Angiotensin II Administration in Patients with COVID-19 Shock

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Abstract:

Purpose:
To understand the hemodynamic effect of angiotensin II as a vasopressor in patients with shock secondary to COVID-19 infection.

Methods:
A retrospective analysis was performed on all patients at a single center with COVID-19 infection and shock who were treated with angiotensin II. The hemodynamic response to angiotensin II was estimated by recording the mean arterial pressure, norepinephrine equivalent dose (NED) and urine output.

Results:
Ten patients with COVID-19 related shock were treated with angiotensin II. Over the initial 6 hours, the average the norepinephrine equivalent dose decreased by 30.4% (from 64.6 mcg/min to 44 mcg/min) without a significant change in the mean arterial pressure (0.7% decrease). Six patients experienced at least a 25% reduction in norepinephrine equivalent dose by 6 hours, and two experienced at least a 50% reduction.

Conclusions:
On average, the hemodynamic response to angiotensin II in COVID-19 related shock was favorable. Two patients had a marked rapid improvement. Given the relationship of SARS-CoV-2 with the renin angiotensin aldosterone system, further evaluation of angiotensin II for the treatment of COVID-19 related shock is warranted.
Introduction:

The coronavirus disease 2019 (COVID-19) pandemic has caused significant illness and death across the world over the past several months. In addition to respiratory failure, shock related to sepsis or cytokine release syndrome may occur. The true prevalence of shock in this population is not clearly defined; however, shock seems to be a complicating factor in most patients who are admitted to the intensive care unit and therefore the use of vasopressors in these critically ill patients is common (1-3). Angiotensin II has been shown to be an effective vasopressor in vasodilatory shock in the ATHOS 3 trial (4). The severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) virus utilizes the angiotensin-converting enzyme 2 (ACE2) receptor to gain entry into host cells. Given this interaction with the renin-angiotensin-aldosterone system, some have proposed that angiotensin II as a vasopressor would be worth further scientific investigation (5).

We have compiled our experience of angiotensin II use in ten patients with shock secondary to COVID-19 and describe the hemodynamic response and outcomes.

Methods:

We conducted a review of all patients with COVID-19 who were treated with angiotensin II for shock at our institution. Using a pharmacy database, all patients who were treated with angiotensin II from March 1st, 2020, until April 25th, 2020 at a single academic institution (Lahey Hospital and Medical Center, Burlington, MA, U.S.A) were reviewed. The Institutional review board at our institution approved this study. To be included in the analysis, patients were required to have tested positive for SARS-CoV-2 infection by polymerase chain reaction (PCR) either with a nasopharyngeal or tracheal sample. No patients were excluded from our analysis. A thorough review of the electronic medical record was performed. Baseline characteristics,
imaging, laboratory data, and hemodynamic data were tabulated. Hourly mean arterial pressure, 
vasopressor or inotrope dose, and urine output were tabulated starting at time -6 hours prior to 
the start of angiotensin II until +12 hours after angiotensin II was started. Given the small 
sample size and the case series design of this study, statistical analysis was not performed.

**Results:**

Ten patients were identified during the study period as being treated with angiotensin II 
and testing positive for SARS-CoV-2. The patients were 64.5 +/- 6.15 years old on average and 
10% were female. Patients on average tested positive 3.8 days prior to intensive care unit (ICU) 
admission and had been in the ICU for 17.6 hours prior to the initiation of angiotensin II. All ten 
were intubated and receiving mechanical ventilation, nine of the ten underwent prone positioning 
at some point during their hospitalization. Angiotensin II was added as a third vasopressor in 
two (20%) patients and as a fourth vasopressor in six (60%) patients (second vasopressor and 
fifth vasopressor in one patient each). The starting dose of angiotensin II was 20 ng/kg/min in 
seven (70%) patients (10 ng/kg/min in one patient, 30 ng/kg/min in one patient and 40 ng/kg/min 
in one patient). Seven patients had received tocilizumab, an interleukin-6-receptor inhibitor, and 
all ten had received glucocorticoids. Of the seven patients who had received tocilizumab, five 
had received this medication following resolution of shock and were no longer receiving 
angiotensin II at that time, one patient received tocilizumab 15 minutes prior to initiation of 
angiotensin II and died shortly thereafter, and one patient received tocilizumab 16 hours prior to 
angiotensin II initiation.

Selected baseline characteristics, the hemodynamic impact of angiotensin II within 6 
hours, and outcomes are shown in the table. On average the norepinephrine equivalent dose 
decreased by 30.4% (from 64.6 mcg/min to 44 mcg/min) without a significant change in the
mean arterial pressure (0.7% decrease). Six patients experienced at least a 25% reduction in norepinephrine equivalent dose by 6 hours, and two experienced at least a 50% reduction (figure). By the writing of this manuscript, five of the ten patients (50%) have died (care was withdrawn in all five patients, two secondary to refractory shock and three secondary to refractory hypoxemia), none have been discharged alive and five (50%) remain in the hospital. One patient died within 6 hours after starting angiotensin II.

