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Utilization of Synthetic Human Angiotensin II for Catecholamine-Resistant Vasodilatory Shock in Critically Ill Children: A Single-Center Retrospective Case Series

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OBJECTIVES: To describe our institutional experience utilizing adjunctive synthetic angiotensin II in critically ill children with catecholamine-resistant vasodilatory shock (CRVS).

DESIGN: Single-center, retrospective case series.

SETTING: PICU and cardiac ICU (CICU) at a large, quaternary children's hospital in the United States.

PATIENTS: Twenty-three pediatric patients with CRVS who were prescribed synthetic angiotensin II at the discretion of bedside clinicians from January 2018 to April 2023.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Twenty-three patients (20 in PICU, 3 in CICU) with a median age of 10.4 years (interquartile range [IQR] 1.5–18.5) received angiotensin II over the study period, 70% of whom died. At the time of angiotensin II initiation, 17 patients (74%) were receiving one or more forms of extracorporeal therapy, and median Pediatric Logistic Organ Dysfunction-2 Score-2 in the prior 24 hours was 9 (IQR 7–11). The median time between initiation of the first vasoactive agent and angiotensin II was 127 hours (IQR 13–289), and the median total norepinephrine equivalent (NED) at initiation was 0.65 μg/kg/min (IQR 0.36–0.78). The median duration of therapy was 27 hours (IQR 4–68), and at each timepoint assessed, patients had median improvement in NED and mean arterial pressure (MAP) with treatment. Survivors initiated angiotensin II nearly 3 days earlier in vasoactive course (91.5 hr vs 161 hr, $p = 0.23$), and had both greater reduction in NED (−75% [IQR −96 to −50] vs +2.1% [IQR −55 to 33], $p = 0.008$) and greater increase in MAP (+15 mm Hg [IQR 10–27] vs −1.5 mm Hg [IQR −27 to 18], $p = 0.052$) at angiotensin II discontinuation.

CONCLUSIONS: We demonstrate reduction in NED and improved MAP following initiation of angiotensin II in critically ill children with CRVS. Further prospective work is needed to examine optimal timing of angiotensin II initiation, appropriate patient selection, and safety in this population.

KEY WORDS: angiotensin II; pediatrics; sepsis; shock

Vasodilatory shock is common in critically ill children and those affected are at increased risk for morbidity, mortality, and healthcare resource utilization (1–5). Vasoactive medications are a cornerstone of therapy; however, there are no consensus recommendations for a specific first-line vasoactive agent, nor for the optimal threshold at which adjunctive therapies should be considered (6). Coupled with the increasing evidence of untoward effects of high-dose catecholamines (7–9), these realities highlight

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KEY POINTS

Question: What are the clinical features and outcomes of children with catecholamine-resistant vasodilatory shock (CRVS) who were treated with adjunctive angiotensin II at a large, quaternary children's hospital?

Findings: In this retrospective case series, 23 critically ill pediatric patients received adjunctive angiotensin II for CRVS over a 5-year period and demonstrated improvements in norepinephrine dose equivalent and mean arterial pressure.

Meaning: Angiotensin II appears to reduce norepinephrine dose equivalent and improve mean arterial pressure in critically ill children with CRVS. Further work is needed to examine the optimal timing of angiotensin II initiation, appropriate patient selection, and safety in this population.

the need for a better understanding of how to optimally manage children with catecholamine-resistant vasodilatory shock (CRVS).

Synthetic human angiotensin II is a vasoactive agent approved by the U.S. Food and Drug Administration that raises mean arterial pressure (MAP) in adults with CRVS (10). Angiotensin II is a downstream component of the renin–angiotensin–aldosterone system and plays an integral role in blood pressure regulation (10). It is proposed that adults with septic shock and associated endothelial injury develop angiotensin-converting enzyme (ACE) dysfunction and thus are particularly responsive to angiotensin II, with several studies providing evidence to support this hypothesis (11–13). Recently, we demonstrated reduced ACE activity in children with septic shock to corroborate this theory (14). Yet, despite these theoretical benefits, angiotensin II use remains off-label in children as limited data exist regarding its safety and efficacy (15).

