Diagnostic and Predictive Values of Thirst, Angiotensin II, and Vasopressin During Trauma Resuscitation

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Abstract

Background. Thirst perception involves neurochemical signals attributed to acute elevation of arginine vasopressin (AVP) and angiotensin II (AT2) levels, and may accompany acute hemorrhage. **Objective.** To determine whether thirst or plasma AVP or AT2 levels predict hemorrhagic shock, injury severity, or outcome in trauma patients at initial presentation. **Methods.** This was a prospective case series of adult subjects presenting as trauma activations to an urban level I trauma center. Subjects were included if they were alert and nonintoxicated. During resuscitation, subjects were queried for thirst perception using binary and continuous data formats employing a 100-mm nonhatched visual analog scale. Blood for AT2 and AVP assessment was obtained during initial laboratory collection. Other data were abstracted retrospectively from our trauma registry. Crude and stratified analyses (blunt and penetrating trauma) assessed the correlation of thirst, AVP, and AT2 to the initial shock index, base deficit, blood transfusion requirement, admission, and Injury Severity Score (ISS). Our institutional review board (IRB) granted a waiver of informed consent. **Results.** Of 105 subjects, the average age was 35 years (95% confidence interval [CI] 32 to 38), with 31% penetrating trauma. For AVP, there was no difference in thirst perception between subjects with normal (59 mm, 95% CI 47 to 71) versus elevated (63 mm, 95% CI 56 to 70) plasma levels. For AT2, results were likewise insignificant for normal (63 mm, 95% CI 56 to 70) versus elevated (58 mm, 95% CI 46 to 70) plasma levels. Thirst, AT2 level, and AVP level demonstrated no correlation to shock index, base deficit, transfusion requirement, hospital admission, or ISS. **Conclusion.** The results of this study imply that thirst severity and AVP and AT2 plasma levels are not reliable predictors of impending hemorrhagic shock, injury severity, or outcome. The presence or absence of severe thirst should not be employed as a primary marker for dismissing or suspecting incipient shock. **Key words:** emergency medical services; trauma; triage; thirst; hemorrhagic shock; injury severity; angiotensin; vasopressin

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Introduction

Throughout the historical record, caregivers engaged in triage and casualty care in combat and at disaster scenes have recorded their anecdotal observations that many patients in acute hemorrhagic shock complain of severe thirst. Scant evidence exists to support this observation in the clinical literature, limited as it is primarily to surveys in the surgical intensive care setting,[1] or in studies involving healthy volunteers.[2]

In addition to direct response to changes in serum osmolality, thirst perception is believed to involve neurochemical signals attributed to the acute elevation of arginine vasopressin (AVP) and angiotensin II (AT2), and may accompany acute hemorrhage.[3] Animal studies of experimental induction of acute hemorrhage and hypovolemia in general have confirmed a correlation among the severity of acute hemorrhage, the increase in serum AT2 and AVP levels during the initial 120–180 minutes after the hemorrhage, and drinking behavior (inferred to be analogous to thirst in human subjects).[4–8] One human physiologic experiment correlated both thirst and elevation of serum AVP level to hypertonic saline administration in healthy adult volunteers.[2] This phenomenon has not yet been studied clinically in a human population experiencing acute hemorrhagic shock.

The potential utility of thirst perception as a clinical marker of the presence and degree of impending hemorrhagic shock is of limited value in the trauma center setting. The implications are significant, however, for its utility as a potential triage tool in the setting

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of out-of-hospital mass-casualty incidents. In such settings, large numbers of casualties may be present who meet the criteria for "immediate" evacuation and surgical intervention. If quantified thirst perception is found to be a reliable surrogate marker for the degree of acute hemorrhage, it may be a valuable tool in further determining the order of precedence for evacuation and/or urgent hemostatic intervention within this already-identified "immediate" population. It may also aid further in differentiating potentially immediate patients who are otherwise declared to be among the "delayed" or "minimal" categories based on current triage algorithms.

