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Clinical paper

Thrombin-antithrombin levels are associated with survival in patients resuscitated from cardiac arrest☆

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ABSTRACT

Background: Following successful resuscitation from cardiac arrest, a prothrombotic state may contribute to end-organ dysfunction. We examined whether the level of serum thrombin-antithrombin (TAT) in patients hospitalized after cardiac arrest was associated with survival or the development of multiple organ failure (MOF).
Methodology: A prospective cohort study of subjects with in-hospital cardiac arrest (IHCA) or out-of-hospital cardiac arrest (OHCA) treated between 1/1/2007 and 5/30/2010 at a single tertiary care referral center. TAT levels were measured at hospital arrival and 24 h after cardiac arrest. Logistic regression was used to determine associations between TAT levels and survival and development of MOF.
Results: Data were available for 86 subjects. TAT levels decreased over time. Initial TAT levels (OR 0.03; 95%CI 0.001, 0.62) and category of illness severity (OR 0.39; 95% CI 0.21, 0.73) were associated with survival. Male gender (OR 3.86; 95% CI 1.17, 12.75) and category of illness severity (OR 1.86; 95% CI 1.09, 3.20), but not TAT levels were associated with development of MOF. Neither the 24-h TAT level, nor the change in TAT from initial to 24 h was associated with survival when adjusted for category of illness severity.
Conclusions: Initial serum TAT levels and category of illness severity are associated with survival. TAT levels are not associated with development of MOF. Initial TAT levels may be a useful prognostic adjunct in the post arrest population.

1. Introduction

Cardiovascular disease (CVD) accounts for 35% of all deaths annually, making it a significant public health concern.[1] Cardiac arrest results in approximately 300,000 deaths per year in the United States.[2] After cardiac arrest only about 8% of patients survive to hospital discharge, illustrating the significant morbidity and mortality in this commonly encountered condition.[2]

Neurological injury, multiple organ failure (MOF), and cardiovascular collapse (recurrent arrest or cardiogenic shock) are the three most common causes of death after cardiac arrest.[3] One physiologic change that may contribute to each of these endpoints is the activation of thrombogenesis after cardiac arrest. Intravascular thrombosis may impair microcirculation, reduce end-organ blood flow, and prolong ischemia. Plasma thrombin-antithrombin (TAT), the irreversible product of thrombin inhibition by antithrombin, is a biological marker of ongoing coagulation. Elevated TAT in blood sampled during cardiopulmonary resuscitation (CPR) is negatively associated with return of spontaneous circulation (ROSC) in patients with out-of-hospital cardiac arrest.[4] In this study, we tested whether TAT levels measured in the hospital after ROSC were associated with survival or development of MOF in patients resuscitated from cardiac arrest.

2. Methods

2.1. Study type

We conducted a prospective cohort study of 100 in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA) subjects treated in a single tertiary care center between 1/1/2007 and 5/30/2010.[5] This study was approved by the University of Pittsburgh Institutional Review Board and either the subject or their proxy provided written informed consent prior to enrollment in the study. Subjects who later awakened were approached for approval to continue in the study.

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2.2. Selection of participants

All subjects greater than 18 years of age, regardless of location of arrest (IHCA or OHCA) or primary rhythm of arrest (VF/VT, non-VF/VT) were eligible for the study. Patients who were comatose after resuscitation from cardiac arrest were treated with a standardized protocol, including therapeutic hypothermia (TH). The details of this protocol have been described previously.[5]

2.3. Data collection

Subject demographics including age, gender, presenting rhythm of arrest, development of MOF, Charlson Comorbidity Index, and category of initial post-cardiac arrest illness severity were abstracted from the chart. We defined four categories of initial post-cardiac arrest illness severity: (I) awake, (II) coma (not following commands but intact brainstem responses)+ mild cardiopulmonary dysfunction (SOFA cardiac + respiratory score <4), (III) coma + moderate-severe cardiopulmonary dysfunction (SOFA cardiac + respiratory score $\geq$4), and IV) coma with loss of some or all brainstem reflexes.[6] MOF was defined as a score of $\geq$3 on 3 or more subscores of the sequential organ failure assessment within the first 72 h after ROSC.[7] Primary outcomes were survival to 28 days or hospital discharge and development of MOF during the first 72 h of hospitalization.