We have used angiotensin II at our institution for the past 5 years. We describe the demographics, clinical characteristics, and outcomes of children who received adjunctive angiotensin II for CRVS.

MATERIALS AND METHODS

Study Design

We performed a retrospective case series of all patients admitted to the PICU or cardiac ICU (CICU) at Cincinnati Children's Hospital Medical Center (CCHMC) who received angiotensin II for CRVS from January 2018 to April 2023. Angiotensin II was prescribed at the discretion of bedside clinicians, with decision-making aided by our institutional guidelines (**Appendix 1**, http://links.lww.com/CCX/B250). There were no exclusion criteria as we aimed to capture all patients treated. This study was approved by the CCHMC institutional review board with a waiver of informed consent (Study ID: 2022-0707, approved September 7, 2022), and procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and the Helsinki Declaration of 1975, as most recently amended.

Data, Outcomes, and Definitions

Demographic, clinical, and laboratory data were collected at ICU admission, in the 24 hours before angiotensin II initiation, and the duration of treatment up to 7 days. If obtained for a clinical indication, data included serum renin (LIASON Direct Renin; normal: < 59 pg/mL), which is clinically available at CCHMC. Vasoactive burden was quantified at angiotensin II initiation, at 3-, 6-, 12- and 24-hour postinitiation (as applicable), and at discontinuation using total norepinephrine equivalent dose (NED) (16). The primary outcome was ICU mortality. Secondary outcomes included ICU-free days (calculated as 28 d—ICU length of stay; patients who died were assigned "0") and change in NED and MAP with initiation of angiotensin II. **Appendix 2** (http://links.lww.com/CCX/B250) includes additional methodological details.

Statistical Analysis

Demographic and clinical characteristics are summarized using means or medians (continuous variables) or frequencies and percentages (categorical variables). Wilcoxon rank-sum, Chi-square, or Fisher exact tests were used to compare variables among those with and without ICU mortality. All statistical analyses were performed using Sigma plot 15.0 (Systat Software Inc., Palo Alto, CA).

RESULTS

Twenty-three patients received angiotensin II over the study period, 20 in the PICU and 3 in the CICU.

TABLE 1.
Demographic, Clinical, and Outcome Data for Critically Ill Children Receiving Angiotensin II

Variable	Cohort Data (*n* = 23)
Demographics	
Age, yr	10.4 (1.5 to 18.5)
Sex at birth (% female)	14 (61)
Admission diagnosis	
Shock/infection/major trauma	7 (30.4)
Respiratory failure	9 (39.1)
Postsurgical/minor trauma	1 (4.4)
CNS dysfunction	4 (17.4)
Primary cardiac/congenital heart disease	2 (8.7)
Pediatric Risk of Mortality III score	10 (4 to 16.5)
Number of comorbid conditions	2 (1 to 2)
Immunocompromised, yes (% cohort)	13 (57)
Pre-Ang II data (24 hr prior or at initiation)	
Presence of sepsis, yes (%)	21 (91)
Time between ICU admission and Ang II, days	13 (6 to 20)
Time between initiation of vasoactive and Ang II, hr	127 (12.8 to 289)
Pediatric Logistic Organ Dysfunction-2 score	9 (7 to 11)
Serum direct renin, pg/mL[a]	3,796 (1,924 to 6,000)
Lactate, mmol/L	5.7 (3.4 to 11.8)
Total NED, µg/kg/min	0.65 (0.36 to 0.78)
Extracorporeal support, yes (%)	17 (74)
Extracorporeal membrane oxygenation	2 (8.7)
Continuous renal replacement therapy	17 (74)
Severe acute kidney injury, yes (%)	21 (91)
Baseline serum creatinine known, yes (%)	14 (61)
Invasive mechanical ventilation, yes (%)	23 (100)
Stress dose steroids, yes (%)	14 (61)
Ang II therapy data and outcomes	
Duration of Ang II therapy, hr	27 (4.2 to 68)
% Change in total NED	
3 hr after initiation of Ang II	−18 (−32 to 0)
6 hr after initiation of Ang II	−28 (−47 to −1)
12 hr after initiation of Ang II	−25 (−48 to 7)
24 hr after initiation of Ang II	−19 (−66 to 1)
At Ang II discontinuation	−25 (−75 to 11)

