breathlessness induced in normal volunteers. Am Rev Respir Dis 1989;140:1021–1027.
5. Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, et al.; American Thoracic Society Committee on Dyspnea. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. Am J Respir Crit Care Med 2012;185:435–452.
6. Morélot-Panzini C, Demoule A, Straus C, Zelter M, Derenne JP, Willer JC, et al. Dyspnea as a noxious sensation: inspiratory threshold loading may trigger diffuse noxious inhibitory controls in humans. J Neurophysiol 2007;97:1386–1404.

Is the Angioedema Associated with COVID-19 a Real Entity, a Mimic, or Both?

To the Editor:

Batarseh and coworkers (1) reported four patients with angioedema that they ascribed to severe coronavirus disease (COVID-19). We are appreciative of the described mechanisms by which ACE (angiotensin-converting enzyme), ACE2, and other peptidases are able to degrade and/or inactivate bradykinin and its metabolites. Furthermore, they posited that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), by binding to ACE2, may prevent such inactivation, and in the presence of reduced activity of other peptidases, bradykinin and its metabolites accumulate to predispose to angioedema.

We have several thoughts that we hope will stimulate further investigations. First, given that symptoms began 2–7 days before the diagnosis of COVID-19, and endotracheal intubation occurred 1–5 days later but angioedema did not occur until 10–14 days after intubation, we estimated that these four patients did not develop angioedema until 14–21 days after onset of symptoms of COVID-19. Most of the hyperinflammatory response described with COVID-19—manifested as severe pneumonia and sepsis—typically occurs 7–10 days after onset of symptoms, similar to what the authors observed. This delayed onset of severe disease helps explain why 1) the antiviral remdesivir may be effective in the early stage of COVID-19 (when viral load is increasing) but not so in later stages when fulminant inflammatory disease has manifested; and, conversely, 2) glucocorticoids given ≥7 days into the symptomatic stage reduced mortality in those requiring supplemental O2 or mechanical ventilation (markers of more severe and perhaps hyperinflammatory disease) but not in those with less severe disease. However, the estimated onset of angioedema 14–21 days after symptom onset (or 10–14 d after endotracheal intubation) in the four patients described seems to be much later than the aforementioned “delayed hyperinflammatory” stage. Because bradykinin-mediated angioedema is typically acute in onset, can the authors speculate on why there might be such a delay in this COVID-19–related complication if indeed this is a bradykinin-mediated phenomenon?

Second, it is hard to understand how the patient with angioedema the authors referenced (2) was bradykinin mediated, as the functional level of C1 inhibitor (C1-INH) was increased, which would be a potent inhibitor of bradykinin production. Perhaps in this patient, the reduced ability to degrade bradykinin (because of inhibition of ACE by lisinopril) or its metabolite (because of downregulation of ACE2 by SARS-CoV-2) outpaced the inhibition of bradykinin production by the high functional C1-INH level measured (2).

Third, were any of these mechanically ventilated patients proned for their respiratory failure? If so, facial edema is common with prone positioning and may mimic angioedema (3). Isolated lower lip edema, which may also be mistaken for angioedema, has been described as a complication of prone positioning as well (4).

Fourth, if bradykinin-mediated angioedema was occurring, it has been shown that low-molecular-weight heparin could help treat acute episodes of hereditary angioedema—albeit controlled studies comparing various forms of heparin with icatibant and/or ecallitide for exacerbations of hereditary angioedema have not been performed (5). We would assume that these critically ill patients were on heparin for prophylaxis against venous thrombosis. Heparin also has anticoagulation-independent properties that may antagonize COVID-19 (6). Because we have found low-molecular-weight heparin to be more effective than unfractionated heparin in augmenting C1-INH activity in an in vitro assay using sera from patients with hereditary angioedema (E. D. Chan and colleagues, unpublished results), were the four patients on heparin prophylaxis? If so, how many were on unfractionated heparin versus low-molecular-weight heparin? However, if COVID-19–induced angioedema is found to be bradykinin mediated but not dependent on impaired C1-INH activity, then heparin may have no impact on this phenomenon because heparin is posited to enhance C1-INH activity. ☑

*Corresponding author (e-mail: chane@njhealth.org).

Author disclosures are available with the text of this letter at www.asil.org.

Edward D. Chan, M.D.*
Rocky Mountain Regional Veterans Affairs Medical Center
Aurora, Colorado
National Jewish Health
Denver, Colorado
and
University of Colorado Anschutz Medical Campus
Aurora, Colorado

Abraham Majluf-Cruz, M.D.
Instituto Mexicano del Seguro Social
Mexico City, Mexico

Correspondence

Copyright © 2021 by the American Thoracic Society

This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (http://creativecommons.org/licenses/by-nc-nd/4.0/). For commercial usage and reprints, please contact Diane Gem (dgem@thoracic.org).