In addition, if proven to provide a high correlation to the depth of acute hemorrhage, AVP and/or AT2 levels may prove to be valid biochemical markers warranting development as point-of-care tests for acute hemorrhage.

The primary objective of this study was to determine whether thirst or plasma AVP or AT2 levels could predict impending hemorrhagic shock, injury severity, or outcome in trauma patients at initial presentation.

METHODS

Potential subjects for this study were selected from the population of patients presenting to the emergency department (ED) of Brooke Army Medical Center as level I trauma activations (including blunt or penetrating trauma to the torso or proximal extremities). Inclusion criteria were as follows: age 17 to 80 years; conscious, alert, and oriented to person, general location, and time; will undergo phlebotomy and urine collection as a matter of standard treatment for the subject's presenting condition; possess a reported heart rate over 100 beats per minute at initiation of advanced life support care (this criterion was waived for patients taking systemic beta-adrenergic antagonists); and will have available 4 mL of excess blood collected as part of routine phlebotomy as noted above for testing of AVP and AT2 levels. Subjects were excluded if they possessed symptoms or signs of clinical ethanol or sympathomimetic intoxication, or if their clinical data set was incomplete at the time of analysis.

Each subject underwent standard-of-care emergency stabilization and definitive treatment as required by his or her respective presenting diagnosis. Upon study enrollment, and during the initial phase of ED resuscitation, each enrolled subject had an individual data sheet completed by the attending emergency physician. This instrument included the following data points: study identification number and trauma record number for subsequent retrieval of clinical data from the Brooke Army Medical Center (BAMC) trauma registry; date of encounter; a binary query regarding thirst ("are you thirsty?" with check boxes for "yes" or "no"); and a 100-mm nonhatched, zero-anchored visual analog scale for thirst (VAS–thirst) with 0 interpreted as no thirst and 100 as being the thirstiest that the subject had ever been in his or her recollection.

Clinical data were abstracted retrospectively from the institutional trauma registry, and included the following data points: age, gender, mechanism of injury, mode of hospital arrival, initial pulse rate, initial systolic blood pressure, serum pH, measured base deficit and source (arterial or venous), admission status and intensive care unit (ICU) length of stay; packed red blood cell (PRBC) transfusion requirement within the initial 24 hours; calculated Injury Severity Score (ISS), and final outcome. The initial ED shock index (SI) was calculated by dividing the initial pulse rate by the systolic blood pressure.

From the blood samples obtained as part of the routine trauma panel during initial trauma resuscitation, plasma AVP and AT2 levels were determined via enzyme-linked immunoassay (Phoenix Pharmaceuticals, Burlingame, CA). Normal values were established from a plasma bank obtained from 10 normotensive and normovolemic volunteer donors maintained by the 59th Clinical Research and Experimental Squadron's clinical laboratory facility. From this normal sample set, we selected an AT2 level of 0.29 ng/L and an AVP level of 0.59 ng/L as maximum normal values.

Data Analysis

The degree of correlation among VAS–thirst score, AVP level, and AT2 level was assessed using Spearman rank correlation analysis. Subsequently, VAS–thirst score, AVP level, and AT2 level were independently compared with several clinical variables employed commonly in the trauma literature as surrogates for the presence of hemorrhagic shock, injury severity, and clinical outcome. These included the aforementioned SI (indicating in this case hemorrhagic shock), the base deficit (indicating acute volume depletion, in this case attributable to hemorrhage), ISS, ICU admission, and requirement for PRBC transfusion, also using Spearman rank correlation analysis. In addition to using these raw data, we performed stratified analyses of normal versus elevated SI, with 0.7 as the cutoff point, and ISS scores implying "minor" versus "severe" injuries, using an ISS greater than 15 as a cutoff point. A receiver-operating characteristic (ROC) curve analysis was performed to calculate the area under the curve (AUC) as a means of ascertaining the optimal cutoff points for sensitivity and specificity of AT2 and AVP in the determination of SI less than versus greater than 0.7.