(*Continued*)

TABLE 1. (*Continued*)
Demographic, Clinical, and Outcome Data for Critically Ill Children Receiving Angiotensin II

Variable	Cohort Data (*n* = 23)
Change in mean arterial pressure, mm Hg	
3 hr after initiation of Ang II	+6.5 (0.5 to 13.5)
6 hr after initiation of Ang II	+7 (0 to 16.5)
12 hr after initiation of Ang II	+9 (0.5 to 18)
24 hr after initiation of Ang II	+5 (−5.5 to 21)
At Ang II discontinuation	+10 (−6 to 20)
Starting dose of Ang II, ng/kg/min	10 (5 to 20)
Maximum dose of Ang II, ng/kg/min	40 (30 to 80)
Received Ang II at > 40 ng/kg/min, yes (%)	10 (43)
Duration of Ang II > 40 ng/kg/min, hr	16.5 (3.8 to 30)
New blood clot on Ang II, yes (%)	1 (4.4)
New digital ischemia, yes (%)	1 (4.4)
ICU mortality, yes (%)	16 (70)
Died while on Ang II, yes (%)	11 (48)
ICU-free days	0 (0 to 0)

Ang II = angiotensin II, NED = norepinephrine equivalent dose.
[a]Eleven patients with serum renin values were obtained clinically before initiation.
Continuous data reported as median (interquartile range).

Demographic and clinical data are presented in **Table 1**. The median age was 10.4 years (IQR 1.5–18.5; range: 1.5 mo–23 yr). All but two patients had pre-existing comorbid conditions (median 2, IQR 1–2) and 13 (57%) were immunocompromised. At angiotensin II initiation, 21 (91%) had sepsis, 21 (91%) had severe AKI, and 17 (74%) were receiving one or more forms of extracorporeal support.

The median time between ICU admission and angiotensin II initiation was 13 days (IQR 6–20). Median time between initiation of the first vasoactive and angiotensin II was 127 hours (IQR 13–289) (Table 1). At initiation, median total NED was 0.65 μg/kg/min (IQR 0.36–0.78). All 11 patients with serum renin concentrations obtained before initiation had elevated values (median: 3796 pg/mL, IQR 1,924–6,000; range: 918–6,000 pg/mL).

The median duration of angiotensin II therapy was 27 hours (IQR 4–68, range: 1.4–449 hr). At each time assessed, patients had improvement in NED and MAP with therapy (Table 1; and **eFig. 1**, http://links.lww.com/CCX/B250). The median starting dose was 10 ng/kg/min (IQR 5–20), with median maximum dose of 40 ng/kg/min (IQR 30–80). Ten patients (43%) received doses greater than 40 ng/kg/min (maximum of 80 ng/kg/min) for a median duration of 16.5 hours (IQR 3.8–30). One patient developed a new blood clot (peripherally inserted central catheter-associated thrombus) and one developed digital ischemia. Sixteen patients (70%) died in the ICU (including 11 who died while on angiotensin II), and median ICU-free days for the cohort was 0 (IQR 0–0). Survivors initiated angiotensin II nearly 3 days earlier in vasoactive course (91.5 hr vs 161 hr, $p = 0.23$), received lower maximal doses (40 ng/kg/min [IQR 20–40] vs 50 ng/kg/min [IQR 40–80], $p = 0.07$), and had both greater reduction in NED (−75% [IQR −96 to −50] vs +2.1% [IQR −55 to 33], $p = 0.008$) and greater increase in MAP (+15 mm Hg [IQR 10–27] vs −1.5 mm Hg [IQR −27 to 18], $p = 0.052$) at angiotensin II discontinuation (**Table 2**; and eFig. 1, http://links.lww.com/CCX/B250). There were no differences in NED at angiotensin II initiation between survivors and those who died.