Originally Published in Press as DOI: 10.1164/rccm.202011-4141LE on December 23, 2020
**References**

1. Batarseh E, Kersten BP, Pinelo AC, Nadler JN, Schwartz SA. Angioedema in African American patients hospitalized for COVID-19 [letter]. Am J Respir Crit Care Med 2020;202:1581–1584.

2. Cohen AJ, DiFrancesco MF, Solomon SD, Vaduganathan M. Angioedema in COVID-19. *Eur Heart J* 2020;41:3283–3284.

3. Messereiole E, Peine P, Wittkopp S, Marini JJ, Albert RK. The pragmatics of prone positioning. *Am J Respir Crit Care Med* 2002;165:1359–1363.

4. George G, Awad SA, Thampl SM, Philip MA. Isolated lower lip edema: a rare complication of prone positioning. *J Anaesthesiol Clin Pharmacol* 2017;33:274–275.

5. Majuf-Cruz A, Nieto-Martínez S. Long-term follow up analysis of nadroparin for hereditary angioedema: a preliminary report. *Int Immunopharmacol* 2011;11:1127–1132.

6. Hippensteel JA, LaRiviere WB, Colbert JF, Langouët-Astrié CJ, Schmidt EP. Heparin as a therapy for COVID-19: current evidence and future possibilities. *Am J Physiol Lung Cell Mol Physiol* 2020;319:L211–L217.

Copyright © 2021 by the American Thoracic Society

---

**Reply to Chan and Majuf-Cruz**

*From the Authors:*

We wish to reply to the letter by Chan and colleagues that comments on our previous report regarding angioedema and coronavirus disease (COVID-19) (1).

**Risk Factors for Angioedema**

Multiple risk factors are believed to increase the incidence of ACE (angiotensin-converting enzyme) inhibitor (ACEI)–induced angioedema through various pathways, including polymorphisms in the genes encoding NEP and APP, medications that inhibit DPP4, and autoantibodies against C1-INH.

**Onset of Angioedema**

Although we hypothesize similarities between ACEI-induced angioedema and COVID-19–associated angioedema, there is a wide window for the development of angioedema after the onset of COVID-19 symptoms and it can still be related to the kallikrein–kinin system for the following reasons:

First, the timeline for COVID-19 phases and clinical manifestations continues to evolve because of complex multisystem activities. Studies have noted that the onset of the COVID-19 hyperinflammatory state has ranged between 2 and 5 weeks (2).

Second, the presentation of ACEI-induced angioedema can range between weeks and months after starting and discontinuing the medication. Thus, we can anticipate a similar variability in angioedema onset in patients hospitalized for COVID-19 (3).

Third, ACE2 does not inhibit BK but mainly inhibits DABK and Lys-DABK, which are downregulated in the systemic and tissue kallikrein pathway, leading to a later onset in their signaling activity.

Fourth, BK binds primarily to β2R, which is expressed on endothelial cells and does not rely on the inflammatory cascade to induce angioedema. In contrast, DABK and Lys-DABK bind primarily to β1R, which is only upregulated in the setting of inflammation. Therefore, accumulation of DABK and Lys-DABK would not induce angioedema until the establishment of the inflammatory state.

**Proning and Angioedema**

Regarding proning the patients, patients 1, 2, and 3 developed angioedema 6–7 days after the last time they were proned. Patient 4 was never proned. The swelling involved the whole face, tongue, lips, upper airway edema, and laryngeal edema. For those patients who were proned, they were positioned in reverse Trendelenburg position when proned. Therefore, proning was not believed to be related to angioedema.

**Role of C1-INH in Angioedema Associated with ACE2 Dysregulation**

Although the patient with angioedema described by Cohen, referenced in our original letter, had an elevated functional concentration of C1-INH, it may not necessarily prevent angioedema. This is evidenced by data showing that many patients with ACEI angioedema do not respond to C1-INH concentrate. Also, C1-INH is a potent inhibitor of BK release from HMWK (high-molecular-weight kininogen) but it does not directly affect the metabolism of LMWK (low-molecular-weight kininogen) to Lys-BK and subsequently to Lys-DABK, which can precipitate angioedema in the setting of dysfunctional ACE2. However, it is important to note that the rapid improvement in the patient’s angioedema may be related to the inactivation of BK by the elevated C1-INH concentration.

Regarding the issue of LMWH enhancing C1-INH activity, Chan and colleagues raise an interesting point. All of our patients were on deep venous thrombosis prophylaxis; two were receiving heparin and two were receiving LMWH. Current literature suggests that autoimmune phenomena may be increased during COVID-19 and in the post–COVID-19 syndrome (4). Consequently, one can speculate that autoantibodies to C1-INH can develop during COVID-19, increasing the risk of angioedema. Thus, the suggestion by Chan and colleagues to use LMWH to augment the activity of C1-INH bears consideration and could become a potential...