Thromboelastography maximum amplitude as an early predictor of disseminated intravascular coagulation in patients with heatstroke

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ABSTRACT

Objectives: The aim of this study was to investigate the ability of TEG to predict DIC associated with heatstroke.

Methods: We carried out a retrospective, single-center study of 67 patients with heatstroke admitted to an intensive care unit (ICU) at a comprehensive hospital between July 2016 and August 2021. Conventional coagulation tests (CCTs) and TEG were performed within 2 h of admission in ICU. Patients were diagnosed with DIC based on International Society of Thrombosis and Hemostasis criteria, and those with or without DIC were compared in terms of CCTs and TEG findings. The ability of individual parameters to predict DIC was assessed based on logistic regression and the area under receiver operating characteristic curves (AUC).

Results: Of the 67 patients, 19 (28.4%) were diagnosed with DIC. Compared to patients without DIC, those with DIC had significantly longer reaction time [14.5(10.6–26.0) vs. 6.2(5.1–10.1) min] (p < 0.001) and kinetic time [10.9(5.9–25.0) vs. 2.7(2.2–4.7) min] (p < 0.001). Conversely, those with DIC had significantly lower alpha angle [22(9.1–43.3) vs. 55.0(44.8–61.7)] (p < 0.001), maximum amplitude (MA) [26.9(17.7–41.4) vs. 52.2(45.8–58.1) mm] (p < 0.001) and coagulation index [-17.3(-39 to –7.9) vs. –2.4(-6.2 to 0.6)] (p < 0.001). MA at a cutoff value of 45.4 mm gave an AUC of 0.9 for predicting DIC, with sensitivity of 77.1%, specificity of 89.5%, positive predictive value of 10.5% and negative predictive value of 22.9%. Multifactorial logistic regression identified MA < 45.4 mm as an independent predictor of DIC (odds ratio 9, 95% confidence interval 1.2–69.2, p = 0.001). MA decreased significantly as DIC score increased and was significantly lower in the non-survivors on admission.

Conclusions: MA < 45.4 mm in patients with heatstroke may predict elevated risk of DIC.

HIGHLIGHTS

- Patients with heatstroke-induced disseminated intravascular coagulation (DIC) have high mortality.
- A retrospective, single-center study was performed to investigate the ability of thromboelastography (TEG) to predict DIC associated with heatstroke.
- The maximum amplitude (MA) value of TEG decreased significantly with the increase of DIC score.
- MA < 45.4 mm was firstly demonstrated to an independent predictor of heatstroke-induced DIC.

1. Background

Heatstroke is a serious disease caused when core body temperature rapidly exceeds 40°C, thermally damaging the central nervous system (leading, for example, to delirium, convulsions, or coma) and multiple organs [1]. The mortality rate of patients with heatstroke in the ICU is up to 60% [2–3]. Around 45% of patients with heatstroke also present disseminated intravascular coagulation (DIC) [4], which further increases the risk of multi-organ damage and mortality [5]. Therefore, early recognition and treatment of DIC in patients with heatstroke may reduce mortality and disability.

DIC is typically diagnosed on the basis of conventional coagulation tests (CCTs), which measure platelet count, prothrombin time (PT) and levels of fibrinogen, fibrinogen degradation product (FDP), or D-dimer [6]. However, these indices of coagulation are poor at predicting DIC because this complication often precedes abnormal CCT findings [7]. A better predictor may be thromboelastography (TEG), which examines whole-blood samples to assess coagulation function as well as interactions between coagulation factors and platelets [8]. TEG has shown promise in predicting DIC in sepsis patients [9].

The present study asked whether TEG may be useful for predicting DIC in heatstroke patients. To this end, we retrospectively analyzed 67 patients with heatstroke admitted to our institution.

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2. Methods

2.1. Study design and patients

We retrospectively recruited a consecutive series of 72 patients with heatstroke admitted to the ICU of our tertiary referral center (Nanchang, China) from July 2016 to August 2021. Patients were excluded from our study if they were under the age of 18, if they were more than 3 days to admission, if they had a congenital coagulation disorder or chronic liver and kidney disease, or if they were using anticoagulant drugs at the time of enrollment.

