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Original Article

Real-world Experience of Angiotensin II and Renin Usage in Patients With Distributive Shock: A Single-center Descriptive Study

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Objective: To evaluate real-life use of angiotensin II, a novel vasopressor, and renin, which can be used as a marker of endogenous angiotensin II deficiency and disease severity.

Design: A retrospective observational single-center cohort study.

Setting: Four intensive care units in one university hospital.

Participants: Adult patients with distributive shock, no limitations of active care, and with ongoing use of vasoconstrictors (norepinephrine base ≥0.3 mcg/kg/min plus vasopressin), who were admitted between August 2022 and August 2023.

Interventions: None.

Measurements and Main Results: Septic shock (38/42, 90.5%) and post-cardiopulmonary bypass vasoplegia (4/42, 9.5%) were the causes of distributive shock. After the initiation of angiotensin II, a decrease in the norepinephrine base dose at 4, 24, and 48 hours (0.40 ± 0.25 mcg/kg/min, 0.21 ± 0.11 mcg/kg/min, and 0.13 ± 0.06 mcg/kg/min, respectively), and a decrease in vasopressin dose were observed. Renin concentration decreased after initiation of angiotensin II from 376.90 ± 168.50 mU/L to 188.24 ± 167.47 mU/L ($p < 0.01$). Control renin was lower in survivors to hospital discharge compared with nonsurvivors (78.06 ± 121.14 mU/L in survivors, *v* 259.07 ± 163.4 mU/L in nonsurvivors, $p < 0.01$).

Conclusions: Angiotensin II can be used to decrease the doses of non-angiotensin II vasopressors, and renin concentration may potentially aid in the prognostication of patients with distributive shock.

Key Words: intensive care medicine; distributive shock; vasopressor; angiotensin II; renin; norepinephrine; vasopressin

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ANGIOTENSIN II IS A NOVEL vasopressor that has been commercially available since 2017, with increased use in the last few years.[1-8] In ATHOS-3, a large randomized trial, angiotensin II use decreased the dose of norepinephrine.[9] However, the trial was not designed to evaluate a mortality difference, which was documented only in post-hoc subgroup analyses.[10-13] A decrease in norepinephrine dose when using angiotensin II has also been shown in a number of observational studies.[1,2,14]

The most interesting subgroup of patients benefiting from angiotensin II in terms of survival is patients with high renin,[10] a finding that could be explained by a negative feedback loop where increased concentrations of angiotensin II inhibit renin release from juxtaglomerular cells.[10,15] Hyper-reninemia could thus identify patients who are most likely to respond to angiotensin II.

Additionally, persistent hyper-reninemia is strongly correlated with mortality, which is probably explained by renin expression driven by endothelial denudation.[16-19] Endothelial damage associated with shock states, and especially septic shock, leads to lower activity of angiotensin-converting enzyme (ACE), leading to lower concentrations of endogenous angiotensin II, and consequently higher renin concentrations because of the loss of the negative feedback loop normally exerted by angiotensin II on renin.[10,15-17] Several other factors also stimulate renin expression from the juxtaglomerular cells, including hypotension, hyponatremia, and activation of the sympathetic nervous system.[15-17] This could explain the association between hyper-reninemia and worse outcomes that have been observed in some studies.[18-21] These studies predate angiotensin II use, and the impact of renin changes after the initiation of angiotensin II is unclear. Also, renin is available only in select hospitals, usually during work hours,[16] which limits its role in identifying patients who should receive angiotensin II but allows for the use of renin as a prognostic marker.

The aim of this study was to report on real-life usage of angiotensin II and renin in four intensive care units (ICUs) in a university hospital in the first year after the introduction of angiotensin II to clinical practice.

Materials and Methods

Study Design and Setting

The study was conducted in four ICUs (medical, surgical, cardiac surgery, and infectious diseases) in a 1,311-bed university hospital from August 2022 to August 2023, the first months of angiotensin II use in this institution. Institutional ethics committee approval was obtained, and informed consent was waived because of the retrospective nature of the study.

Study Population

Due to the novelty and cost of angiotensin II, institutional guidelines were introduced to monitor and limit its use, and every patient who received angiotensin II was reported to the institutional pharmacy. The criteria for angiotensin II use included the following: norepinephrine base infusion $\geq$0.3 mcg/kg/min plus infusion of vasopressin, presence of distributive shock, withdrawal of blood for renin determination, and no limitations on active care in place.

