnobiological studies have hypothesized an evolutionary survival benefit during ancient times for RAS upregulation polymorphisms such as ACE D allele. In tropical areas with sodium scarcity, these polymorphisms promoted sodium and water retention, and maintenance of blood pressure.^{109,154} However, because of the current abundance of dietary sodium, modern descendants face increased damaging consequences from those same polymorphisms.^{109,154}

Other ethnicities with reportedly increased COVID-19 mortality, including Latinos and South Asians, are less well represented in the hypertension literature than African-Americans. There is, nonetheless, some evidence for RAS upregulation. Low-renin hypertension is common in Caribbean Hispanics.¹⁴⁶ The ACE-upregulating D allele has also been found with increased frequency among South Indians with hypertension.¹⁵⁵ These observations suggest again that RAS upregulation portends the worse COVID-19 outcomes seen in some populations.

Gender Disparity in COVID Severity: The Estrogen Advantage

In a retrospective case series of 1591 consecutive patients requiring ICU level care for COVID-19 in Milan, Italy, 82% were male.⁹⁶ Researchers from Beijing retrospectively analyzed mortality data from the earliest 500-plus reported cases of COVID-19 in Wuhan, China.¹⁵⁶ They reported that, while men and women had similar COVID-19 prevalence, men were nearly 2.5 times more likely to die of COVID-19.¹⁵⁶ Simultaneous retrospective re-analysis of mortality data collected in 2003 showed that the original SARS coronavirus also skewed toward higher mortality in men,¹⁵⁶ in keeping with prior published reports.¹⁵⁷

Although gender-specific differences in immune response¹⁵⁸ may play a role in unequal outcomes of both SARS and COVID-19, there are definitive differences between the genders in the RAS system and, in keeping with Occam's Razor, these differences likely contribute to worse male outcomes.

Sex hormones regulate the expression and function of RAS components.¹⁵⁹ Males generally have higher levels of RAS than premenopausal females,¹⁶⁰ perhaps explaining why male hypertensive rats show a greater blood pressure decrease with ACEIs.¹⁶¹ Estrogen downregulates the expression of the AT1 gene^{162,163} and suppresses both ROS production in vascular smooth muscle and the enzymatic activity of ACE.¹⁵⁹ Estrogen also promotes the production of NO, the counterweight to AII in the endothelium.¹⁵⁹

Estrogen also positively impacts the protective arms of RAS, including increasing ACE2 levels in rats.¹⁶⁰ Female mice display higher renal AT2 expression than male counterparts, an effect that dissipates if ovaries are removed,⁵⁵ and estrogen upregulates AT2 levels in the mouse kidney.⁵⁵ Both the AT2 and ACE2 genes are found on the X chromosome,^{164,165} so it is reasonable to conclude that women would regulate and express these genes differently than men. In keeping with this, women have been reported to have higher levels of protective A1–7 than men, both in plasma¹⁶⁶ and in urine,¹⁶⁷ suggesting higher levels of ACE2 activity both in the circulation and at the renal tissue level. These factors likely synergize to confer comparative COVID-19 protection in females, especially pre-menopausally.

Very High COVID Mortality in Cancer Patients: Collaterals to Invasion

When assessing the elevated death rates among cancer patients who develop COVID-19,¹⁶⁸ immune impairment evoked by therapies and nutritional depletion cannot be ignored as contributory factors. However, RAS dysregulation has also been shown to be associated with cancer.^{169,170}

Increased ACE and AT1 expression have been reported in patients with metastatic ovarian cancer and prostate cancer, compared to those with benign neoplasms.¹⁷¹ AT1 is also increased in squamous cell carcinoma, and in 20% of estrogen-receptor-positive breast cancers.¹⁷⁰

The cellular growth-promoting aspects of RAS are brought into play by tumor cells to facilitate tumor expansion and invasion. AII promotes differentiation of tumor-associated macrophages (TAMs) from immature progenitors.¹⁷⁰ TAMs are abundant in the stroma surrounding the tumor, and they release factors that modulate tumor progression and metastatic migration.¹⁷⁰ TAMs also inhibit the body's anti-tumor immune mechanisms.¹⁷⁰ TAMs express AT1, whose effect profile is proangiogenic, augmenting levels

of vascular endothelial growth factor (VEGF), and VEGF type 2 receptor.¹⁷¹ AT1 facilitates epithelial-to-mesenchymal transition, which is crucial to metastatic progression.¹⁷⁰