Blood samples were obtained from indwelling central venous lines or arterial lines after ROSC and 24 h after cardiac arrest. A subset of 44 patients had additional samples obtained at 6, 12, 48, and 72 h after cardiac arrest. Blood was collected in citrated tubes and centrifuged within 30 min (3000 × *g* × 10 min at room temperature). Plasma aliquots (200 μl) were placed in individual tubes and frozen at −80 °C until analysis. We measured TAT in thawed plasma samples using a commercial ELISA assay (Dade Behring, Marburg, Germany) according to the kit instructions

We excluded TAT levels following blood product transfusion (packed red blood cells, platelets, fresh frozen plasma, or cryoprecipitate) in 20 subjects.

2.4. Data analysis

Univariate logistic regression was used to determine predictors of survival and development of MOF. As there were a limited number of cases with the outcomes of interest (survival and development of MOF), the top 4 variables with $p < 0.1$ were included in the multivariate model for survival and the top 2 variables with $p < 0.1$ were included in the multivariate model for development of MOF. Two separate analyses were examined, one including only initial TAT levels and another including TAT levels at 24 h as well as the change in TAT levels between arrival and 24 h. Clinical variables included those associated with outcomes in prior studies: age, gender, Charlson Comorbidity Index, category of post-arrest illness severity, location of arrest, and ventricular fibrillation/ventricular tachycardia (VF/VT) as the primary rhythm of arrest.[8,9] For the analyses, TAT levels were log-transformed as they were not normally distributed. Interaction terms were evaluated as appropriate, but were not significant and not included in the final multivariate model. The Hosmer–Lemeshow test was used to determine goodness of fit. Levels of TAT on arrival were compared among categories of initial illness severity using regression. We used ANOVA to test for association between primary rhythm of arrest and TAT levels. Student's *t*-test was used to examine TAT levels based on survivorship, TH use, and history of diabetes or malignancy. Data were analyzed with STATA version 11.0 (College Station, TX).

Table 1
Demographic characteristics of subjects.

	N = 86
Age, in years (SD)	58 (16)
Male	50 (58%)
OOHCA	59 (69%)
Rhythm	
VF/VT	39 (45%)
PEA	20 (23%)
Asystole	16 (19%)
Unknown	11 (13%)
Category of arrest	
I	9 (10%)
II	30 (35%)
III	15 (17%)
IV	32 (37%)
Charlson Comorbidity Index	1 (0, 3; range 0–8)
Charlson Comorbidity Index, age adjusted	3 (1, 5; range 0–12)
Hypothermia Treatment	71 (84%)
Survival	39 (45%)
CPC	
1	6 (8%)
2	1 (1%)
3	31 (39%)
4	1 (1%)
5	47 (55%)
MRS	
0	4 (5%)
1	2 (3%)
2	1 (1%)
3	1 (1%)
4	27 (34%)
5	4 (5%)
6	47 (55%)
ICU LOS, days (IQR)	5 (3, 11)
Hospital LOS, days (IQR)	9 (4, 14)
MOF	26 (30%)
Transfusion	20 (23%)
Heparin	31 (36%)
Hemodialysis	3 (3%)
Gastrointestinal bleeding	1 (1%)

3. Results

3.1. Subject characteristics

A total of 100 subjects were enrolled in the study. Subject characteristics are summarized in Table 1. Overall, fourteen subjects were excluded (5 subjects received a transfusion prior to enrollment and 9 subjects did not provide consent) leaving 86 subjects for analysis. Median time from ROSC to initial sample was 4.6 h (IQR 3, 6.5). The majority of subjects were males with OHCA and category of post-arrest illness severity II or IV. VF/VT was the most common rhythm on arrival. A total of 71 (84%) subjects received TH, and 39 (45%) subjects survived to 28 days or hospital discharge (Table 1).