We wished to detect an estimated difference in thirst of 20 mm between subjects classified as not in hemorrhagic shock (SI less than or equal to 0.7) versus those classified as in hemorrhagic shock (SI greater than 0.7).

TABLE 1. Descriptive Statistics

	n	Minimum	Maximum	Mean	SD	99% CI Low	99% CI High
Thirsty	101	0	1	0.88	0.33		
VAS*	99	0	100	61.69	30.56	−17.02	140.40*
AT2	105	0	2.6	0.59	0.48	−0.65	1.83
AVP*	105	0	158.49	3.11	17.02	−40.73	46.96*
AT2 abnormal	105	0	1	0.74	0.44		
AVP abnormal	105	0	1	0.31	0.47		
ED SI*	103	0	1.5104167	0.70	0.22	0.14*	1.26*
ED SI elevated	105	0	1	0.44	0.50		
ED base excess*	94	−13.9	4.7	−2.03	3.13	−10.10*	6.04*
ISS*	105	1	43	7.90	8.55	−14.14	29.93*
ISS > 15	105	0	1	0.16	0.37		
PRBC requirement*	6	2	2	2.00	0.00	2.00	2.00*
ICU admission	105	0	1	0.27	0.44		
Age*	105	17	90	34.97	15.34	−4.55	74.50*
Valid *n* (listwise)	4						

*Significant.
AT2 = angiotensin II; AVP = arginine vasopressin; CI = confidence interval; ED = emergency department; ISS = Injury Severity Score; SI = shock index; VAS = visual analog scale.

Presuming a standard deviation of 40 mm, we determined that a sample of 126 subjects would detect the 20-mm difference with an alpha error of 0.05 and a power of greater than 80%.

We also anticipated conducting correlation analyses. A sample of 30 subjects would be required in order to detect a correlation of greater than or equal to 0.5 with a power of 80% and a two-tailed level of confidence of 95%.

This study was reviewed and approved by our institution's human subjects review board, and granted waivers of informed consent and Health Insurance Portability and Accountability Act (HIPAA) consent for release. In the board's judgment, querying subjects regarding "thirst" was a reasonable clinical question that might be asked in the process of normal patient care. In addition, blood samples for determination of AVP and AT2 levels were obtained from surplus blood that was available after filling standard tubes for the trauma panel that our institution orders with each trauma activation.

RESULTS

We performed an interim analysis of data after enrolling 116 of the intended 130 subjects. After statistical analyses were performed, the investigators concurred that further subject accumulation would be futile, and the study was closed to further enrollment.

From the sample of 116 subjects, 11 (9%) were excluded retrospectively (one was under the age of 17 years, seven had incomplete AVP or AT2 results, two had no VAS–thirst score recorded on the data sheet, and one had no clinical data recoverable from the trauma registry).

Descriptive data for the remaining 105 subjects composing the final sample set are depicted in Table 1. The average age was 35 years (95% confidence interval [CI]

TABLE 2. Spearman Rank Correlation Analysis of the Visual Analog Scale–Thirst Score by Independent Variables

Spearman's rho		Angiotensin II	Vasopressin
VAS–thirst	Correlation coefficient	−0.017	0.050
	Significance (2-tailed)	0.866	0.621
	n	99	99

		Correlations					
Spearman's rho		ED SI	ED SI Elevated	ED Base Excess	ISS	ISS > 15	ICU Admission
VAS–thirst	Correlation coefficient	0.074	0.090	0.055	0.075	−0.042	−0.062
	Significance (2-tailed)	0.472	0.377	0.611	0.458	0.678	0.542
	n	97	99	88	99	99	99

ED = emergency department; ICU = intensive care unit; ISS = Injury Severity Score; SI = shock index; VAS = visual analog scale.