Knockout mice lacking the murine version of AT1 have decreased tumor growth compared to normal counterparts. ARBs blunt tumor size in animal models,¹⁷¹ and they also decrease VEGF levels, metastatic burden, and tumor vascularization.¹⁷⁰ Similarly, ACEIs have been reported to inhibit tumor growth, angiogenesis, and metastasis.¹⁷⁰

Among gastric cancer patients taking either ACEIs or ARBs, prolonged survival has been noted.¹⁶⁹ Also, five-year recurrence-free survival was significantly higher among patients with non-invasive bladder cancer who were receiving RAS-blocking drugs.¹⁶⁹ A small retrospective study of advanced non-small-cell lung cancer estimated a 3-month prolongation in survival with RAS blockers.¹⁶⁹

Human studies of RAS blockade to limit cancer progression may be confounded by the invisible effects of RAS polymorphisms, which are only rarely assessed in trial subjects.¹⁶⁹ In the prospective Rotterdam Study, however, ACE genotyping was performed and revealed that the high ACE-activity DD genotype had the most significant benefit in cancer risk reduction with RAS blockade.¹⁶⁹ The ACE DD genotype has been associated with a higher risk of cancer, while the ACE II homozygote pools with a lower risk.^{169,170} These findings are congruent with RAS overactivation portending poorer COVID-19 prognosis.

Very High COVID Mortality in the Elderly: Unprotected from ACE

From the outset of the COVID-19 epidemic, elderly patients have accounted heavily among fatalities. A retrospective comparison of COVID-19 data from Italy and China revealed a large increase in case fatality rates with increasing age in both population groups.¹⁷² The Italian case fatality rate was 1% in patients aged 50–59, 3.5% in those aged 60–69, 12.8% in those aged 70–79, and 20.2% in persons above 80 years of age.¹⁷² Among the Chinese patients, case fatality rate was 1.3% in those 50–59, 3.6% in the 60–69 age group, 8% in those 70–79, and 14.8% above age 80.¹⁷³

Elderly people often have nutritional deficiencies that can impair immune function.¹⁷⁴ Increasing age is also associated with impairment of mucociliary clearance, which contributes to increased susceptibility to respiratory infections in the elderly,¹⁷⁵ because mucociliary clearance

is the primary barrier defense mechanism of the lungs.¹⁷⁶ The elderly account for a higher percentage of patients having the various co-morbidities associated with poor COVID-19 prognosis, such as hypertension, diabetes, cardiovascular disease, and cancer. However, even healthy aging also leads to RAS imbalance, with elevated tissue RAS components, and lower levels of counterbalancing protective arms of RAS.⁵⁸

It is well described that circulating AII levels typically decline in the elderly.^{55,177} Importantly, however, tissue levels of AII, ACE, AT1, and angiotensinogen increase with aging in the heart, kidney, and vasculature.^{55,177} Data from African-American hypertensives, including those treated with ACEIs and ARBs, revealed that tissue RAS has a more significant deleterious effect on organ function than circulating RAS.^{142,146} It is reasonable to expect that tissue RAS levels, rather than circulating levels, would also be the more important variable in elderly individuals, coinciding with the higher incidence of the RAS dysregulation-associated comorbidities in aged adults, such as hypertension and diabetes, which portend worse COVID-19 outcomes.

At the same time, there is evidence of lower levels of the protective counterbalancing arms of RAS,¹⁷⁸ leaving the elderly comparatively more vulnerable to the damaging effects of the ACE axis. Animal experiments showed that the aortic vasodilatory response to A1–7 is lost in elderly female rats, but restored by exogenous estrogen replacement.¹⁷⁸ In rat lungs of both genders, ACE2 levels have been found to decrease with aging^{61,179,180} This loss of ACE2 was more pronounced in elderly male rats than in similarly aged females,^{61,179,180} which is in keeping with the worse prognosis reported for men compared to women with COVID-19.

It has been posited that patients with baseline ACE2 deficiency would be particularly vulnerable to severe outcomes because of unchecked ACE activity with SARS2 virus downregulating ACE2 expression.⁶¹ In elderly COVID-19 patients, the higher basal tissue ACE axis components and lower counterweight ACE2 levels even at the start of infection would disadvantage these patients for poor outcome.