Echocardiography was always used to differentiate distributive shock from cardiogenic or hypovolemic shock, and additional hemodynamic monitoring devices (Pulse index Continuous Cardiac Output [PiCCO], Pulsion Medical Systems, Feldkirchen, Germany, and pulmonary artery catheters) were used as per the treating physician's decision to help outline patients with distributive shock. The authors recorded whether other vasopressor drugs or vasopressor-sparing strategies (epinephrine, methylene blue, hydrocortisone, thiamine, ascorbic acid, and cytokine adsorption membrane) were used in addition to norepinephrine, vasopressin, and angiotensin II. Chronic use of ACE inhibitors (ACEi) and angiotensin receptor blockers (ARBs) was also recorded. Norepinephrine was always started as the first-line vasopressor, and the dose of norepinephrine base at which vasopressin, the second-line vasopressor, was added was around 0.25 mcg/kg/min. Angiotensin II was used as a third-line "rescue" therapy vasopressor. Angiotensin II was generally used primarily to decrease the dose of norepinephrine and, if possible, vasopressin. The initial dose of angiotensin II was 20 ng/kg/min, and up-titration was in increments of 20 ng/kg/min until a satisfactory response was achieved; the maximum dose of angiotensin II was 100 ng/kg/min. Down-titration of angiotensin II was usually started when the dose of norepinephrine base was around 0.2 mcg/kg/min, with the aim of stopping angiotensin II when the patient required $<$0.2 mcg/kg/min of norepinephrine base. There were no prespecified time limits regarding the duration of angiotensin II infusion, but the aim was to limit the duration of angiotensin II therapy to around 24 hours. Norepinephrine, vasopressin, and angiotensin II were present in departmental pharmacies, with at least one vial of angiotensin II present in every ICU.

Measurements

Basic demographic data and data relevant to ICU stay (ICU and hospital survival, APACHE II score on admission to ICU, lactate on admission to ICU and at start of infusion of angiotensin II and renal replacement therapy [RRT]), data relevant to the use of vasopressors (4-hourly doses of norepinephrine, vasopressin, and angiotensin II; 4-hourly mean arterial pressure [MAP] measurements; and duration of treatment with vasopressors), and data regarding renin concentration were collected. Actual body weight was used for the calculation of the dose of norepinephrine and angiotensin II. The source data were paper-based temperature and therapeutic charts, and electronic for all other data.

Blood samples for renin determination were collected in ethylenediaminetetraacetic acid tubes and transported to the central laboratory immediately after sample withdrawal. All samples were centrifuged at 3,500 g for 10 minutes to obtain plasma. From Monday to Friday, within the collection time frame of 8 AM to 2 PM, plasma samples were analyzed

immediately (within 2 hours of collection). If samples were obtained outside the aforementioned working time frame, patients' plasma samples were aliquoted and stored at −85°C until analysis on the next working day.

When reporting on renin dynamics, the first reported values were of renin obtained immediately before the initiation of angiotensin II ("renin before angiotensin II"), and the second reported values were calculated using the last measurement ("renin after angiotensin II") if multiple additional measurements were performed. Control renin measurements were taken 24 or 48 hours after blood for the first renin was withdrawn.

Renin concentration in plasma samples was measured as direct renin using the chemiluminescent immunoassay method on the LIAISON fully automated analyzer platform (LIAISON, Diasorin S.p.A., Saluggia, Italy). In the LIAISON Direct Renin assay, renin is sandwiched between a capture antibody adsorbed on magnetizable beads and a second isoluminol-linked antibody that detects the reaction. The relative light units developed by the mixture when exposed to an essential environment are proportional to the concentration of renin and allow its quantification. Renin concentration is expressed in mU/L (μU/mL), with a normal range of 4-50 mU/L and an upper reported limit at a value of 500 mU/L.

Data Analysis

Data were analyzed using R programming language 4.2.3 (R Core Team 2021, Vienna, Austria) using the Wilcoxon signed-rank test for the determination of statistically significant differences between paired samples after the Shapiro-Wilk test of normality. Statistically significant differences in continuous variables between groups were determined using the Mann-Whitney U-test after the Shapiro-Wilk test of normality. To further correct the statistics and adjust for age, weight, sex, admission lactate levels, and admission APACHE II score, generalized linear models and linear mixed models using the lme4 package were used. To account for paired samples, linear mixed models were fitted using the blocking technique (paired samples) with the block factor set as a random variable.[22] Statistically significant differences were considered at a p-value < 0.05.