TABLE 3. Spearman Rank Correlation Analysis of Angiotensin and Vasopressin by Independent Variables

		Correlations					
Spearman's rho		ED SI	ED SI Elevated	ED Base Excess	ISS	ISS > 15	ICU Admission
AT2	Correlation coefficient	−0.071	−0.084	0.143	−0.014	−0.121	−0.085
	Significance (2-tailed)	0.475	0.393	0.168	0.884	0.218	0.391
	n	103	105	94	105	105	105
AVP	Correlation coefficient	−0.151	−0.072	−0.009	0.170	0.124	−0.017
	Significance (2-tailed)	0.129	0.464	0.934	0.084	0.207	0.866
	n	103	105	94	105	105	105

AT2 = angiotensin II; AVP = arginine vasopressin; ED = emergency department; ICU = intensive care unit; ISS = Injury Severity Score; SI = shock index.

32 to 38), with 31% experiencing penetrating trauma. All subjects presented as level I trauma activations by ground or air ambulance. As a means of depicting the relative acuity of our sample population, we developed a composite index of morbidity, utilizing elevated SI, ISS > 15, and ICU admission as binary markers. (Results of this analysis are depicted in Table 4.) Forty-five subjects had none of these markers, 35 had one, 19 had two, and three had six. The VAS–thirst score was first compared with the plasma AVP and AT2 levels for correlation.

Using the established maximum normal values for AVP and AT2 levels at our laboratory facility, we compared the VAS–thirst scores for both markers, respectively. For AVP, there was no difference in VAS–thirst scores between subjects with normal (59 mm, 95% CI 47 to 71) versus elevated (63 mm, 95% CI 56 to 70) plasma levels. For AT2, results were likewise insignificant for normal (63 mm, 95% CI 56 to 70) versus elevated (58 mm, 95% CI 46 to 70) plasma levels. Subsequently, a Spearman rank correlation analysis was performed comparing VAS–thirst score with AVP and AT2 levels, respectively. Results are depicted in Table 2, and reflect no correlation (correlation coefficients for AVP and AT2 of 0.050 and −0.017, respectively).

We then analyzed the respective correlation between AVP and AT2 levels and our predetermined clinical predictors, including initial SI, abnormal SI, base deficit, ISS, ISS > 15, ICU admission, and requirement for PRBC transfusion. Results for Spearman rank correlation analyses for all markers except PRBC requirement are depicted in Table 3. They each reflect correlation coefficients within the range of −0.2 to 0.2, implying little or no correlation.

Despite these findings, we employed a composite index of morbidity (see Table 4) to assess potential correlations with VAS–thirst score, AVP level, and AT2 level, and to seek a potential clinical decision guideline. The results of Spearman rank correlation on the composite indexes of shock by thirst, AT2 level, and AVP level are shown in Table 5. While no correlations between VAS–thirst or AVP level and the composite index of morbidity were detected, we identified a weak inverse correlation (−0.219, $p < 0.03$) between AT2 level and the subject's possessing at least one of the three selected markers (elevated SI, ISS > 15, or ICU admission). We performed a ROC curve analysis using AT2 level as a diagnostic test to predict a positive outcome on the composite index of morbidity; the results are depicted in Table 6. Predictors with ROC curve areas from 0.600 to <0.700 are poor discriminators, from 0.700 to <0.800 are fair, from 0.800 to <0.900 are good, and from 0.900 to 1.000 are excellent. The AT2-based logistic regression model was a poor discriminator for events on the composite index of morbidity, with a ROC curve area of 0.628 (95% CI 0.518 to 0.738, $p = 0.025$). The optimum cutoff point was an AT2 level of <0.429 ng/L, where the sensitivity and specificity curves crossed at a sensitivity of 0.667 and a specificity of 0.644.

