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Review Article

Angiotensin II - A Brief Review and Role in Severe SARS-COV-2 Sepsis

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The renin-angiotensin-aldosterone system (RAAS), whose major vasopressor effector is angiotensin II (ATII), has multiple activities and regulates sodium-water homeostasis and fluid and blood pressure homeostasis. RAAS plays a crucial role in cardiocirculatory shock because it counteracts hypotension and hypovolemia by activating different physiologic responses. Based on the encouraging results of the ATHOS-3 trial, the US Food and Drug Administration and the European Medicines Agency approved the use of ATII for catecholamine-resistant vasodilatory shock. More recently, ATII was used for the compassionate treatment of critically ill patients with COVID-19. Beyond its vasopressor properties, ATII was hypothesized to have antiviral activity because it induces internalization and degradation of angiotensin-converting enzyme 2 receptors used by SARS-Cov-2 to infect cells. Overall, the use of ATII in patients with COVID-19 showed promising results because its administration was associated with the achievement and maintenance of target mean arterial pressure, increased P_aO_2/F_IO_2 ratio, and decreased F_IO_2. The aim of this narrative review is to summarize the available knowledge on the use of ATII in patients with COVID-19.

Key Words: angiotensin-II; vasopressor; COVID-19; shock

Two-thirds of ventilated patients with COVID-19 develop distributive shock requiring vasopressor support.[1] The recent approval by the US Food and Drug Administration and European Medicines Agency of angiotensin II (ATII) for vasodilatory shock[2,3] marks a potential turning point in the treatment of hypotensive critically ill patients with COVID-19. The rationale behind the use of ATII in these patients is not restricted merely to the vasopressor properties of ATII, but also includes its potential ability to block SARS-CoV-2 cell entry because ATII induces internalization and degradation of angiotensin-converting enzyme 2 (ACE2) receptors, which are used by the SARS-CoV-2 spike protein to enter cells.[4,5]

The renin-angiotensin-aldosterone system (RAAS) is one of the most important physiologic control systems in the human body, and regulates sodium-water and blood pressure homeostasis. The major effector of the RAAS is the ATII octapeptide.

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Renin cleaves angiotensinogen into angiotensin I ATI, which is converted subsequently to ATII by (ACE) and, to a lesser extent, by other chymases stored in secretory granules of mast cells.[6] Circulating ATII regulates blood pressure and electrolyte balance through its actions on vascular tone, aldosterone secretion, renal sodium handling, thirst, water intake, sympathetic activity, and vasopressin release.[7,8] ATII exerts its action by binding to 2 main receptors (ATII type 1 receptor [AT1R] and ATII type 2 receptor [AT2R]). Both AT1R and AT2R are transmembrane G-protein-coupled receptors, and have counter-regulatory actions in the cardiovascular and renal systems.[7,9] In a negative feedback loop, ATII levels regulate and lower renin levels (Fig 1).

RAAS plays a crucial role in cardiocirculatory shock. In the presence of severe hypotension and hypovolemia, several main mechanisms are activated to restore volume and arterial blood pressure—activation of the sympathetic nervous system, release of vasopressin, inhibition of atrial and cerebral natriuretic peptides secretion, increase in renin secretion, and, subsequently, ATII-mediated increase in aldosterone secretion (Fig 1).[10,11] However, an extreme RAAS activation may become deleterious, leading to increased production of reactive oxygen species, excessive arteriolar vasoconstriction, endothelial dysfunction, and an enhanced procoagulant state.[11-13] This may contribute to the development of multiorgan failure, including acute respiratory distress syndrome (ARDS) and acute renal injury.[13] On the other hand, endothelial disruption, especially if primarily restricted to the lungs, as in the case of ARDS, causes the reduced expression of ACE, which then leads to a decrease in ATII production.[13,14] In addition, systemic inflammation also might decrease ACE activity and, subsequently, ATII levels, leading to hyperreninemia. The lack of ACE expression and diminished ATII production are part of the rationale behind the use of exogenous ATII in patients with vasodilatory shock or ARDS.[15]