Results

Baseline Characteristics

A total of 42 adult patients, 28 (66.7%) males and 14 females (33.3%), age 61 ± 12.2 years, were enrolled. Thirty-eight patients (90.5%) received angiotensin II because of septic shock, and four patients (9.5%) because of vasoplegic syndrome after cardiopulmonary bypass. Eighteen (42.9%) patients were receiving RRT when angiotensin II was initiated. The cumulative vasopressor dose before the initiation of angiotensin II expressed in norepinephrine-base-equivalent dose[14] was 0.69 ± 0.26 mcg/kg/min. The admission APACHE II score was 24 ± 7.3. Twenty-one (50%) patients were discharged alive from the ICU, and fifteen (35.7%) from the hospital. Mean ICU admission lactate was 5 ± 2.9 mmol/L, and mean lactate on initiation of angiotensin II was 5.8 ± 3.4 mmol/L. Chronic use of ACEi was recorded in 9 patients (21.4%) and chronic use of ARBs in 4 patients (9.5%). No significant differences between survivors and nonsurvivors to hospital discharge in demographic data or in baseline parameters were observed except for requirement for RRT, which was less frequent in survivors (RRT was used in 2 [13.3%] survivors *v* 16 [59.3%] nonsurvivors, $p < 0.01$), and in the previous use of ARBs, which was more frequent in survivors (4 [26.7%] survivors *v* 0 [0%] nonsurvivors, $p = 0.01$). General demographic data and parameters describing the course of treatment in the ICU are described in Table 1.

Angiotensin II Usage Results

Mean infusion rates of norepinephrine base and vasopressin before initiation of angiotensin II were 0.54 ± 0.23 mcg/kg/min and 0.047 ± 0.017 IU/min, respectively, and MAP was 62 ± 9.2 mmHg. Angiotensin II was started on the day of admission to the ICU in 23 patients (54.7%), on ICU day 2 in 13 patients (30.9%), on ICU day 3 in 2 patients (4.8%), and on ICU days 4, 5, 18, and 36 in 1 patient each (2.4%). The initial dose of angiotensin II was 20 ng/kg/min in 36 patients (85.7%), 10 ng/kg/min in 5 patients (11.9%), and 40 ng/kg/min in 1 patient (2.4%). There were 18 patients with ongoing angiotensin II at 24 hours (6 survivors and 12 nonsurvivors), and 4 patients at 48 hours (1 survivor and 3 nonsurvivors). The maximum dose of angiotensin II was 80 ng/kg/min, and this was used in 3 nonsurvivors for a duration of 16 hours each. The maximum dose in a survivor was 60 ng/kg/min, which was used for a duration of 20 hours.

A significant decrease in the dose of norepinephrine base at 4, 24, and 48 hours after the initiation of angiotensin II (0.54 ± 0.23 mcg/kg/min *v* 0.40 ± 0.25 mcg/kg/min, $p < 0.01$; *v* 0.21 ± 0.11 mcg/kg/min, $p < 0.01$; and *v* 0.13 ± 0.06 mcg/kg/min, $p < 0.01$, respectively) were observed. Similarly, decreases in vasopressin doses were observed at 4, 24, and 48 hours after initiation of angiotensin II (0.047 ± 0.017 IU/min *v* 0.038 ± 0.017 IU/min, $p < 0.01$; *v* 0.035 ± 0.024 IU/min, $p = 0.02$; *v* 0.025 ± 0 IU/min, $p = 0.16$). Statistically significant observations were additionally confirmed for both norepinephrine at 4 and 24 hours after initiation of angiotensin II ($p < 0.01$; $p < 0.01$) and vasopressin at 4 and 24 hours after initiation of angiotensin II ($p < 0.01$; $p < 0.01$), when adjusting for sex, age, weight, admission lactate levels, and admission APACHE II score using linear mixed models. Additionally, it was observed that the admission APACHE II score was independently associated with both norepinephrine at 4 and 24 hours after initiation of angiotensin II ($p < 0.01$; $p < 0.01$). Moreover, sex was also independently associated with norepinephrine at 4 hours after initiation of angiotensin II ($p < 0.01$).

Table 1
General Demographic Data and Parameters Describing the Course of Treatment in the ICU in the Overall Population and Divided Into Survivors and Nonsurvivors to Hospital Discharge