TABLE 4. Composite Index of Morbidity Using Elevated Shock Index, Injury Severity Score Greater than 15, and Intensive Care Unit Admission

		SI, ISS, and ICU*			
		Frequency	Percentage	Valid Percentage	Cumulative Percentage
Valid	0	45	42.9	42.9	42.9
	1	35	33.3	33.3	76.2
	2	19	18.1	18.1	94.3
	3	6	5.7	5.7	100.0
	Total	105	100.0	100.0	

*To calculate this index, the numerical value of 0 was assigned to variables that were negative, and 1 was assigned to those that were positive. Elevated shock index (SI) was defined as >0.7. Thus, a subject who had an elevated SI and an Injury Severity Score (ISS) >15 and who was admitted to the intensive care unit (ICU) would receive a score of 3.

TABLE 5. Spearman Rank Correlation Analysis, Outcome Variables by Predictors

		Correlations					
Spearman's rho		Thirsty	VAS	Angiotensin II	Vasopressin	AT2 Abnormal	AVP Abnormal
SI, ISS, and ICU	Correlation coefficient	−0.094	0.002	−0.168	−0.023	−0.086	−0.088
	Significance (2-tailed)	0.350	0.982	0.087	0.814	0.386	0.371
	n	101	99	105	105	105	105
SI, ISS, and ICU 01*	Correlation coefficient	−0.061	0.020	−0.219†	−0.088	−0.113	−0.160
	Significance (2-tailed)	0.541	0.844	0.025†	0.371	0.250	0.103
	n	101	99	105†	105	105	105

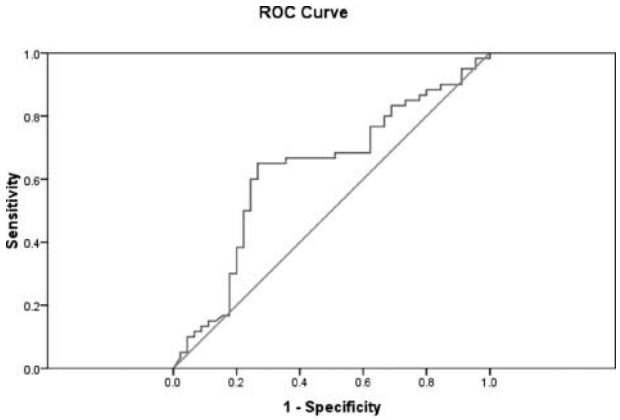
*Denotes a binary analysis comparing subjects with a 0 for their composite index of morbidity (see Table 4) with those having a score of 1, 2, or 3.
AT2 = angiotensin II; AVP = arginine vasopressin; ICU = intensive care unit admission; ICU 01 = intensive care unit admission for one or more days; ISS = Injury Severity Score; SI = shock index.

Lastly, and because only six subjects required PRBC transfusion within the first 24 hours of admission, we performed separate analyses comparing VAS–thirst, AVP level, and AT2 level between subjects who received PRBCs and those who received none. Results of t-tests for these continuous data comparisons are depicted in Table 7, and reflect no differences between the PRBC and no-PRBC groups with regard to relative thirst perception or AVP or AT2 levels.

TABLE 6. Receiver-Operating Characteristic Curve Analysis of the Composite Index of Shock by Angiotensin II

Area under the Curve				
Test Result Variable: Angiotensin II				
			Asymptotic 95% Confidence Interval	
Area	SE*	Asymptotic Significance†	Lower Bound	Upper Bound
0.628	0.056	0.025	0.518	0.738

Angiotensin II has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.
*Under the nonparametric assumption.
†Null hypothesis: true area = 0.5.
ROC = receiver-operating characteristic; SE = standard error.



