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In the Know

A RAS and Bradykinin-Mediated Mechanism for COVID-19

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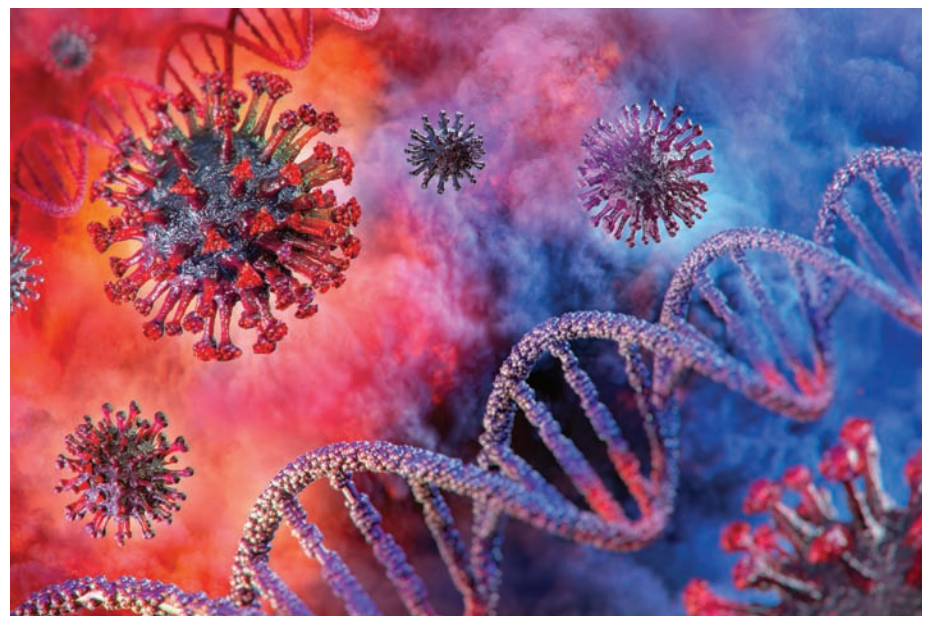
Editor-in-Chief



Since the initial outbreak of SARS-CoV-2 in Hubei province, China, in late 2019, infected individuals have displayed a number of different and seemingly unrelated clinical presentations, which has led to much confusion regarding the mechanism(s) by which SARS-CoV-2 affects human hosts.

SARS-CoV-2 gains entry to cells through attachment to angiotensin converting enzyme 2 (ACE2), one of the many peptides that comprise the renin-angiotensin system (RAS), which plays a key role in regulating blood pressure, electrolytes, and intravascular volume.

Since SARS-CoV-2 directly targets the ACE2 surface-bound enzyme, scientists have attempted to explain the protean symptoms of COVID-19 in terms of dysregulation of the RAS. Garvin and colleagues intended to provide further detail into dysregulation of the RAS by RNA sequencing of nine bronchoalveolar lavage samples from patients with

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Psychological Distress of COVID-19: Are You at Risk?

Adam Roth, PhD

As we experience the collective trauma of COVID-19, medical professionals remain one of the most impacted groups. The exposure to stressors, either directly or witnessed, in which one feels overwhelmed by and helpless to risk and harm is prevalent. In their range of responsibilities, medical professionals directly experience or

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Perspectives: Is Anesthesia a Human Right?

Dibash Kumar Das, PhD

The Universal Declaration of Human Rights by the United Nations General Assembly declared that all human beings are entitled to certain universal, inalienable, indivisible rights, including access to adequate health care, regardless of their socioeconomic status or location (asamonitor.pub/2YWFntT; asamonitor.pub/31Pk9jE). The right to health implies access to all care, including anesthesia. Yet, there is an urgent need to address large gaps in anesthesia services globally. Examples of the anesthesia care gap include:

- Of the world's 7.8 billion people, 5 billion are without access to safe and affordable surgical care when needed (asamonitor.pub/2EQU1fc). Access is worst in low-income and middle-income countries, where as much as 90% of the population cannot access basic surgical care.
- Out of the 313 million surgical procedures performed globally each year, only 6% occur in low-income and middle-income countries, where over one-third of the world's population lives (asamonitor.pub/2EQU1fc).
- A significant proportion of the global population has limited access to opioid analgesics for pain relief. 250 million (4%) have moderate access, 460 million (7%) have adequate access, and insufficient data are available for 430 million people (7%) (*J Pain Palliat Care Pharmacother* 2011;25:6-18).