	All Patients	Survivors	Nonsurvivors	p-Value
Age, y	61 ± 12.2	59.3 ± 11.7	61.9 ± 12.5	0.51
Male sex, %	66.7	60.0	70.4	0.52
Height, cm	174.2 ± 7.3	173.5 ± 9.1	174.6 ± 6.3	0.66
Weight, kg	90.8 ± 17.4	92.7 ± 20.2	89.7 ± 16.2	0.60
Hospital day of initiation of angiotensin II, d	2.83 ± 5.88	1.53 ± 0.64	3.56 ± 7.27	0.29
Admission lactate, mmol/L	5 ± 2.9	4.4 ± 2.2	5.4 ± 3.2	0.27
Lactate before initiation of angiotensin II, mmol/L	5.8 ± 3.4	6.4 ± 3.9	5.4 ± 3.1	0.39
Lactate 4 h after initiation of angiotensin II, mmol/L	4.9 ± 2.8	3.9 ± 1.9	5.3 ± 3.1	0.21
Lactate 24 h after the initiation of angiotensin II, mmol/L	3.4 ± 3.0	3.1 ± 1.7	3.7 ± 3.9	0.68
Admission APACHE II score	23.9 ± 7.3	25.5 ± 7.0	23.1 ± 7.5	0.32
Septic shock (%)	38 (90.5)	15 (35.7)	23 (54.8)	0.28
Source pneumonia (%)	23 (54.8)	11 (26.2)	12 (28.6)	0.11
Source abdomen (%)	5 (11.9)	1 (2.4)	4 (9.5)	0.64
Source urinary tract infection (%)	5 (11.9)	1 (2.4)	4 (9.5)	0.64
Source soft tissues (%)	4 (9.5)	1 (2.4)	3 (7.1)	1.00
Source vascular catheters (%)	1 (2.4)	0 (0)	1 (2.4)	1.00
Intubation (%)	38 (90.5%)	13 (31.0)	25 (59.5)	0.61
Highest creatinine on day of initiation of angiotensin II, mmol/L	236.3 ± 199.4	248.3 ± 229.4	229.6 ± 185.0	0.77
Renal replacement therapy (%)	18 (42.9)	2 (4.8)	16 (38.1)	0.01
Cytokine adsorbing membrane (%)	7 (16.7)	1 (2.4)	6 (14.3)	0.39
Cumulative dose of vasopressors expressed in norepinephrine-equivalent dose before initiation of angiotensin II, mcg/kg/min	0.69 ± 0.26	0.70 ± 0.23	0.68 ± 0.28	0.80
Simultaneous use of hydrocortisone (%)	36 (85.7)	14 (33.3)	22 (52.4)	0.40
Simultaneous use of epinephrine (%)	1 (2.4)	0 (0)	1 (2.4)	1.00
Simultaneous use of methylene blue (%)	9 (21.4)	3 (7.1)	6 (14.3)	1.00
Simultaneous use of hydroxocobalamin (%)	10 (23.8)	2 (4.8)	8 (19.0)	0.28
Simultaneous use of dobutamine (%)	7 (16.7)	2 (4.8)	5 (11.9)	1.00
Chronic use of angiotensin-converting enzyme inhibitors (%)	9 (21.4)	1 (2.4)	8 (19.0)	0.12
Chronic use of angiotensin receptor blockers (%)	4 (9.5)	4 (9.5)	0 (0)	0.01
Survival to ICU discharge (%)	21 (50)	15 (35.7)	6 (14.3)	0.01
Survival to hospital discharge (%)	15 (35.7)	15 (35.7)	0 (0)	/

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit.

Of the 42 patients assessed, 22 (52.4%) were receiving norepinephrine 24 hours after initiation of angiotensin II (27 patients [64.3%] survived to 24 hours after initiation of angiotensin II), and 11 (26.2%) were receiving norepinephrine at 48 hours after initiation of angiotensin II (22 patients [52.4%] survived to 48 hours after initiation of angiotensin II). Regarding vasopressin, 38 patients (90.5%) were receiving vasopressin at 4 hours after initiation of angiotensin II (39 patients [92.9%] survived to 4 hours after initiation of angiotensin II), 11 patients (26.2%) at 24 hours, and 2 patients at 48 hours (27 [64.3%] and 22 patients [52.4%] were alive at 24 and 48 hours, respectively). Vasopressor doses and MAP measurements in the first 48 hours after the initiation of angiotensin II are presented in Fig 1.

In total, 125 vials of angiotensin II (2.5 mg of angiotensin II per vial) were used during the study period, meaning a consumption of around 3 vials per patient, or, from an institutional viewpoint, around 10 vials per month.

No adverse events were reported in patients who received angiotensin II during the study period. No new-onset deep vein thromboses were diagnosed (regular screening was not performed, only as clinically indicated). Ischemic changes on fingers were present in four patients before starting angiotensin II infusion, of whom three patients died in the ICU, and one patient was discharged from the hospital with a partial amputation of a distal thumb.

Renin Usage Results

Blood samples for renin were obtained from 28 patients (66.7%) immediately before initiation of angiotensin II (376.9 ± 168.5 mU/L), and from 18 patients (42.9%) on day 1 after initiation of angiotensin II (200.9 ± 183.1 mU/L), and from 6 patients (14.3%) on day 2 (144.7 ± 110.5 mU/L).

A significant decrease in renin concentration between the renin obtained before and after the initiation of angiotensin II was observed (376.9 ± 168.5 mU/L *v* 188.24 ± 167.47 mU/L, $p < 0.01$) (Fig 2). This was additionally confirmed using linear mixed models adjusted for sex, age, weight, admission lactate levels, and admission APACHE II score, where the decrease in renin remained statistically significant ($p < 0.01$).