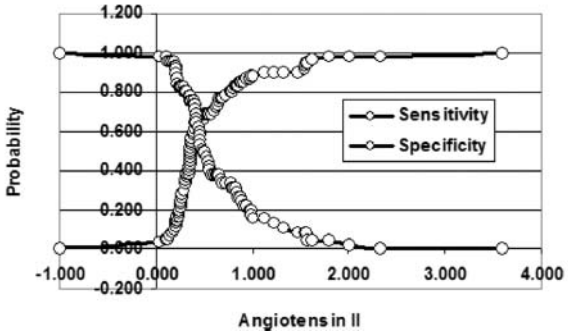


TABLE 7. Analysis Based on Packed Red Blood Cell Transfusion Requirement Within 24 Hours after Initial Trauma Resuscitation

	Average	95% CI
VAS–thirst		
PRBC requirement	66	51.14 to 80.40
No PRBC requirement	61	55.04 to 67.95
AVP		
PRBC requirement	3.77	−3.41 to 10.95
No PRBC requirement	2.97	−0.67 to 6.60
AT2		
PRBC requirement	0.49	0.28 to 0.70
No PRBC requirement	0.60	0.50 to 0.71

AT2 = angiotensin II; AVP = arginine vasopressin; CI = confidence interval; PRBC = packed red blood cell; VAS = visual analog scale.

DISCUSSION

This study represents, to our knowledge, the first quantitative analysis of the clinical correlation of thirst perception, and its putative neurochemical signals, with acute hemorrhage in the setting of initial trauma resuscitation. Despite aforementioned anecdotal reports implying a link between increased thirst and acute hemorrhage, including the clinical experiences of several of the investigators, our analysis concluded that thirst perception and AT2 and AVP levels demonstrated correlation neither to each other nor to the SI, base deficit, transfusion requirement, hospital admission, or ISS.

Combat may be the ultimate mass-casualty incident. Inherently, the combat environment presents both the patient and caregiver with austerity, limited technology and resources, and the necessity for rapid clinical judgments, which often have fatal implications. By confirming or refuting the utility of thirst perception as a potential marker of the degree of acute hemorrhagic shock, we hoped to add another valuable and simple triage tool to the combat casualty care diagnostic armamentarium, or otherwise dismiss a clinically inaccurate dogma. The demonstrated lack of any significant correlation (with correlation coefficients ranging from −0.219 to 0.170 for all analyses) would lead us to conclude that neither thirst perception nor its signals, AVP and AT2 levels, are reliable as a field triage tool in the initial assessment of casualties.

LIMITATIONS

This study is limited by its nonconsecutive enrollment design (which was a consequence of limited logistical and research personnel support), retrospective recovery of clinical data from our trauma registry, and the fact that, by design, we studied patients who had not yet shown signs of overt clinical decompensation, such as altered mental status associated with hypotension. Our logic in making this decision was that we were seeking to discover a potential field triage tool (thirst perception) or a potential point-of-care test (AT2 or AVP level) that might identify subjects early in the course of traumatic hemorrhage or compensated hypovolemia, who might progress to full shock if early hemostatic maneuvers were not performed. Patients already undergoing clinical decompensation were expressly excluded, as their presentation in extremis obviated the need for surrogate markers of impending shock. Nonetheless, it is possible, in a population of patients suffering severe hemorrhagic shock (loss of greater than 30% of intravascular volume), that thirst, AVP level, and AT2 level might offer greater correlation to depth of shock.

CONCLUSION

In this study, which comprised a population of patients who were undergoing level I trauma resuscitation and who were hemodynamically normal on initial presentation, we compared self-reported thirst perception and plasma AVP and AT2 levels with each other and with SI, base deficit, PRBC transfusion requirement within the initial 24 hours, ICU admission, and ISS. The results of this study imply that thirst severity, AVP level, and AT2 level are unreliable predictors of impending hemorrhagic shock, injury severity, or clinical outcome. The presence or absence of severe thirst should not be employed as a primary marker for dismissing or suspecting incipient hemorrhagic shock. Further investigation of thirst and plasma AVP and AT2 levels across a broader spectrum of hemorrhagic shock severity may be warranted.

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