Blood product transfusions were administered in 20 subjects: 4 prior to the initial TAT level, 4 prior to the 6 h TAT level, 4 prior to the 12 h TAT level, 3 prior to the 24 h TAT level, 3 prior to the 48 h TAT level, and 2 prior to the 72 h TAT level. These subjects were removed from the TAT analysis at the time of blood product transfusion and thereafter. All subjects had initial TAT levels obtained prior to initiation of anticoagulant medications.

Primary rhythm of arrest was not associated with initial TAT levels (VF/VT 44.3 μg mL^{-1}, PEA 54.9 μg mL^{-1}, asystole 57.8 μg mL^{-1}; unknown 49.8 μg mL^{-1}; $p = 0.28$). Category IV subjects demonstrated the highest initial levels of TAT ($p = 0.001$) (Fig. 1). Levels of TAT were not different between category of illness severity at other time points. TAT levels decreased over time in category II ($\beta = -0.32$, $p = 0.001$), category III ($\beta = -0.38$, $p = 0.001$), and category IV ($\beta = -0.77$, $p < 0.001$).

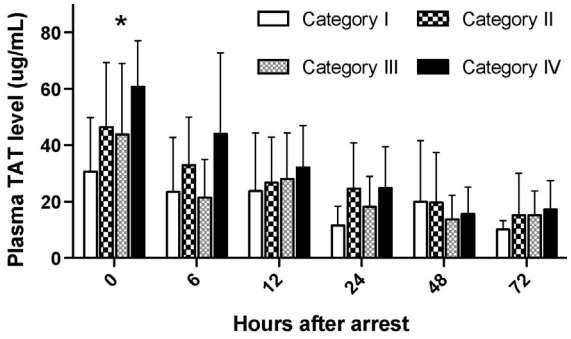

Fig. 1. TAT levels by category of initial illness severity over time. *Delineates $p = 0.001$ between categories of initial illness severity.

Table 2A
Survival regression model using initial TAT level. Bold delineates $p < 0.05$. TAT – thrombin-antithrombin, CCI – Charlson Comorbidity Index, OHCA – out-of-hospital cardiac arrest, VF/VT – ventricular fibrillation/ventricular tachycardia.

	Odds ratio	95% CI	p
Univariate model			
Log TAT on arrival	0.01	0.001, 0.16	0.001
Age	0.99	0.96, 1.02	0.54
Male	0.67	0.28, 1.66	0.38
Age adjusted CCI	0.86	0.73, 1.02	0.08
Category	0.30	0.17, 0.52	<0.001
OOHCA	0.81	0.29, 2.29	0.70
VF/VT	2.85	1.14, 7.14	0.03
Multivariate model			
Log TAT arrival	0.03	0.001, 0.62	0.02
Category	0.39	0.21, 0.73	0.003
Age adjusted CCI	0.94	0.76, 1.16	0.55
VF/VT	1.09	0.30, 3.96	0.89

Hosmer Lemeshow value 0.99 for the multivariate model.

Category I did not demonstrate a change in TAT levels over time ($\beta = -0.23$, $p = 0.09$).

In the univariate analysis, initial TAT level, category of illness severity, and a primary rhythm of VF/VT were associated with survival. In the multivariate model, initial TAT level and category of illness severity was associated with survival (Table 2A). The Hosmer–Lemeshow value demonstrated good fit with a value of 0.99. Male gender and category of illness severity were associated with development of MOF in the univariate and multivariate models. The multivariate model demonstrated good fit with a Hosmer–Lemeshow value of 0.58 (Table 2B).