Patients were diagnosed with heatstroke according to the Chinese Expert Consensus on the Diagnosis and Treatment of Heatstroke [1]. In other words, patients had to have a medical history of exposure to high temperature and high humidity, or high-intensity exercise. They also had to manifest at least one of the following: central nervous system dysfunction, such as coma, convulsions, delirium, or abnormal behavior; core temperature over 40 °C; functional impairment of at least two organs, such as the liver, kidney, transverse muscle, or gastrointestinal tract; or severe coagulation dysfunction or DIC.

2.2. Definitions

Acute liver injury [10]: serum TBIL ≥34.2 μmol/L and INR ≥1.5, or with any grade of hepatic encephalopathy.

Acute kidney injury [11]: Serum creatinine increased to ≥26.5 μmol/L (≥0.3 mg/dl) within 48 h, or serum creatinine ≥1.5 times the baseline within 7 days, or urine output <0.5 ml/ (kg·h) for 6 h.

Rhabdomyolysis [12]: serum creatine kinase >1000 U/L or 5-10 times the upper limit of normal reference range.

Gastrointestinal injury [13]: gastrointestinal symptoms related to a known cause and perceived as transient.

DIC[6]: The diagnostic criteria were established by the International Society of Thrombosis and Hemostasis. DIC scores were calculated according to as follows: platelet count <100 × 10^9/L was scored as 1 point, <50 × 10^9/L as 2 points; PT prolongation of >3 s was scored as 1 point, >6 s as 2 points; FIB <1.0 g/L was scored as 1 point; a moderate increase in FDP or D-dimer levels was scored as 2 points, while a significant increase was scored as 3 points. DIC was diagnosed as a total score at least 5.

2.3. Laboratory tests

After diagnosis with heatstroke, all patients underwent CCTs and TEG within 2 h of being admitted to the ICU as routine process. Blood (2 ml, 1:9 ratio of citrate to blood) was collected from the peripheral veins by a qualified nurse into a citrate anticoagulant tube for coagulation assays. CCTs included assays of activated partial thromboplastin time (APTT), PT, thrombin time, international normalized ratio (INR), platelet count, fibrinogen, D-dimer, and FDP. CCTs were performed on an automatic coagulation analyzer (TOP700, Wolfen Group, Barcelona, Spain).

All blood samples were monitored for 40 min by TEG (system 8800, Beijing Lepu Medical Technology, Beijing, China) and the manufacturer’s associated reagents. TEG data were analyzed to extract reaction time (R), kinetic time (K), alpha angle (angle), maximum amplitude (MA) and coagulation index (Cl).

2.4. Data collection

Demographic and clinical characteristics were retrieved from electronic medical records, including age, sex, temperature, heart rate, systolic blood pressure, medical history, Glasgow coma scale (GCS) score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score (calculated within 24 h after admission to the intensive care unit), and mortality. Data were also collected on white blood cell count, packed cell volume, and levels of hemoglobin levels, ALT, AST, total bilirubin, direct bilirubin, creatinine, myoglobin, and creatine kinase. This study was approved by the Ethics Committee of the 908th Hospital of Chinese Logistical Support Force (approval number: 908yyLL031), which waived the requirement for informed consent because the enrolled patients, at the time of treatment, had signed written consent for their anonymized medical data to be analyzed and published for research purposes.

2.5. Statistical analysis

All statistical analyses were performed using SPSS 26.0 (IBM SPSS Statistics for Windows, Version 26.0, Chicago, IL, USA), and differences associated with p < 0.05 were considered statistically significant. Continuous data with a normal distribution were expressed as the mean ± standard deviation, while data with a skewed distribution were expressed as the median and interquartile range (IQR). Categorical data were expressed as counts and percentages. For continuous variables showing normal distribution and uniform variance, differences between DIC and non-DIC patients were assessed for significance using Student’s t test; otherwise, differences in continuous variables were assessed using the Mann-Whitney U test. Differences in categorical variables were assessed using the χ^2 test. When the conventional chi-square test is not available, the data were compared with the use of either the continuity correction or Fisher’s exact test.

