Hypotension, Systemic Inflammatory Response Syndrome, and Coronavirus Disease 2019: A Clinical Conundrum

To the Editor

Clinicians who have treated large number of critically ill patients with coronavirus disease 2019 (COVID-19) would generally agree on several core observations: (1) intensive care unit (ICU) admissions for COVID-19 patients occurred almost exclusively for worsening respiratory failure; (2) doses of sedatives and analgesics to facilitate mechanical ventilation in COVID-19 patients were substantially elevated when compared with critically ill patients without COVID-19[1]; and (3) systemic hemodynamics of most COVID-19 patients, including those with acute respiratory distress syndrome (ARDS), are remarkably preserved, unless heart failure, acute thrombotic event, or superimposed bacterial sepsis complicated the disease.

The first clinical description of ICU hospitalizations in the United States concluded that "most patients did not present with evidence of shock."[2] This is supported by a larger study from ICUs in New York City area where mean lactate value of 223 studied critically ill patients was 1.5 mmol/L.[3] Isolated cases of COVID-19–induced shock continue to be discussed as case reports.[4]

Hence, the most typical clinical picture of a critically ill patient with COVID-19 that one encounters in the ICU is a patient who is deeply sedated and sometimes paralyzed, has a severely impaired alveolar gas exchange, and requires none or relatively low doses of intravenous vasopressors (eg, norepinephrine at rates typically lower than 5 μg/min). These mild degrees of hypotension can often be attributed to high doses of sedatives, positive pressure ventilation with high levels of positive end-expiratory pressure (PEEP), restrictive fluid management, and aggressive diuresis. In the absence of elevated lactate, these physiologic characteristics do not fulfill criteria of shock. In our own experience, many patients in fact required resumption of their home antihypertensives while being mechanically ventilated.

These observations of preserved hemodynamics and the absence of shock[2,3] in the syndrome that has been characterized by "cytokine storm" with markedly elevated levels of certain interferons, interleukins, and chemokines[5] are curious and stand in contrast to other cohorts of critically ill patients with ARDS who commonly present with distributive shock and require fluid resuscitation and higher levels of hemodynamic support.[6]

Due to significant increases in plasma levels of interleukin (IL)-6 in COVID-19,[7] similarities have recently been drawn to cytokine release syndrome and acute lung injury that sometimes occur after CAR T-cell therapy. Consequently, trials targeting IL-6 are ongoing in patients with COVID-19. Having managed patients after CAR T-cell infusions ourselves,[8] we must question these proposed similarities between COVID-19 disease and CAR T-cell therapy—CAR T-cell patients with cytokine release syndrome often require large amounts of fluid resuscitation due to capillary leak, resulting in pulmonary or even airway edema, and hypotension is present even in milder cases of cytokine release resulting in the need for vasopressor support in the ICU.

With these observations and data as a backdrop, one now needs to reconcile the following: we have historically attributed the hypotension of ICU patients with sepsis and ARDS to the "systemic inflammatory response syndrome (SIRS)" after ensuring that patients are euvolemic and their cardiac function is adequate. We have believed that SIRS drives vasodilation, capillary leak, and hypotension. Critically ill COVID-19 patients with ARDS would certainly meet clinical SIRS criteria (tachypnea, fever, and lymphopenia), further supported by markedly elevated levels of inflammatory markers (eg, ferritin, C-reactive protein) and proinflammatory cytokines. Distributive shock, however, is rare compared to other patients with similar inflammatory cytokine elevations (non-COVID sepsis, ARDS, CAR T-cell therapy). In addition, lactate levels have been only rarely reported in large COVID-19 observational studies, and we may only hypothesize that this is due to their generally normal values.

While COVID-19–related ARDS has been proposed to be a "unique type of ARDS" (due to extensive microcapillary thrombosis, pulmonary angiogenesis, preserved respiratory system compliance in a subset of patients), it is also important to investigate why this hyperinflammatory syndrome is accompanied by a remarkably preserved hemodynamic picture. Clearly not all severe systemic inflammatory responses are equal.

Dusan Hanidziar, MD, PhD
Edward A. Bittner, MD, PhD
Department of Anesthesia, Critical Care and Pain Medicine
Massachusetts General Hospital
Boston, Massachusetts
dhanidziar@partners.org

Funding: D.H. is supported by a Clinical Investigator Award from the National Heart, Lung and Blood Institute (K08HL141694).

REFERENCES

1. Hanidziar D, Bittner E. Sedation of mechanically ventilated COVID-19 patients: challenges and special considerations. *Anesth Analg*. 2020. doi: 10.1213/ANE.0000000000004887.
2. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state. *JAMA*. 2020;323:1612–1614.
3. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet*. 2020;395:1763–1770.
4. Bobeck K, Holtzclaw A, Brown T, Clark PA. Effective use of angiotensin II in coronavirus disease 19-associated mixed shock state: a case report. *A A Pract.* 2020;14:e01221.
5. Coperchini F, Chiovato L, Croce L, Magri F, Rotondi M. The cytokine storm in COVID-19: an overview of the involvement of the chemokine/chemokine-receptor system. *Cytokine Growth Factor Rev*. 2020;53:25–32.
6. Famous KR, Delucchi K, Ware LB, et al. Acute respiratory distress syndrome subphenotypes respond differently to randomized fluid management strategy [published correction appears in *Am J Respir Crit Care Med*. 2018;198(12):1590] [published correction appears in *Am J Respir Crit Care Med.* 2019;200(5):649]. *Am J Respir Crit Care Med*. 2017;195:331–338.
7. Herold T, Jurinovic V, Arnreich C, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. *J Allergy Clin Immunol.* 2020. doi: 10.1016/j.jaci.2020.05.008.
8. Hanidziar D, Bittner E. A growing problem of critical illness due to chimeric antigen receptor T-cell therapy. *Crit Care Med.* 2018;46:e1086–e1087.

DOI: 10.1213/ANE.0000000000005062