Unexpected Severity in Young, Otherwise Healthy: Through the Smokescreen

The COVID-19 outbreak in the west brought unexpectedly severe cases affecting younger adults. The explanation for

this situation remains undefined and is probably multifactorial. Lifestyle factors may impair immune defense against COVID-19 in younger people. For instance, dehydration which may occur during strenuous exercise, impairs mucociliary clearance,¹⁸¹ as does aerobic exercise in polluted urban environments.¹⁸² Rising obesity rates may play a role, as well as genetic factors, including high RAS activity polymorphisms in the general population.^{183–185} Acquired, non-genetic RAS dysregulation may also be playing a role here, due to the resurgence of inhaled nicotine and its effects upon RAS expression.

Data reported on 191 patients with confirmed COVID-19 from two hospitals in China showed that the odds ratio of dying among current smokers, compared to nonsmokers, was 2.23 (95% CI: 0.65).⁹⁷ The impact of e-cigarettes (“vaping”) has not yet been reported in the context of COVID-19. But experimental evidence has been accumulating, showing that e-cigarettes may be even more deleterious than traditional cigarettes, so it is reasonable to suppose that vaping will also influence COVID-19 outcomes.

Smoking is known to inhibit mucociliary clearance,¹⁸⁶ an essential defense feature against airway pathogens. Recent experimental evidence suggests that high nicotine levels in vaping may be even more harmful to this critical defense against inhaled pathogens.^{181,187} In a sheep model, high-nicotine-containing e-cigarettes caused a 50% reduction in experimentally modelled mucociliary clearance.¹⁸⁸

Moreover, nicotine also adversely impacts RAS levels, which would be deleterious during COVID-19 infection. Nicotine has been shown to decrease levels of Mas receptor and A1–7, while increasing ACE, AII, and AT1.¹⁸⁹ Additionally, nicotine decreased both ACE2 and AT2 expression in several cell types, including cardiac fibroblasts.¹⁹⁰

The rising use of e-cigarette products among young Americans has alarmed the medical community and public health officials. CDC data showed that 3.7% of US adults—more than 9 million people—used e-cigarettes in 2014.¹⁹¹ A 2018 Gallup poll reported that vaping had increased to more than 9% of US adults; in addition, 20% of respondents reported smoking traditional cigarettes.¹⁹² The National Youth Tobacco Survey revealed that 5 million teenagers vaped in 2019, up from 3.6 million in 2018.¹⁹³ This constitutes a sizable portion of the younger US population who would be at increased risk during the current pandemic, given the evidence that baseline ACE2 deficiency predisposes to poorer COVID-19 outcomes.⁶¹

Conclusion: Taking Aim at RAS

With COVID-19 deaths now surpassing 500,000 worldwide, and further increases becoming evident in some areas as economies reopen—let alone the possibility of a second wave of infections surging late in the year—developing a therapeutic means to mitigate the severity of COVID-19 has taken on utmost urgency. With the evidence of ACE axis overactivation at the root of varied organ system pathology in COVID-19, the most obvious recourse to attempt to blunt COVID-19 progression and mortality would seem to be ACEIs and ARBs. These drugs are widely available, inexpensive, and they target the very system that is unbalanced in COVID-19. Yet the use of these drugs in COVID-19 is not clear cut.

Early in the COVID-19 pandemic, concerns were raised that ACEIs and ARBs might predispose to increased COVID-19 severity.¹⁹⁴ In COVID-19, the role of ACE2 appears paradoxical.⁶¹ ACE2 facilitates entry of SARS2 virus into cells, but at the same time, ACE2 expression in alveolar cells protects against experimentally induced lung injury.^{61,64,66} After viral entry into alveolar cells, the spike protein of the SARS-CoV-2 virus downregulates further expression of ACE2,⁶¹ thereby reducing the protective effect of ACE2 on lung tissue.⁶⁰

In animal models, ACEIs and ARBs elevate the expression of ACE2 in the heart.^{195,196} During fetal kidney development, AT1 exerts negative feedback to downregulate ACE2 levels.¹⁹⁷ It has been suggested that ACEIs and ARBs upregulate ACE2 levels in cardiac and diabetic patients,^{179,198} and therefore could potentially accelerate SARS2 entry.^{61,198} Yet these drug classes have shown clear cardiovascular and renal protective effects,^{199,200} which might prove beneficial in blunting COVID-19 organ damage.²⁰¹

In the midst of this “double-edged sword” debate,¹⁹⁴ the European Society of Cardiology and the American College of Cardiology recommended that, without clear clinical evidence, already-prescribed ACEIs and ARBs should not be discontinued. A case series of 1178 patients from Wuhan, China found that ACEIs and ARBs were not associated with increased COVID-19 case severity or mortality.²⁰² An Italian case-control study comparing records of 6272 COVID-19 positive patients to more than 30,000 registered recipients of Lombardy’s Regional Health Service came to the same conclusion.²⁰³ An observational study of Medicare Advantage health records, conducted by Yale University in partnership with United