In a group of patients with renin greater than three times upper limit (which has been reported as a group of patients who should benefit most from the addition of angiotensin II),[10] no association between renin and significant decrease in norepinephrine base dose after the initiation of angiotensin II was observed (≤3 times upper limit: 0.36 ± 0.26 mcg/kg/min *v* >3 times upper limit: 0.43 ± 0.24 mcg/kg/min at 4 hours;

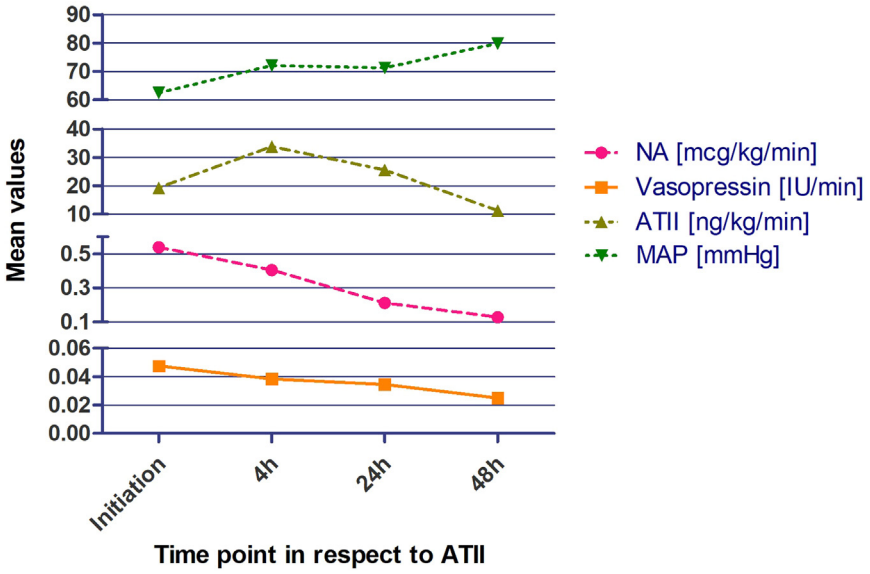

Fig 1. Vasopressor doses and MAP measurements in the first 48 hours after initiation of angiotensin II. ATII, angiotensin II; MAP, mean arterial pressure; NA, norepinephrine.

≤3 times upper limit: 0.27 ± 0.13 mcg/kg/min *v* >3 times upper limit: 0.22 ± 0.08 mcg/kg/min at 24 hours; ≤3 times upper limit: 0.16 mcg/kg/min *v* >3 times upper limit: 0.14 ± 0.06 mcg/kg/min at 48 hours). This was further confirmed using generalized linear models adjusted for sex, age, weight, admission lactate levels, and admission APACHE II score (at 4 hours after initiation of angiotensin II p = 0.18, at 24 hours p = 0.28, and at 48 hours p = 1.00, respectively).

Comparing renin concentrations before the initiation of angiotensin II between ICU- and hospital-based survivors and nonsurvivors, nonsignificantly lower concentrations were observed in survivors (313.05 ± 195.0 mU/L *v* 450.54 ± 92.5 mU/L, p = 0.05 for survival to ICU discharge, and 311.35 ± 199.9 mU/L *v* 419.29 ± 134.5 mU/L, p = 0.11 for survival to hospital discharge). Comparing renin concentrations after the initiation of angiotensin II between ICU and hospital survivors and nonsurvivors, significantly lower renin in survivors to ICU discharge (87.04 ± 106.04 mU/L *v* 298.54 ± 162.29 mU/L, p < 0.01) and significantly lower renin in survivors to hospital discharge (78.06 ± 121.14 mU/L *v* 259.07 ± 163.4 mU/L, p < 0.01 for survival to hospital discharge) were observed (Fig 3). Differences were even greater after adjusting for age, weight on admission to ICU, sex, admission lactate levels, and admission APACHE II score using generalized linear models (p < 0.01 for survivors to ICU discharge, and p = 4.2 × 10-5 for survivors to hospital discharge). It was also observed that high weight on admission to ICU was independently associated with ICU (p < 0.01) and hospital survival (p < 0.01).

Subsequently, a higher renin decrease in association with survival to ICU (survived: −207.12 ± 176.95 mU/L *v* deceased: −145.07 ± 167.06 mU/L) and hospital discharge

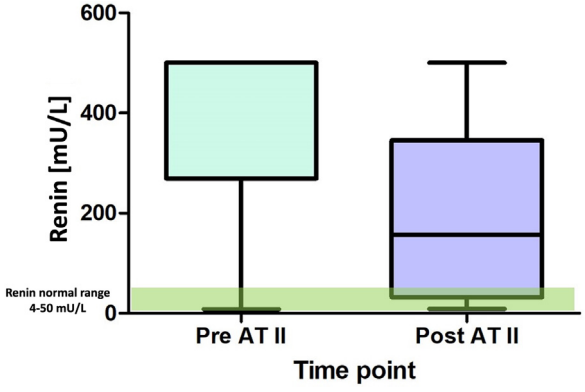

Fig 2. Renin concentration before and after the initiation of angiotensin II. Post AT II, renin concentration 24 hours or 48 hours after initiation of angiotensin II; Pre AT II, renin concentration before initiation of angiotensin II.