The ability of the TEG indicators R, K, angle and MA to diagnose DIC associated with heatstroke was assessed using receiver operating characteristic (ROC) curves and the area underneath them (AUC). The optimal cutoff values for these indicators were determined using the Youden index [14].

Univariate analysis was used to identify potential risk factors of DIC associated with heatstroke, and factors associated with p < 0.01 were checked for multicollinearity using linear regression, and then added into multivariate analysis by forward stepwise regression. The results of multifactorial logistic regression were expressed in terms of odds ratios (OR) and 95% confidence intervals (CIs). Sensitivity, specificity, positive
predictive value (PPV), and negative predictive value (NPV) were calculated using standard methods.

3. Results

3.1. Baseline characteristics
We initially considered 72 patients with heatstroke who were admitted to our hospital between July 2016 and August 2021. We excluded one patient under the age of 18, two patients because their data were incomplete, and another two who were admitted to the ICU more than 3 days. In the end, 67 patients (57 men) with a median age of 44 (23–65) years were included in the study, among whom 19 (28.4%) had DIC. Of all the 67 enrolled patients, 56 patients (83.6%) survived. Nine deaths in the DIC group accounted for 81.8% of the total (Figure 1).

3.2. Laboratory findings
Compared with patients without DIC, those with DIC showed significantly higher heart rate, ALT, AST, total bilirubin, creatinine, Creatine kinase, APACHE II score, but significantly lower hemoglobin, packed cell volume, GCS scores and longer length of ICU stay (Table 1). DIC patients also showed significantly longer PT and APTT, lower serum fibrinogen levels and platelet count as well as higher FDP and D-dimer (Table 2). Compared to non-DIC patients, those with DIC showed significantly prolonged R and K, significantly narrower alpha angle, and significantly lower MA, and CI. Among the TEG indices, MA < 45.4 mm was able to differentiate patients with or without DIC with the highest specificity (89.5%), sensitivity (77.1%), PPV (10.5%), and NPV (22.9%) (Table 3).

3.3. Risk factors for heatstroke-associated DIC
Various candidate risk factors for heatstroke-associated DIC emerged from the univariate analysis: MA (>45.4 vs. ≤45.4 mm), ALT, R (>10.5 vs. ≤10.5 min), K (>5.7 vs. ≤5.7 min), alpha angle (>43.9 vs. ≤43.9°), APTT, TT, Temperature, classification, hemoglobin, creatine kinase and MODS (Table 4). Of these, only MA < 45.4 mm was confirmed to be an independent predictor in multivariate logistic regression.

3.4. Relationship between MA and prognosis
The MA TEG value decreased significantly with the increase of DIC score and remarkably to approximately 50% at a DIC score of 5 (Figure 2). Compared to survival patients, those non-survivors showed significantly lower MA on admission (p < 0.001) (Figure 3).

4. Discussion
This is one of the few studies to investigate the characteristics of coagulation disorder associated with heat stroke, and the first to explore the use of TEG to predict DIC related to it. We found several differences in TEG indices between DIC and non-DIC group, and multivariate analysis indicated that MA was an independent risk factor for heatstroke-induced DIC (OR 9, 95% CI 1.2–69.2). In fact, MA < 45.4 mm was able to predict DIC in heat stroke patients with a sensitivity of 77.1%, specificity of 89.5%, positive predictive value of 10.5%, and negative predictive value was 22.9%.

The incidence of DIC in our study (28.4%) and the rate of mortality among our DIC patients (47.4%) were both higher than those of heat stroke patients in the Japanese national study (21.7%, 17% respectively) [2]. The results gave rise to
The higher proportion of exertional heat stroke (71.6%) at the average age of 44 in our study than at the average age of 68 in the Japanese study. This likely reflects more severity in our patients with heatstroke, reflected in lower GCS score, higher APACHE II score, DIC score, ALT, AST, total bilirubin, creatinine and creatine kinase. Thus, our DIC patients probably had more serious organ dysfunction affecting the central nervous system, heart, liver, kidney and skeletal muscle.