The first study to investigate the role of ATII as a rescue vasopressor in patients with vasodilatory shock was the ATHOS-Trial in 2014.[16] In this small, single-center, double-blind, pilot randomized clinical trial comparing ATII infusion versus placebo in patients with vasodilatory shock, ATII infusion significantly increased mean arterial pressure (MAP), leading to a concomitant reduction in norepinephrine support. Soon after, a large, international, double-blind, placebo-controlled, randomized clinical trial, the ATHOS-3 trial, confirmed the beneficial effects of ATII. In both trials, ATII improved MAP and other hemodynamics parameters in catecholamine-resistant vasodilatory shock, and displayed a trend toward decreased 28-day mortality. A post hoc analysis of those patients with an ATII-deficiency (identified by a high ATI-ATII ratio) enrolled in the ATHOS-3 sudy, found that in such patients, ATII significantly decreased mortality.[17] In fact, the relative decrease in ATII plasma levels led to higher sensitivity to ATII stimulation.[13] Because ATII induces catecholamine secretion by the adrenal glands and by postganglionic sympathetic fibers, the relative decrease in ATII levels also can result in a lack of endogenous catecholamines, which further increases the risk or severity of vasodilatory shock.[13]

A post hoc analysis of data from ATHOS-3 also was conducted to evaluate the effect of ATII on renal function in patients who, at randomization, had dialysis-dependent acute kidney injury as a complication of the vasodilatory shock (renal-replacement therapy [RRT]).[18] This study confirmed a higher MAP in the treated group, and found that 28-day mortality was significantly less in the AT-II group than in the placebo group (hazard ratio 0.52; 95% CI 0.30-0.87; p = 0.012). Moreover, patients in the ATII group were more likely to discontinue RRT on day 7 than patients in the placebo group (38% *v* 15%), possibly due to a direct effect of ATII on renal microcirculation.[18]

Several trials have used ATII in critically ill patients with COVID-19 with vasodilatory shock (Table 1). In a recent, single-center, compassionate-use case series, the authors used ATII either as a primary or rescue vasopressor in 16 ventilated patients with COVID-19–associated vasodilatory shock, and assessed the course of key physiologic variables during the first 48 hours of treatment.[19] Overall, the administration of ATII was associated with the achievement and maintenance of target MAP, an increase in P_aO_2/F_IO_2 ratio (P/F ratio), and a decrease in F_IO_2. Moreover, the authors compared 46 mechanically ventilated patients with COVID-19 receiving ATII therapy with 53 controls.[20] Again, MAP was significantly higher in the ATII-treated group, which also achieved a higher P/F ratio and a decreased risk of liver dysfunction. Furthermore, ATII use was associated with a higher probability of reduced use of RRT. The authors found no association with harm in relation to mortality, length of invasive mechanical ventilation, thromboembolic events, and length of hospital stay. An international, multicenter, registry-based study assessed the impact of ATII therapy on physiologic and patient-centered outcomes in 65 critically-ill patients with COVID-19.[21] During the first 12 hours of infusion, patients treated with ATII had a faster decrease in F_IO_2 and maintained similar MAP levels.

In addition to the established vasopressor properties of ATII, ATII may act as a competitive inhibitor with SARS-CoV-2 for ACE2 binding.[22] Furthermore, ATII binding to AT1R leads to the internalization, downregulation, and lysosome-mediated degradation of ACE2 expressed on the cell surface.[22] Thus, the authors investigated the feasibility and safety of ATII administration in patients not critically-ill with COVID-19 with moderate ARDS outside of the intensive care unit; they observed a median change of 3 points in a 6-category ordinal scale, with clinically relevant improvement in 4 patients at day 28.[23] The main findings on the use of ATII in patients with COVID-19 are summarized in Table 1.

Despite these encouraging results, doubts about the effectiveness and safety of ATII within the management of septic shock have been raised.[11,24] For example, an excessive amount of ATII would further promote the activation of ATR1, which might lead to a potential extreme peripheral vasoconstriction and promotion of a proinflammatory state that may lead to detrimental effects.[9,11,13] Such concerns have been reported in the literature both in acute and chronic situations.[25,26] Acute adverse outcomes include mainly hypertension and