**Discussion:**

Given the interaction of the SARS-CoV2 virus with the renin-angiotensin-aldosterone system, dysregulation of this system may play a role in the vasodilatory shock associated with severe COVID-19 infection. However, there is no clearly identified mechanism to support this hypothesis (5). The severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) virus utilizes the angiotensin-converting enzyme 2 (ACE2) receptor to gain entry into host cells (10). The ACE2 enzyme is responsible for conversion of angiotensin II to angiotensin (1,7), which has vasodilatory actions via both an increase in angiotensin(1,7) as well as a complimentary reduction in angiotensin II. ACE2 thereby balances the vasoconstriction and sodium retention effects exerted by activation of the renin-angiotensin-aldosterone system. Although there is no definite mechanism that has been elucidated to support a hypothesis that angiotensin II would be beneficial in shock related to COVID-19, given the interaction of the virus with the renin-angiotensin-aldosterone system further study of angiotensin II as a vasopressor in this clinical scenario would be worthwhile (8,9).

Angiotensin II is a potent vasoconstrictor that has been shown to effectively increase mean arterial pressure in patients with vasodilatory shock enrolled in the ATHOS 3 trial (4). In this trial, patients with vasodilatory shock (mostly septic shock) who were already on
norepinephrine at a dose of at least 0.2mcg/kg/min were randomized to an infusion of either angiotensin II or placebo. By three hours, the primary endpoint of an increase in baseline mean arterial pressure of at least than 10 mmHg or to greater than 75 mmHg occurred more frequently in the angiotensin II group than the placebo group (69.9% vs 23.4%, odds ratio 7.95, p<0.0001). Based on this short term favorable hemodynamic impact, angiotensin II was approved by the Food and Drug Administration in the United States of America in 2017 for the treatment of vasodilatory shock.

There has been one case report published thus far to our knowledge demonstrating a favorable response to therapy with angiotensin II in patients with shock in the setting of COVID-19 infection (6). Two patients in our series demonstrated a dramatic hemodynamic response to angiotensin II with a greater than 50% decline in norepinephrine equivalent dose within 6 hours. This “sensitivity” to angiotensin II had also been reported in a subset of patients in the ATHOS 3 trial which evaluated the use of angiotensin II in vasodilatory shock (7). It remains possible that there is a subgroup of patients who respond favorably to angiotensin II and therefore there may be reason to use angiotensin II earlier in the course of septic shock related to COVID-19 in certain patients. Further study is necessary to determine if there is a role for the earlier use of angiotensin II as a vasopressor in patients with vasodilatory shock secondary to COVID-19 infection.
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### Table. Demographic, Clinical, and Outcome Data for Ten Patients with COVID-19 and shock treated with Angiotensin II.

| Age/sex | Comorbid Conditions | ACE/ARB | Creatinine (mg/dL) | D-Dimer (ng/mL) |Troponin I (ng/mL) | Lactic acid (mmol/L) | Apache II Score | Viral directed treatment | Immunomodulatory Therapy | Change in MAP in MAP 0 to 6 hours | Change in Norepinephrine Equivalent Dose | Outcome |
|---------|---------------------|---------|-------------------|-----------------|-------------------|---------------------|------------------|---------------------|-----------------------|-----------------------------|----------------------------------------|----------|
| 65M     | HTN, CHD             | No      | 9.3              | 543             | 0.2              | 2.1                | 33               | AZ                  | GC                    | +44.6%                      | -70.1%                                 | Alive in-hospital |
| 66F     | None                | No      | 1                | 2750            | 0.2             | 1.8                | 38               | HCQAZ/Convalescent Plasma | Tocilizumab/GC          | +61.1%                     | -51.9%                                 | Alive in-hospital |
| 60M     | HTN                 | No      | 4.9              | 3000            | 1.19            | 2.0                | 54               | AZ/Convalescent Plasma | Tocilizumab/GC          | +11.6%                     | -42.8%                                 | Alive in-hospital |
| 58M     | HTN, DM             | Yes     | 0.7              | 2000            | 0.91            | 4.5                | 33               | HCQAZ               | Tocilizumab/GC          | -19.2%                     | -39.2%                                 | In-hospital death |
| 52M     | HTN, DM             | Yes     | 1.5              | 2000            | 0.22            | 8.9                | 33               | Convalescent Plasma | Tocilizumab/GC          | +17.6%                     | -20.1%                                 | Alive in-hospital |
| 65M     | HTN                 | Yes     | 1.5              | 200             | 0.27            | 1.7                | 30               | HCQAZ               | Tocilizumab/GC          | -8.8%                      | -34.7%                                 | In-hospital death |
| 61M     | HTN                 | Yes     | 1.1              | 1460            | 0.31            | 1.5                | 27               | HCQAZ               | Tocilizumab/GC          | -12.3%                     | -8.7%                                  | In-hospital death |
| 58M     | HTN, DM             | Yes     | 3.3              | 552             | 0.38            | 1.7                | 25               | HCQAZ               | GC                    | +19.9%                     | -2.4%                                  | Alive in-hospital |
| 71M     | COVID-19, AF, solid organ transplantation, cancer | No | 5.1 | 2000 | 0.11 | 0.9 | 39 | None | Tocilizumab/GC | -1.5% | 0% | In-hospital death |
| 60F     | HTN                 | No      | 1                | 1240            | 0.06            | 2.2                | 30               | HCQAZ               | Tocilizumab/GC          | Died 5 hours after initiation of Angiotensin II | In-hospital death |
**Figure.** Mean arterial pressure, norepinephrine equivalent dose, over an 18 hour time period starting 6 hours prior to the initiation of angiotensin II in 10 patients with COVID-19 and shock (Panel A). Individual hemodynamic response based on norepinephrine equivalent dose in 10 patients at time 0 compared to 6 hours after initiation of angiotensin II (Panel B).
Figure 1