In a separate univariate analysis, TAT level at 24 h, the change in TAT between initial and 24 h, category of illness severity, and a primary rhythm of VF/VT were associated with survival.

Table 2B
Multiple organ failure regression model using initial TAT level. Bold delineates $p < 0.05$. TAT – thrombin-antithrombin, CCI – Charlson Comorbidity Index, OHCA – out-of-hospital cardiac arrest, VF/VT – ventricular fibrillation/ventricular tachycardia.

	Odds ratio	95% CI	p
Log TAT arrival	3.98	0.46, 34.5	0.21
Age	1.01	0.98, 1.04	0.38
Male	2.95	0.95, 9.09	0.06
Age adjusted CCI	1.02	0.86, 1.21	0.81
Category	1.65	0.99, 2.73	0.053
OOHCA	1.13	0.35, 3.64	0.83
VF/VT	1.15	0.43, 3.09	0.78
Multivariate model			
Male	3.86	1.17, 12.75	0.027
Category	1.86	1.09, 3.20	0.024

Hosmer–Lemeshow value 0.58 for multivariate model.

Table 3A
Survival regression model using TAT level 24 h after resuscitation. Bold delineates $p < 0.05$. TAT – thrombin-antithrombin, CCI – Charlson Comorbidity Index, OHCA – out-of-hospital cardiac arrest, VF/VT – ventricular fibrillation/ventricular tachycardia.

	Odds ratio	95% CI	p
Univariate model			
Log TAT 24 h	0.10	0.01, 0.79	0.03
Delta TAT (arrival to 24 h)	1.04	1.01, 1.08	0.02
Age	0.99	0.97, 1.02	0.66
Male	0.83	0.32, 2.14	0.71
Age adjusted CCI	0.84	0.71, 1.00	0.05
Category	0.26	0.14, 0.48	<0.001
OOHCA	0.89	0.30, 2.65	0.83
VF/VT	3.42	1.29, 9.13	0.01
Multivariate model			
Delta TAT (arrival to 24 h)	1.04	0.99, 1.07	0.064
Category	0.30	0.13, 0.68	0.004
Age adjusted CCI	0.89	0.70, 1.13	0.33
VF/VT	1.91	0.39, 9.48	0.43

Hosmer Lemeshow value 0.48 for the multivariate model.

Category of illness severity was associated with survival in the multivariate analysis (Table 3A). This model had good fit with a Hosmer–Lemeshow value of 0.48. No variable was associated with development of MOF in the 24-h model (Table 3B). TAT levels changed less between the initial sample and those obtained at 24 h in survivors than in those who died (survivors: $-21.5\ \mu g\ mL^{-1}$ vs. non-survivors: $-33.6\ \mu g\ mL^{-1}$; $p = 0.027$). Similarly, initial TAT levels were lower in survivors than in non-survivors (TAT level $59.3\ \mu g\ mL^{-1}$ in non-survivors vs. $39.8\ \mu g\ mL^{-1}$ in survivors; $p = 0.0002$). TAT levels at 24 h were not different between comatose subjects treated with TH ($23.0\ \mu g\ mL^{-1}$) and not treated with TH ($20.0\ \mu g\ mL^{-1}$; $p = 0.76$). Levels of TAT at 24 h were not different between diabetics ($26.0\ \mu g\ mL^{-1}$) and non-diabetics ($21.9\ \mu g\ mL^{-1}$; $p = 0.85$); those with a history of solid tumor ($25.2\ \mu g\ mL^{-1}$) and not ($22.0\ \mu g\ mL^{-1}$; $p = 0.68$); and metastatic solid tumor ($27.5\ \mu g\ mL^{-1}$) and not ($22.8\ \mu g\ mL^{-1}$, $p = 0.51$).