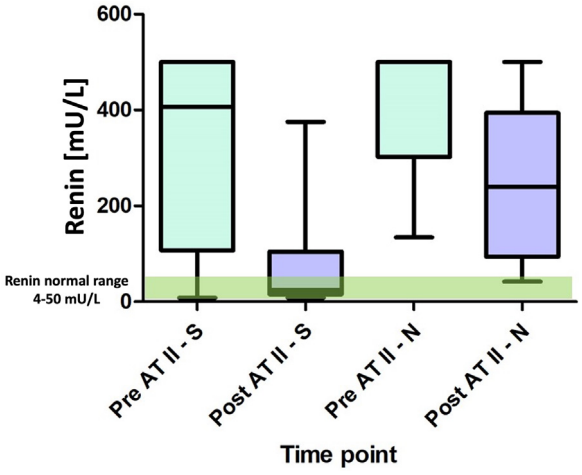

Fig 3. Renin concentration before and after initiation of angiotensin II in survivors and nonsurvivors to hospital discharge. Pre AT II-N, renin concentration before initiation of angiotensin II in nonsurvivors to hospital discharge; Pre AT II-S, renin concentration before initiation of angiotensin II in survivors to hospital discharge; Post AT II-N, renin concentration 24 hours or 48 hours after the initiation of angiotensin II in nonsurvivors to hospital discharge; Post AT II-S, renin concentration 24 hours or 48 hours after initiation of angiotensin II in survivors to hospital discharge.

(survived: −231.16 ± 161.64 mU/L *v* deceased: −145.08 ± 174.28 mU/L) we observed; however, a statistically significant difference was not observed.

Discussion

In patients with distributive shock admitted to four ICUs, angiotensin II significantly reduced norepinephrine base doses from 0.54 mcg/kg/min to 0.40 mcg/kg/min, continuing to decrease at 24 and 48 hours, along with a decrease in the dose of vasopressin. Renin remained high in nonsurvivors and almost normalized in survivors. No new thromboses occurred.

Similar short-term (0-3 hours) reductions in other vasoconstrictors (norepinephrine-base-equivalent doses from 0.55 mcg/kg/min to 0.39 mcg/kg/min) were observed in a multicenter, observational study, ARTEMIS, with 162 patients included in a 4-year study period.[14] Decreased norepinephrine-base-equivalent doses of non-angiotensin II vasopressors of around 0.06 mcg/kg/min in the 0-3-hour period were also observed in a multicenter, randomized trial (ATHOS-3 trial).[9] As per institutional guidelines, the use of angiotensin II in the current study was limited to patients with presumed distributive shock, with >90% of patients receiving angiotensin II because of septic shock, and the rest receiving angiotensin II because of vasoplegic shock following cardiac surgery. This is similar to the ATHOS-3 trial, where 90.3% of patients received angiotensin II because of sepsis or potential sepsis,[9] while in other studies, around 30% of patients received angiotensin II for nondistributive shock.[2,14] The current authors included a similar patient cohort regarding most parameters of disease severity, apart from a lower APACHE-II score (24 in the current study and around 30 in other studies), which could potentially be explained by different methodology—the admission APACHE-II score was used, rather than the APACHE-II score at the initiation of angiotensin II. The mortality in the ICU (50%) and in the hospital (64%) observed in the current study was high but similar to that described in other works studying patients on multiple vasopressors,[2,9] while the current authors reported cumulative doses of vasopressors expressed in norepinephrine-base-equivalent doses[23] that was slightly higher (0.69 mcg/kg/min in the current study) than that reported in the other studies (0.58 and 0.34 mcg/kg/min, respectively).[2,9] Notably, even higher mortality rates can be expected in patients who are receiving multiple vasopressors, and in some studies, mortality in patients on three vasopressors reached 90%.[24] The current authors used similar initial and maximum doses of angiotensin, with maximum doses in other studies reported between 33 and 52 ng/kg/min, compared with 38 ng/kg/min in the current study.[1,2,9] There are no standardized protocols prescribing the use of angiotensin II. A great variety exists within the cohort of patients receiving angiotensin II, so the current authors chose not to report in terms of responders and nonresponders to angiotensin II in terms of a clinical response (which is mostly reported as an increase in MAP and/or a decrease or stabilization of the total dose of vasopressors). Nonresponders could have been responders if they had received a higher dose of angiotensin II. Actual body weight was used for the calculation of the vasopressor dose; however, a rationale exists that for obese patients (body mass index >30 kg/m^2) adjustment for body weight should be used, based on the observation that total norepinephrine dose is similar in patients with body mass index <30 kg/m^2.[25] In addition to norepinephrine, vasopressin, and angiotensin II, other vasopressors were also used in the current patients, namely, epinephrine in 1 patient, methylene blue in 9 patients, and hydroxocobalamin in 10 patients. In all cases, these agents were used before angiotensin II, most likely because they were available in the institution before angiotensin II and clinicians would have used them as third- or fourth-line vasopressors in patients who required high doses of norepinephrine before angiotensin II became available. A great majority of the authors' patients were receiving hydrocortisone (85.7%), most likely because of the high incidence of sepsis as the cause of vasoplegia in these patients. The use of these agents could have impacted the course of treatment. Methylene blue counteracts vasoplegia by directly inhibiting the inducible nitrous oxide synthase, inhibiting the action of soluble guanylate cyclase, and reducing the dose of catecholamines. It has been used in the setting of refractory vasoplegia for more than 20 years.[26] Hydroxocobalamin prevents the formation of both nitrous oxide and hydrogen sulfide, which are both elevated in sepsis and associated with poor outcomes, and in a pilot trial, it was associated with a reduced norepinephrine dose compared with placebo.[27] The indication for hydrocortisone in this case series was septic shock with ongoing vasopressors with the aim of shortening the duration of shock.[28] The use of the aforementioned adjunct therapies was not protocolized and represents an important limitation when interpreting the observed effect of angiotensin II on norepinephrine and vasopressin dose reduction.