We explored here the possibility of TEG for diagnosing DIC associated with heatstroke because the current diagnostic method based on a DIC score can fail to detect the condition early. As a result, many patients are diagnosed when DIC is already in a late stage and prognosis is worse [15]. TEG can quickly and accurately diagnose coagulation dysfunction, and it has shown potential for early diagnosis and monitoring of DIC associated with traumatic bleeding [16] or septic shock [17]. MA value represents stiffness of the developed clot, which is the result of the modest contribution of fibrin and the much more significant contribution of the platelets. Kim SM et al reported that MA < 60 mm was an independent predictor of septic DIC (odds ratio 5.616). In our study, MA value was negatively correlated with DIC score and MA ≤ 45.4 mm was confirmed to be an independent predictor of heatstroke-induced DIC.

In our study, DIC patients presented significantly longer R, K, PT and APTT than non-DIC patients, but significantly lower platelet counts, fibrinogen levels, angle, MA and CI. This reflects the ‘hypoagulable’ state of DIC patients with heatstroke, in which coagulation substrates such as blood coagulation factors, fibrinogen, and platelets are progressively consumed [18]. DIC associated with heatstroke may arise when elevated blood temperature increases vascular permeability to allow plasma exudation, which increases blood viscosity. Heatstroke-induced DIC has the similar pathophysiological mechanism with sepsis-induced DIC. They both begin with endothelial cell damage, but heatstroke induced DIC has more severe endothelial cell damage and faster development of coagulation dysfunction. The heat exerts a direct cytotoxic effect and activates inflammatory coagulation pathways [19,20], both of which damage vascular endothelial cells, leading to excessive release of tissue-type plasminogen activator and activation of the fibrinolytic system, observable as increased levels of plasmin alpha2-plasmin inhibitor complex and D-dimer as well as decreased levels of plasminogen [21,22]. At the same time, platelets become activated and promote extensive thrombosis, consuming large amounts of coagulation substrate, exacerbating the hypoagulable state arising from heat shock [23,24].

Table 1. Baseline characteristics and outcomes for heatstroke patients with or without DIC.

| Characteristics                              | Total (N = 67) | Non-DIC group (N = 48) | DIC group (N = 19) | p Value |
|----------------------------------------------|---------------|------------------------|-------------------|---------|
| Age, yr                                       | 44 (23–65)    | 44 (22–67)             | 47 (39–58)        | 0.840   |
| Sex                                           |               |                        |                   | 0.310   |
| Male                                         | 57 (85%)      | 39 (81%)               | 18 (95%)          |         |
| Female                                        | 10 (15%)      | 9 (19%)                | 1 (5%)            |         |
| Temperature (°C)                              | 40 (39.6–41)  | 40 (39.5–41)           | 40.7 (39.6–42)    | 0.079   |
| Heart Rate, bpm                               | 99.8 ± 27.1   | 94.0 ± 27.7            | 114.4 ± 19.5      | 0.005   |

Characteristics

Classification

- Classic heatstroke
- Exertional heatstroke

Medical history

- Any comorbidity
- Diabetes
- Hypertension
- Chronic lung disease
- Paroxysmal supraventricular tachycardia
- Congenital atrial septal defect

Laboratory findings

- White blood cell count (× 10⁹/L)
- Hemoglobin, g/L
- Packed cell volume, %
- ALT, U/L
- AST, U/L
- Total bilirubin, mmol/L
- Creatinine, μmol/L
- Myoglobin, μg/L
- Creatine kinase, U/L
- MODS, n (%) (56.7%)
- Glasgow Coma Scale score
- APACHE II score
- Mortality, %

Classification of heatstroke

- Classic heatstroke
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Medical history

- Any comorbidity
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Laboratory findings

- White blood cell count (× 10⁹/L)
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- ALT, U/L
- AST, U/L
- Total bilirubin, mmol/L
- Creatinine, μmol/L
- Myoglobin, μg/L
- Creatine kinase, U/L
- MODS, n (%) (56.7%)
- Glasgow Coma Scale score
- APACHE II score
- Mortality, %

Values are mean ± standard deviation, median (interquartile range), or n (%).