Health Group Insurance Corporation, announced that ACEIs—but not ARBs—might even be protective against more severe COVID-19 outcomes, since ACEI use correlated with a lower rate of COVID-related hospitalization in persons over 65 years of age in this study.²⁰⁴ Multiple ongoing prospective trials are attempting to assess whether differences in COVID-19 outcomes result from maintaining versus stopping ACEIs and ARBs (eg, study NCT04330300 in the WHO International Clinical Trials Registry Platform). Readers may access the database of international clinical studies at <http://www.WHO.int.ictrp>.

Independent of a potential impact on virus entry into cells, these two drug classes have been shown in human studies and animal models to lower the risk and severity of numerous problems that COVID-19 precipitates. Among their many benefits, ACEIs are lung protective in ARDS,⁷⁵ and ACEIs and ARBs reduce stroke rates.⁵⁵ ARBs reduce cardiovascular oxidative stress, reverse endothelial dysfunction, and decrease inflammatory and oxidative renal damage in patients with diseases associated with RAS dysregulation, such as hypertension and diabetes.^{205,206} ARBs have mitigated the severity of experimental myocarditis¹¹⁰ and have been shown to upregulate AT2 in vascular endothelial cells.⁵² Moreover, AT1 blockade may shunt existing AII to activate AT2, yielding anti-inflammatory effects.^{205,206}

Therefore, ACEIs and ARBs might hold the potential to mitigate COVID-19 organ damage. But clarity may come only once the drugs have been assessed as individual agents, rather than as ACEIs and ARBs *en masse*. Although there are definitive class effects of ACEIs and ARBs, such as blood pressure lowering,²⁰⁷ the drugs themselves each have unique pharmacological characteristics. Evaluating them *en masse* may wash out otherwise important distinctions.

For example, not all ACEIs have equivalent tissue penetration, due to differences in lipophilicity.²⁴ In a rat model, fosinopril had better cardiac entry than captopril, lisinopril, and ramipril.²⁴ Similarly, quinapril had higher tissue penetration and better prevention of left ventricular hypertrophy than enalapril.²⁴ In spontaneously hypertensive rats, moexipril more potently inhibited lung, aortic, and cardiac ACE than enalapril.²⁰⁸ And among ARBs, the unique structure of eprosartan seems to confer high renal affinity.²⁰⁹

In addition, some ACEIs, such as captopril and perindopril, cross the blood brain barrier (BBB); others, such as enalapril and imidapril, do not.¹⁰⁹ This distinction could

potentially hold importance, given that neurons express ACE2,²¹⁰ and some severe COVID-19 patients have manifested CNS dysfunction, including encephalitis and a neurocognitive, dementia-like syndrome.²¹¹ Parenthetically, these reports are consistent with accumulating evidence that RAS is also involved in the amyloid pathology of Alzheimer's dementia.²¹²

Among the ARBs, only telmisartan has been shown to cross the BBB,¹⁸⁵ thereby reinforcing the importance of carefully evaluating ARBs individually, rather than as whole drug classes, in COVID-19 studies.

There may be potential pitfalls deploying ACEIs and ARBs against COVID-19. ARBs have two broad categories of action: irbesartan, candesartan, and telmisartan are noncompetitive inhibitors of AT1, while losartan, valsartan, and eprosartan are competitive blockers.^{209,213} High concentrations of AII have been shown to overcome competitive blockade *in vitro*,²¹³ possibly negatively impacting the therapeutic potential of competitive AT1 blockers in COVID-19.

Additionally, many ACEIs are prodrugs, dependent on hepatic metabolism for activation, but there is evidence that, in some cases, the prodrugs may inhibit the function of the activated counterpart.²⁰⁷ Lisinopril, by contrast to other class members, is orally formulated as the active drug.²¹⁴ In the ARB class, losartan and candesartan are prodrugs, but activated candesartan has 10 times higher affinity for AT1 than activated losartan.²¹³ Such pharmacological differences may impact the outcome of these therapies in COVID-19.

At least some ACEIs are dialyzable, but ARBs are not,²⁰⁹ and this may introduce additional difficulties using these agents in COVID-19 patients with renal failure. Because RAS blockade inhibits HPV,^{89,90} it is not known whether ACEIs and ARBs would worsen hypoxia in COVID-19 patients, or alternatively, push V/Q matching back toward normal.