RRT (continuous venovenous hemodialysis was used in all cases) was required more frequently in nonsurvivors to hospital discharge compared with survivors (59.3% *v* 13.3%). The use of RRT in the setting of vasoplegia is important, as it can impact the requirement for vasopressors by correcting metabolic acidosis, which impairs the effectiveness of catecholamines and vasopressin.[29] In the current case, more frequent use of RRT in nonsurvivors could have been associated with higher acuity of illness in nonsurvivors. The authors have no satisfactory explanation for the higher frequency of chronic use of ARBs in survivors, as exposure to ARBs should have reduced the effect of angiotensin II by antagonism at the level of the receptor.[30]

Patients who develop vasoplegia after cardiopulmonary bypass because of cardiac surgery could present a specific subset of patients. Exogenous angiotensin II could be a reasonable therapeutic modality because of a presumed lack of endogenous angiotensin II due to a transient interruption of pulmonary circulation and subsequent disturbance of pulmonary conversion to angiotensin II.[31,32] Only four patients after cardiac surgery were included, and they all died in the ICU. All four patients underwent emergency cardiac surgery (two emergency coronary artery bypass grafting, one Bentall procedure, and one mitral valve replacement and coronary artery bypass

grafting). In all four patients, vasoplegia after extracorporeal circulation was identified as the most significant factor contributing to circulatory shock. They all received norepinephrine, vasopressin, and methylene blue in the operating theatre, and angiotensin II after ICU admission.

Regarding the changes in renin in the current patients, overall (all patients received angiotensin II), it was halved from before to after the initiation of angiotensin II. Renin decreases were significantly more pronounced in survivors to ICU and hospital discharge. Renin almost normalized in survivors to ICU and hospital discharge, compared with nonsurvivors, in whom it remained elevated to around 6 times above the upper normal level. Renin concentrations comparable to the results of post-hoc analysis of data from the ATHOS-3[10] and VICTAS[20] studies were observed, with median baseline renin concentrations reported at 172.7 pg/mL (288.4 mU/L) and 188.7 pg/mL (315.1 mU/L), respectively, compared with 225.7 pg/mL (376.9 mU/L) in the current study.[10,20,33] No decrease in the dose of norepinephrine in a subgroup of patients with initial renin levels elevated to >3 times above the upper level was observed. Renin concentrations were not reported in other retrospective observational studies on patients with angiotensin II, and subsequent analysis of the ATHOS-3 patient cohort data revealed that patients with renin >3 times above the upper level benefited most from angiotensin II.[10] The current observations are closer to pre-angiotensin II era studies on renin changes, where an association was observed between persistently elevated renin and mortality.[18-21] Chung et al. retrospectively included 105 patients with septic shock and observed significantly lower renin in survivors, with renin both lower and decreasing between ICU day 1 and day 3 in survivors, and persistently elevated between ICU day 1 and 3 in nonsurvivors. They also observed a positive correlation between elevated renin and higher disease severity scores.[19] The current results are also consistent with findings by Lesnik et al.[18] and Jeyaraju et al.[34]; a decrease in renin in survivors compared with nonsurvivors, and no changes in lactate in survivors compared with nonsurvivors were observed (Table 1). Lesnik et al. observed in 48 patients with sepsis and septic shock that renin decreased by approximately two-thirds in survivors between ICU day 1 and day 3 and increased by around 10% in nonsurvivors. Conversely, both survivors and nonsurvivors normalized lactate levels, and there were no differences in lactate changes between survivors and nonsurvivors.[18] Similarly, Jeyaraju et al. observed in a prospective observational study of 53 adult patients who required vasopressors that renin, and not lactate concentration, was associated with in-hospital mortality.[34]