A sensitivity analysis examining clinical features by time period (2018–2020 vs 2021–2023) was performed to assess for differences as experience with angiotensin II increased (**eTables 1** and **2**, http://links.lww.com/CCX/B250). Patients treated more recently initiated angiotensin II almost 6 days sooner in vasoactive course (109 hr [IQR 9.4–217] vs 248 hr [IQR 23.5–396], $p = 0.21$), had lower

TABLE 2.
Demographic and Clinical Characteristics For Children Receiving Angiotensin II Who Died Compared to Survivors

Variable	Alive	ICU Mortality	*p*
n (% cohort)	7 (30)	16 (70)	–
Age, yr	10.4 (1.3 to 19.1)	11.7 (1.6 to 17.9)	1.0
Sex at birth (% female)	4 (57)	10 (63)	1.0
Pediatric Risk of Mortality III score	12 (2 to 17)	9 (4 to 16.5)	1.0
Number of comorbid conditions	2 (1 to 2)	2 (1 to 2)	0.69
Immunocompromised, yes (% cohort)	2 (29)	11 (69)	0.17
Presence of sepsis at Ang II initiation, yes (%)	7 (100)	14 (88)	1.00
Receipt of stress dose steroids, yes (%)	3 (43)	11 (69)	0.36
Time between ICU admission and Ang II, d	6 (2 to 21)	14 (7.5 to 17.8)	0.69
Time between initiation of vasoactive and Ang II, hr	91.5 (6.6 to 245)	161 (25 to 356)	0.23
Serum direct renin, pg/mL	918[a]	4040 (1959 to 6000)	–
Pediatric Logistic Organ Dysfunction-2 score	8 (5 to 11)	9.5 (8 to 11)	0.46
Total NED at Ang II initiation, µg/kg/min	0.67 (0.46,0.78)	0.62 (0.32,0.89)	0.35
Severe acute kidney injury at Ang II initiation, yes (%)	5 (71)	16 (100)	0.08
Extracorporeal support at Ang II initiation, yes (%)			
Extracorporeal membrane oxygenation	0 (0)	2 (13)	1.0
Continuous renal replacement therapy	5 (71)	12 (75)	1.0
Duration of Ang II therapy, hr	42.7 (21 to 68)	22.8 (3.5 to 86)[b]	0.46
% Change in total NED			
3 hr after initiation of Ang II	−29 (−41 to −26)	−9.5 (−23,0)	0.03
6 hr after initiation of Ang II	−47 (−71 to 16)	−25 (−36 to −1)	0.19
12 hr after initiation of Ang II	−61 (−85 to −1)	0 (−39 to 14)	0.07
24 hr after initiation of Ang II	−77 (−95 to −8)	−14 (−31 to 10)	0.13
At Ang II discontinuation	−75 (−96 to −50)	2.1 (−55 to 33)	0.008
Change in mean arterial pressure, mm Hg			
3 hr after initiation of Ang II	+8 (5 to 19)	+5 (−1 to 12)	0.29
6 hr after initiation of Ang II	+14 (3.8 to 23)	+4 (−3 to 16)	0.27
12 hr after initiation of Ang II	+13.5 (−9 to 27)	+9 (4 to 13)	0.76
24 hr after initiation of Ang II	+2 (−10.5 to 24)	+5.5 (−5.3 to 22)	0.83
At Ang II discontinuation	+15 (10 to 27)	−1.5 (−27 to 18)	0.052
Maximum dose of Ang II, ng/kg/min	40 (20 to 40)	50 (40 to 80)	0.07
Received Ang II at > 40 ng/kg/min, yes	1 (14)	7 (44)	0.35