Because ACEIs, but not ARBs, impact the metabolism of the vasodilator bradykinin (BK), the distinction between the two drug classes has the potential to differentially impact the course of treatment in COVID-19 patients. Bradykinin (BK) is the major vasoactive peptide in the kallikrein-kinin system,^{215–217} interfacing with two principal receptors:^{218,219} constitutively expressed B2, and inflammation-inducible B1.²¹⁸ In the lungs, BK receptors are situated on the endothelial cells of alveolar capillaries, with B1 upregulated in patients with COVID-19.²²⁰ ACE metabolizes BK

to inactive fragments; thus, ACEIs may prolong the action of BK.^{221–225}

BK dysregulation can cause angioedema.^{226–228} B2 receptors inhibit the function of adherens junctions between vascular endothelial cells, leading to plasma fluid extravasation into the interstitium²²⁹ (Figure 1). Clinical data indicate that this occurs as a side effect in about one or two patients per 1000 people taking an ACEI,^{227,228} but the reason why only such a small percentage of patients are affected remains unknown.^{230–232} The concept that angioedema-like changes occur in the lungs of patients with COVID-19 is supported by both indirect (radiologic and clinical observation) evidence^{233,234} and by more direct evidence at autopsies.^{234–236,237}

Other than producing AII and inactivating bradykinin, ACE also contributes to the production of A1–7, the counterbalance to AII. So, the interruption of these additional effects by ACEIs may potentially impact outcomes in COVID-19 in ways that the ARBs do not.

As of this time, a small number of prospective clinical trials have begun enrolling patients to assess the potential of individual ACEI and ARB drugs as a therapy to lessen COVID-19 severity. Among them, a study at the University of California San Diego is evaluating the ACEI Ramipril (NCT04366050). Trials at the University of Kansas Medical Center (NCT04335123) and the University of Minnesota (NCT04312009) are assessing the ARB losartan, and telmisartan is being assessed at Universidad de Buenos Aires (NCT04355936). Many other agents remain to be separately evaluated.

Aside from ACEIs and ARBs to downregulate the ACE axis, there are also potential agents to augment the activity of the protective arms of RAS. Recombinant ACE2 has shown benefit in animal models of ARDS,⁶⁴ so it may prove beneficial in COVID-19 treatment. Apeiron Biologics has announced that its recombinant ACE2, called APN01, will enter Phase II trials in COVID-19 patients.²³⁸

In animal models, an AT2 agonist called C21 has proven effective at countering damaging effects of RAS. For example, C21 decreased collagen deposition fibrosis after MI and decreased arterial stiffness.⁵³ In addition, C21 blocked the rise in AII that accompanies a high sodium diet in obese Zucker rats and blunted progression of glomerulosclerosis.⁵⁴ C21 also decreased renal AT1 protein levels as measured by Western blot.⁵⁴ A human trial of C21 in pulmonary fibrosis has been conducted in Europe (The European Union Registry number of this trial is EUDRACT 2017–004923–62).⁷⁵ This agent could potentially be studied in COVID-19 patients.

In animal studies, the vitamin D receptor inhibits RAS activity, especially at the tissue level.¹⁰⁶ In human studies, vitamin D supplementation did not significantly lower blood pressure, although these studies were small and had few African-American participants, who are at elevated risk from COVID-19 and who typically exhibit lower vitamin D levels than Caucasians.¹⁰⁶ Perhaps vitamin D could have a positive impact on COVID-19 course if given to high-risk patients.

No outcome in medicine is ever guaranteed, but the evidence of RAS dysregulation in COVID-19 supports attempting to mitigate COVID-19 outcomes by modulating RAS. Such an approach would not be a shot in the dark, but rather would be guided by decades of experience modifying RAS in other diseases. Trials of RAS-modulating therapies in COVID-19 could be tailored to patients with high-RAS profiles, and would likely need initiation of medication early in the symptomatic course, before the tipping point of severe organ damage has occurred. Unfortunately, outpatient therapy opens doors to patient noncompliance, but enrollment of patients early in a hospitalization course may also be beneficial. Despite potential pitfalls, the urgency to combat COVID-19 requires tapping the full armamentarium of RAS modifier agents for possible efficacy. A recent model predicts that even with continued social distancing, COVID-19 fatalities could triple in the US alone by year's end.²³⁹ Human beings are now the ones with no time to lose.

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