The current authors believe that monitoring changes in renin concentration in patients who are receiving angiotensin II is important primarily as a prognostic marker. Due to the limited availability of laboratory measurement of renin, it cannot currently be used to identify potential responders to angiotensin II (and in this small sample, this association was not observed). Still, it could be used with hindsight to help guide treatment decisions in patients who have received angiotensin II based on clinical criteria.[16]

This study has some limitations. It was a single-hospital study with a relatively small number of included patients (albeit including patients from four ICUs), with inherent limitations due to its observational design. So far, data on both angiotensin II and renin usage have been published from one post-hoc analysis of data from 255 patients from a randomized controlled trial,[10] and four small observational studies.[3-6] The number of patients who had renin measurements is smaller than expected because of the novelty of renin and limited availability of real-time renin analysis (renin results were available within approximately 2 hours, Mondays through Fridays from 8 AM to 2 PM, but clinicians were encouraged to withdraw renin from next-day analysis), lack of clear cutoff values to directly impact treatment (optimal interpretation of renin results is still not clear), and death of patient or clearly improving patient before control renin withdrawal (out of the initial 42 patients 27 were alive at 24 hours, and 22 were alive at 48 hours; 6 survivors were free from vasopressors on day 1, and control renin was not withdrawn in 3 of them). The novelty of angiotensin II and the lack of any standardized dosing regimens present additional limitations regarding the generalization of the results. Angiotensin II was used as a third-line vasopressor in patients who were simultaneously receiving multiple treatment modalities aimed at restoring circulation. Also, although the institutional guidelines limit the use of angiotensin II to patients with distributive shock, there were no prespecified thresholds for cardiac index. Even if no patient had a diagnosis of septic cardiomyopathy, a component of cardiogenic shock (eg, via septic or other cardiomyopathy) might have been present in a few patients, which could have contributed to circulatory failure. However, this could have been relevant only in a minority of patients in this study, since all patients underwent echocardiography and additional hemodynamic monitoring, none were diagnosed with septic cardiomyopathy, and only seven patients (16.7%) received the first-line inotrope (dobutamine). Currently, the limited availability of laboratory renin diagnostics is an important limitation affecting the applicability of these results. An important preanalytical limitation of renin measurement is the lack of stability of the renin molecule, with concentration changes due to possible cryoactivation of prorenin to renin in conditions of prolonged plasma storage in a refrigerator at 4-8°C or frozen at -−20° C,[35] which the authors aimed to avoid by freezing samples rapidly to −85°C. It should also be acknowledged that the relatively high cost of angiotensin II (approximately 1,500 EUR per vial at the time of manuscript preparation) could have influenced clinicians' perception of the target patient population and their decisions regarding the continuation of angiotensin II and other treatment modalities.

Future Developments

Angiotensin II administration and renin measurements offer a new management approach for critically ill patients. Important research areas that need to be addressed include

identifying patients who could benefit most from angiotensin II,[36] determining the optimal ratio and timing of initiation of all three currently available vasopressors, individualization of vasopressor therapy, and understanding renin changes and their impact on treatment.

Conclusions

After the initiation of angiotensin II, doses of norepinephrine and vasopressin significantly decreased at 4 hours and continued to decrease at 24 and 48 hours after the discontinuation of angiotensin II. A high initial and persistently high concentration of renin in nonsurvivors, and a clearly pronounced decrease in renin to almost normal levels in survivors, were observed. Angiotensin II could be used to reduce the need for other vasopressors, and renin concentration could help prognosticate patients with distributive shock.

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Declaration of competing interest

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CRediT authorship contribution statement

Andreja Möller Petrun: Writing – original draft, Investigation, Conceptualization. **Mario Gorenjak:** Software, Methodology, Formal analysis. **Franc Svenšek:** Investigation. **Nives Matković Lonzarić:** Investigation. **Alenka Strdin Košir:** Investigation. **Maja Cvikl Knehtl:** Resources, Investigation. **Evgenija Homšak:** Resources, Investigation. **Žiga Kalamar:** Validation, Data curation, Conceptualization. **Giovanni Landoni:** Writing – review & editing, Methodology, Conceptualization. **Andrej Markota:** Writing – original draft, Visualization, Resources, Project administration, Funding acquisition, Conceptualization.

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