Ang II = angiotensin II, NED = norepinephrine equivalent.
[a]Only 1 of 11 patients with renin data survived.
[b]Eleven of 16 patients (69%) died while receiving Ang II.
Continuous data reported as median (interquartile range).
Dashes indicate no statistical comparison performed.

mortality (57% vs 89%, $p = 0.18$), and used lower maximal doses of angiotensin II (40 ng/kg/min [IQR 20–47.5] vs 60 ng/kg/min [IQR 45–80], $p = 0.03$). Comparison of outcomes between survivors and those who died in the contemporary cohort was similar to the full cohort (eTable 2, http://links.lww.com/CCX/B250), although

duration of angiotensin II use was shorter in survivors (35 hr [IQR 15–58] vs 51 hr [7–128], $p = 0.76$).

DISCUSSION

We report experience from our single-center case series of critically ill children with CRVS treated with adjunctive angiotensin II, and describe their demographic, clinical, and outcome characteristics. Children supported with angiotensin II were medically complex, had prolonged ICU stays before initiation, and commonly had sepsis and severe AKI. Therapy was started more than 5 days into vasoactive treatment and at very high NED, with a reduction in NED and improvement in MAP seen after initiation. Not unexpectedly, ICU mortality was high at 70%; however, our data suggest that initiation earlier in vasoactive course and more robust response (by change in NED and MAP) may be associated with improved survival.

Comparing these data to adult literature is challenging due to the severity of illness in our cohort. The median NED at initiation was 0.34 μg/kg/min in the Angiotensin II for the Treatment of High-Output Shock (ATHOS-3) trial (10), much lower than the median of 0.65 μg/kg/min seen in our cohort. Importantly, ATHOS-3 patients with NED greater than 0.5 μg/kg/min were less likely to respond to angiotensin II (10), and a recent post hoc analysis demonstrated that initiation at NED less than 0.25 μg/kg/min (relevant for only three patients in our study) was associated with improved survival (9). Similar results regarding the impact of earlier angiotensin II initiation on response were also shown in a recent multicenter study (17). However, despite initiating angiotensin II later and at higher NED, children in our study still had a reduction in NED at all time points measured. Interestingly, it does appear that earlier initiation of angiotensin II (by time from first vasoactive) may be beneficial, though this was not associated with differences in NED at initiation. Given these findings, we believe studies examining earlier use of angiotensin II are needed to demonstrate improvement in outcomes.

Although angiotensin II compared to placebo did not show a mortality benefit in ATHOS-3(10), a post hoc analysis did demonstrate patients with renin levels greater than 173 pg/mL (as a surrogate for ACE dysfunction/deficiency) had improved survival with receipt of angiotensin II (11). In our study, all children who received angiotensin II had serum renin levels higher than this threshold when measured (median 3796 pg/mL, range 918–6,000), although only one of these children survived. Given these data, our recent study demonstrating similar renin concentrations in pediatric septic shock (18), and the rapid clinical availability of this assay, further work is needed to understand if (and at what concentrations) renin levels may be considered to help guide angiotensin II therapy in children.

We report comprehensive demographics, clinical characteristics, and outcomes of children with CRVS receiving angiotensin II. Our study is limited by its retrospective nature, use in an incredibly sick population, and small sample size, which makes drawing conclusions regarding impact on outcomes and safety challenging. Future prospective work to examine these gaps is necessary.

CONCLUSIONS

We demonstrate a reduction in NED and improved MAP following initiation of angiotensin II in critically ill children with CRVS. Further prospective work is needed to examine the optimal timing of angiotensin II initiation, appropriate patient selection, and safety in this population.

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