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severe COVID-19 and comparing the results with 40 control samples (*eLife* 2020;9:e59177). However, the results led them to a surprising hypothesis, suggesting unexpected therapeutic approaches.

Curious findings

As the authors expected, the bronchial-alveolar lavage fluid showed profound dysregulation of the RAS. Angiotensinogen, the precursor of angiotensin, was increased 34-fold. Renin, produced by the kidney in response to hypotension, was increased 380-fold. As you may recall, renin cleaves angiotensinogen to produce angiotensin I, which is then cleaved by angiotensin converting enzyme (ACE) to angiotensin II. With increased angiotensinogen and renin, one might expect increased production of angiotensins I and II, leading to hypertension. However, COVID-19 patients usually have profound hypotension. How could that be?

The answer can be found in a double whammy from the only protein encoded on the positive-strand RNA. This protein degrades IKK-gamma, blocking production of interferon, likely the reason that the virus evolved this protein. However, IKK-gamma also induces ACE transcription, so an incidental side effect of the virus is blocking ACE transcription. Without ACE, angiotensin I can't be converted to angiotensin II (that's how ACE inhibitors work). This does something useful for the virus, so it may not be incidental at all. Angiotensin II downregulates ACE2, the viral entry point. Without ACE, and the angiotensin II produced by ACE, ACE2 is upregulated (almost 200-fold in the lavage samples). That provides 200-fold more entry points for the virus! It also shunts angiotensin I in an unwelcome direction.

ACE2 converts angiotensin I to the fragment angiotensin1-9. This fragment is known to activate bradykinin receptor signaling (*eLife* 2020;9:e59177). In the lavage samples, bradykinin receptors 1 and 2 were upregulated by ~3,000-fold(!) and 200-fold, respectively.

Bradykinin storm

The thrust of the authors' analysis and resulting hypothesis is that the disruption of the RAS, an expected result of a virus targeting ACE2, shifts the predominant end-product from angiotensin II to the fragment antiogensin1-9. This fragment then triggers a huge upsurge in bradykinin. Additionally, ACE is one of the primary enzymes that cleaves bradykinin. When ACE is downregulated, as described above, bradykinin rapidly rises. The result is a bradykinin storm that releases havoc on the body.

The rise in bradykinin promotes vascular leakage and fluid extravasation. The edema can be diffuse, affecting every organ system. However, it is particularly deadly in the lungs. Bradykinin promotes the synthesis and blocks the degradation of hyaluronic acid. This polysaccharide can trap about 1,000 times its weight in water (think of the Rolaids® ads from years ago). The result is a stiff, viscous hydrogel in the alveoli. The combination of pulmonary edema and hyaluronic acid results in the unusual presentation of COVID-19 associated ARDS.

Potential therapeutic implications

Both bradykinin and the angiotensin1-9 fragment may contribute to hypercoagulability. As the authors note, antiogensin1-9 fragment inhibits fibrinolysis. Bradykinin also promotes inflammation by inducing interleukins 1, 2, 6, and 8. Inflammation directly induces hypercoagulability and thrombosis.

Many of the adverse effects of bradykinin and angiotensin1-9 fragment are offset by angiotensin II. Unfortunately, with the downregulation of ACE, less angiotensin II is available to offset the bradykinin storm.