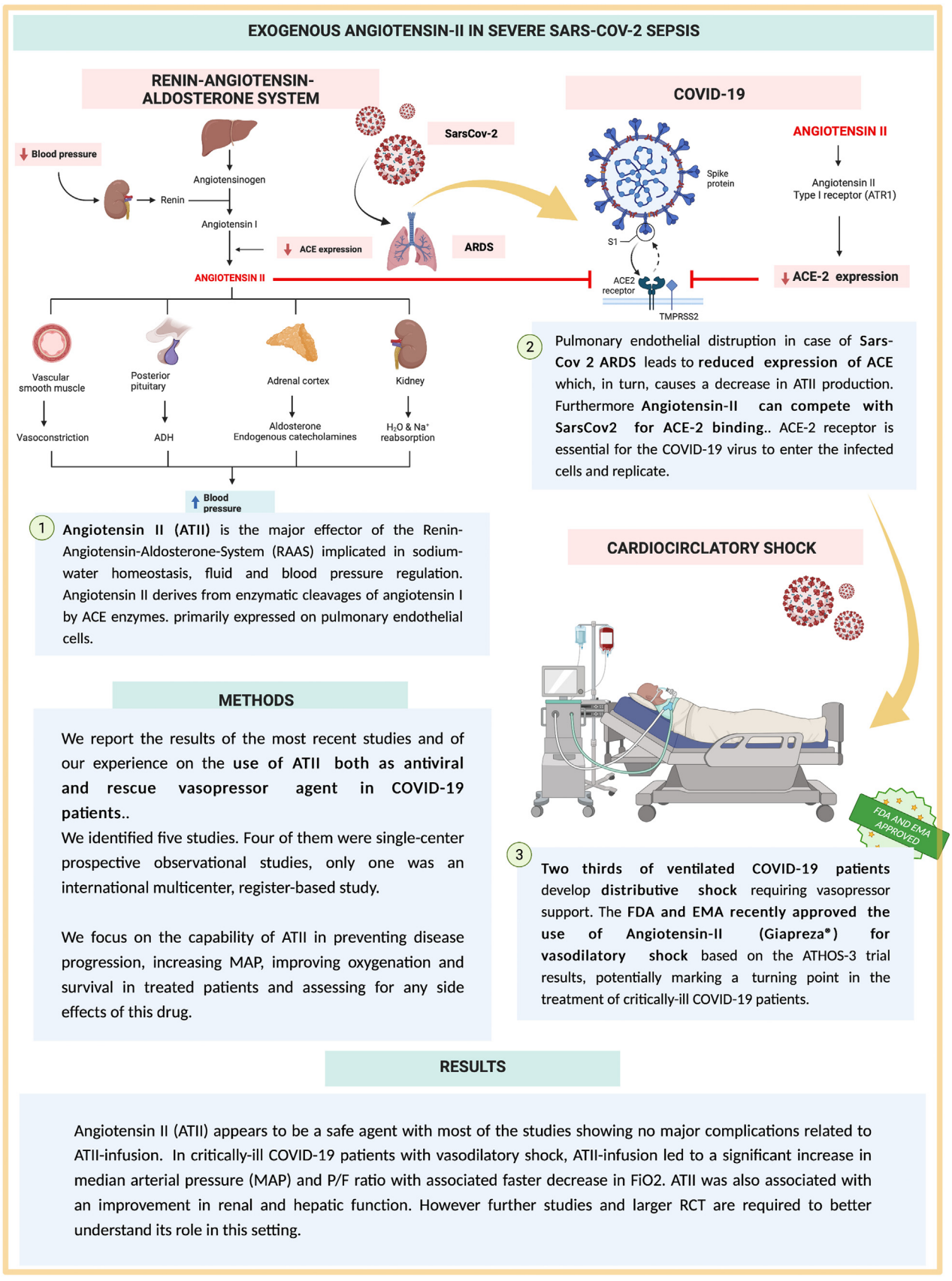

Fig 1. Rationale for the use of exogenous angiotensin-II in severe SARS-CoV2 sepsis. ACE, angiotensin-converting enzyme; ARDS, acute respiratory distress syndrome.