4. Discussion

Initial TAT levels are independently associated with survival after resuscitation from cardiac arrest. The change between initial TAT levels and 24 h after resuscitation is also independently associated with survival. TAT levels are abnormally elevated after cardiac arrest in all subjects. Highest levels of TAT were associated with the category IV illness severity. Category IV subjects have less than 4 points on the FOUR motor and brainstem score, indicating that they likely have a "coma with loss of some or all brainstem reflexes".[6] However, category IV subjects have varying degrees of cardiovascular and respiratory failure. Thus, the degree of initial TAT elevation may be a useful prognostic adjunct after cardiac arrest. If validated,

Table 3B
Multiple organ failure regression model using TAT levels 24 h after resuscitation. Bold delineates $p < 0.05$. TAT – thrombin-antithrombin, CCI – Charlson Comorbidity Index, OHCA – out-of-hospital cardiac arrest, VF/VT – ventricular fibrillation/ventricular tachycardia.

	Odds ratio	95% CI	p
Log TAT 24 h	1.67	0.17, 16.7	0.66
Delta TAT (arrival to 24 h)	0.99	0.96, 1.02	0.48
Age	1.02	0.98, 1.05	0.39
Male	2.07	0.64, 6.68	0.22
Age adjusted CCI	1.06	0.89, 1.26	0.53
Category	1.44	0.84, 2.47	0.19
OOHCA	0.69	0.20, 2.33	0.55
VF/VT	1.03	0.35, 3.07	0.96

our data suggest that TAT levels may add to the clinical categorization of patients using initial illness severity.

Prior work has demonstrated elevated levels of TAT in patients experiencing prolonged arrest and worse neurologic injury.[8,9] Our data add to those studies because they demonstrate that elevated TAT shortly after resuscitation remains associated with survival even in a cohort treated with TH and a standardized post-arrest protocol. The finding that non-survival was associated with a larger decrease in TAT between arrival and 24 h may seem paradoxical. It is possible that the larger decrease was simply from higher initial TAT levels. Total CPR time has been associated with elevated TAT levels in prior work.[4] It is possible that elevation in TAT represents a surrogate marker for total ischemic burden. This would be supported by the finding of category IV illness severity in those with high initial TAT levels. Unfortunately, total CPR time is not reliably documented in our data set.

While prior data have shown an association between TAT levels and cardiovascular collapse, our data did not show an association between TAT levels and development of MOF during the first 72 h following resuscitation. This may reflect one benefit of a standardized post-arrest protocol that rapidly optimizes perfusion in this critically ill population. The association between category of illness severity and development of MOF has been demonstrated previously.[6]

The myriad of interventions (e.g. respiratory and hemodynamic support, hypothermia treatment, IV fluid administration) used in a post-arrest protocol may be one reason for the finding of all serum TAT levels to markedly decrease over time. Martini et al. used a swine model to demonstrate the effects of hypothermia and acidosis on coagulopathy, and noted that each independently decreased the concentration of TAT when compared to control swine.[10] When hypothermia and acidosis coexist, as in many post arrest patients early in resuscitation, the decrease in TAT concentration may be additive. Thus, improvement of the hypercoagulable state may be one mechanism whereby post-arrest bundles of care improve outcomes.

Elevated TAT levels have also been associated with factors other than ongoing coagulation, such as systemic inflammation, diabetes, cancer, and obesity.[11–13] Our data did not demonstrate a difference between those with and without diabetes or cancer. Markers of systematic inflammation and body morphometrics were not recorded in this database.

4.1. Limitations

Our data are limited by the use of a single marker of coagulation and a lack of information regarding total CPR time and total ischemic time. Despite these limitations, our data suggest that TAT may represent a marker that can be used to determine effectiveness of resuscitation interventions in this population.

5. Conclusion

TAT levels are elevated after resuscitation from cardiac arrest and higher levels are associated with non-survival. A decrease in TAT levels at 24 h following resuscitation also predicts survival. TAT levels may represent total ischemic injury and decreasing levels may demonstrate effective post-resuscitation care.

Conflict of interest statement

The authors have no conflicts of interest to report.

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