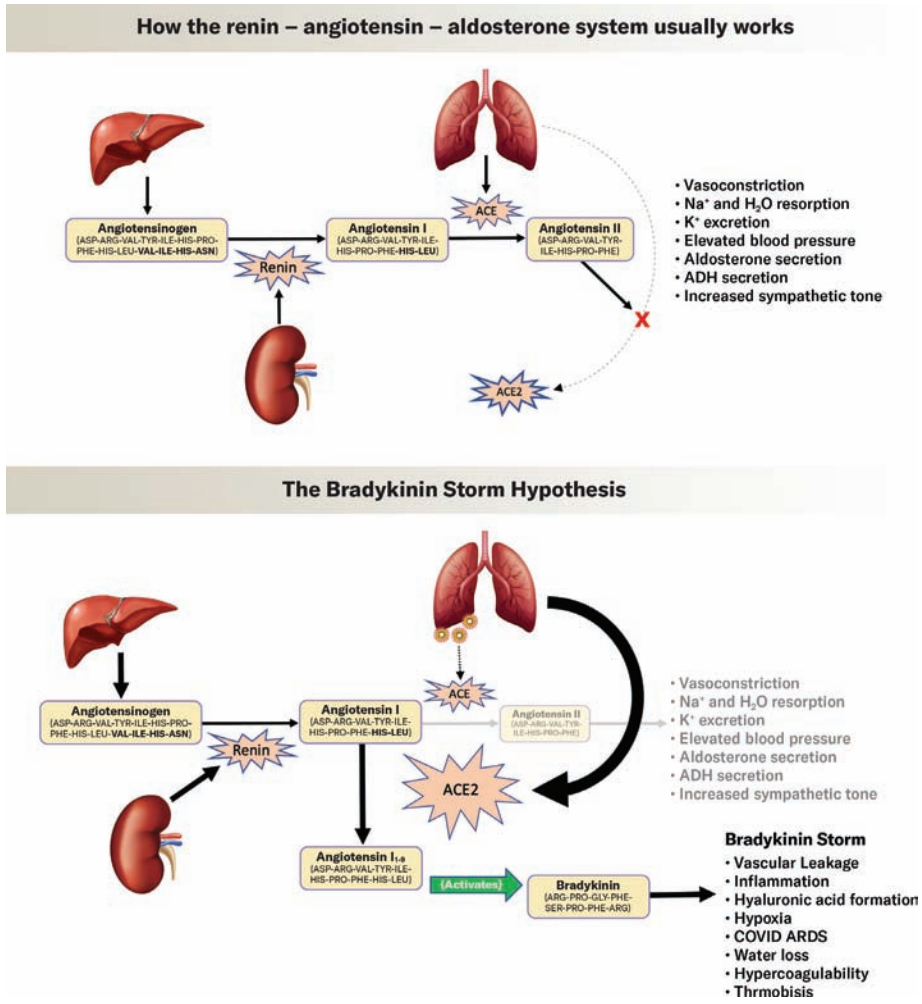
The authors developed their model by integrating the findings of the bronchial lavage samples, known pathways and genes across a vast swath of human biology, and the clinical manifestations of COVID-19. The computational analysis was performed at the Oak Ridge

"With increased angiotensinogen and renin, one might expect increased production of angiotensins I and II, leading to hypertension. However, COVID-19 patients usually have profound hypotension. How could that be?"

Leadership Computing Facility, home of the one of the world's most powerful supercomputers. The computer analysis identified that a model built on pathways that intersect with bradykinin could best explain the known clinical manifestations of COVID-19: hypokalemia, arrhythmia, heart failure, vasodilation, increased vascular permeability, inflammation, hypotension, pulmonary edema with formation of hydrogel in the lungs, encephalopathy, dizziness, headache, stroke, and myalgia.

The model leads to several suggestions for known medications that may be useful in treating serious COVID-19 cases. First, a handful of available medications have the potential to directly reduce bradykinin signaling and production. Additionally, and a little surprisingly, vitamin D may be helpful by reducing renin production. An article in PLoS One from authors at Quest Diagnostics found a strong inverse correlation between the levels of vitamin D and COVID positivity rates (*PLoS One* 2020;15:e0239252). Even zinc may have utility by reducing the conversion of kininogen to bradykinin by inhibiting kallikrein, the enzyme responsible for cleavage to bradykinin. However, the evidence for zinc is less compelling than the evidence for vitamin D (asamonitor.pub/301Hz3E).

Despite the computational pyrotechnics, the bradykinin hypothesis remains a speculation. However, it provides an initial framework for understanding the unusual clinical sequalae of COVID-19 and specific testable hypotheses for understanding the mechanisms of injury and the role of potential therapeutics. ■



Richard Simoneaux *is a freelance writer with an MS in organic chemistry from Indiana University and more than 15 years of experience covering the pharmaceutical industry and an additional seven years as a laboratory-based medicinal chemist.*

Clarification

Nathan Smischney, MD, MS, Assistant Professor, Department of Anesthesiology, Division of Critical Care Medicine, Mayo Clinic, Rochester, was inadvertently omitted from the October Monitor article he co-authored titled The Value of the Anesthesiologist-Intensivist During COVID-19. We would like to acknowledge Dr. Smischney's contribution.