Table 1
Main Trials on ATII in COVID-19

Study	Type of Study	Intervention	Study Population	Results	Harm, Length of Stay in Hospital, and Mortality
Heinicke et al 2020[24]	Single-center prospective observational study	Intravenous ATII administration to severe patients with COVID-19	6 patients with severe COVID-19: 4 with severe vasodilatory shock, 2 without	Study interrupted because 5 out of the first 6 patients died during or shortly after ATII administration. No improvement in respiratory parameters. No controls. No antiviral effect observed.	5 out of 6 patients treated with ATII administration died.
Morselli et al 2020[23]	Single-center prospective observational study	Intravenous ATII administration as antiviral drug	7 patients with moderate COVID-19–related ARDS in non-ICU setting	At day 28, the median change in the 6-category ordinal scale was +3, with clinically relevant improvement in 4 patients (57%).	No patients developed major complications related to ATII administration. One patient had a mild cutaneous hand rash.
Serpa Neto et al 2021[21]	Prospective, international, multicenter, registry-based study	ATII either as second-line vasopressor in addition to norepinephrine or solely as first-line agent	Critically ill patients with COVID-19 (65 treated *v* 67 controls)	ATII group had a faster decrease in F_IO_2 and similar MAP levels during the first 12 hours. During the first 3 days after inclusion, P/F ratio was significantly higher, F_IO_2 remained lower, and MAP was higher in the ATII group.	No difference in ventilator-free days at day 28, ICU, hospital-free days at day 28, and ICU and hospital mortality between the 2 groups (53.8% *v* 40.3%; p 0.226). The need for RRT and ECMO during hospital stay was similar. The incidence of complications was similar.
Zangrillo et al 2020[19]	Single-center prospective observational study	ATII as primary or rescue vasopressor in ventilated COVID-19 with vasodilatory shock	Sixteen invasively ventilated patients with COVID-19 with vasodilatory shock.	MAP and urine output stable, P/F increased significantly with a decrease in F_IO_2, and PEEP CRP decreased. Lactate and creatinine increased.	Absence of early physiologically harm.
Zangrillo et al 2021[20]	Single-center, case-control, prospective observational study	ATII either as rescue vasopressor or as low dose vasopressor support in mechanically ventilated patients with COVID-19	Invasively ventilated patients with COVID-19 (46 treated *v* 53 controls)	ATII increased MAP and P/F ratio and decreased OR of liver dysfunction and the risk of RRT use in patients with abnormal baseline creatinine. No effect on lactate, urinary output, serum creatinine, CRP, platelet count and thromboembolic complications.	ATII therapy was not associated with harm in relation to mortality, length of invasive mechanical ventilation, thromboembolic events, and length of stay in hospital.

Abbreviations: ARDS, acute respiratory distress syndrome; ATII, angiotensin-II; CRP, c-reactive protein; ECMO, extracorporeal membrane oxygenation; F_IO_2, fraction of inspired oxygen; ICU, intensive care unit; MAP, mean arterial pressure; OR, odds ratio; PEEP, positive end-expiratory pressure; P/F ratio, P_aO_2/F_IO_2 ratio; Pts, patients; RRT, renal replacement therapy.

vasoconstriction-associated organ damage and acute vascular injury.[13,24] Chronic adverse effects of ATII include the development of cardiac hypertrophy and fibrosis.[25,26] Moreover, the timing of ATII administration also may alter its effect. According to Salgado et al, ATII may provide benefit only in case of early administration, whereas it may be detrimental and proinflammatory if septic shock already is advanced.[27] However, the findings of the ATHOS-3 study suggested otherwise, and no studies showing a detrimental effect on clinically relevant outcomes have been published so far.

Finally, important reassuring signals on the use of ATII administration in patients with COVID-19 have been provided indirectly by the recent interruption for safety concerns of the Randomized Embedded Multifactorial Adaptive Platform for Community-Acquired Pneumonia (REMAP-CAP) adaptive trial involving the ACE inhibitor / angiotensin-receptor blocker domain in critically ill patients, which suggested harm from either decreasing ATII generation (ACE inhibitors) or blocking its action (angiotensin-receptor blockers).

Conclusions

ATII is an effective vasoconstrictor for vasoplegic patients, according to several trials. Moreover, ATII has been studied as a vasopressor agent in a few patients with COVID-19 in the intensive care unit, with encouraging results, even though further studies are required in this setting. Finally, based on limited available data, further investigations of ATII in several settings and, potentially, as a primary vasopressor appear justified.

Conflict of Interest

Alexander Zarbock received honorariums and research grants from Fresenius, Baxter, Astellas, AM Pharma, Paion, Guard Therapeutics, Novartis, Bayer, BioMerieux, GIF, BMBF, and DFG. Giovanni Landoni received speaker fees from Paion.

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