ALT: glutamic pyruvic transaminase; APACHE: Acute Physiology and Chronic Health Evaluation; AST: glutamic oxaloacetic transaminase; DIC: disseminated intravascular coagulation; MODS: multiple organ dysfunction syndrome; ICU: intensive care unit.

*Significant difference (p < 0.05).
This study has several limitations. First, it was a single-center study and did not reflect the general population. Second, consecutive data on daily TEG profiles and DIC scores were unavailable. Third, patients who could have progressed to DIC after admission were not divided into DIC group.

5. Conclusions

Our findings should be interpreted with caution since they come from a relatively small sample in a single-site retrospective study. Nevertheless, our work justifies further study of MA as a risk factor for DIC associated with heatstroke, and it establishes the potential of TEG for early diagnosis of DIC. Our results should be verified and extended in large, prospective, multicenter studies that can help improve the early detection of DIC in a particularly vulnerable patient population.

Table 2. Conventional coagulation tests and TEG indices for heatstroke patients with or without DIC.

| Parameter | Total (N = 67) | Non-DIC group (N = 48) | DIC group (N = 19) | p Value |
|-----------|---------------|------------------------|--------------------|---------|
| **Conventional coagulation test** | | | | |
| PT, sec | 17.1 (14.3–20.9) | 15.6 (13.4–17.6) | 27.6 (20.9–44.9) | <0.001 |
| APTT, sec | 38.4 (29.8–48.9) | 34.4 (28.2–41.3) | 46.2 (38.4–75.7) | 0.001 |
| TT, sec | 17.0 (14.5–21.0) | 16.3 (14.1–18.2) | 20.0 (16.2–26.2) | 0.007 |
| Fibrinogen, g/L | 1.9 (1.4–2.9) | 2.0 (1.6–2.9) | 1.4 (1.0–2.2) | 0.016 |
| FDP, µg/mL | 8.8 (2.3–25.0) | 3.2 (1.4–10.0) | 30.2 (23.9–44.4) | <0.001 |
| D-dimer, µg/mL | 2.3 (0.5–4.4) | 1.0 (0.3–2.7) | 7.7 (3.4–26.3) | <0.001 |
| **Platelet, x10^12/L** | 107 (44–177) | 146 (74–208) | 35 (21–59) | <0.001 |
| **TEG indices** | | | | |
| R, min | 7.3 (5.2–13.2) | 6.2 (5.1–9.7) | 14.5 (10.6–26.0) | <0.001 |
| K, min | 3.5 (2.3–6.8) | 2.7 (2.2–4.7) | 10.9 (5.9–25.0) | <0.001 |
| Alpha angle, ° | 50.6 (31.4–59.6) | 55.0 (44.8–61.7) | 22 (9.1–43.3) | <0.001 |
| MA, mm | 47.3 (37.1–55.0) | 52.2 (45.8–58.1) | 26.9 (17.7–41.4) | <0.001 |
| Coagulation index | –3.9 (-16.3 to –1.1) | –2.4 (-6.2 to –0.6) | –17.3 (-39 to –7.9) | <0.001 |

Values are expressed as the mean ± standard deviation or median (interquartile range).

PT: prothrombin time; APTT: activated partial thromboplastin time; DIC: disseminated intravascular coagulation; TT: thrombin time; FDP: fibrin degradation products; R: reaction time; K: kinetic time; MA: maximal amplitude.

Normal reference range of TEG parameters: R (5–10) min, K (1–3) min, Alpha angle (55–78)°, MA (50–70) mm, Coagulation index (-3 to 3).

Table 3. Receiver operating characteristic curve analysis of TEG indices for diagnosing heatstroke-related DIC.

| Index | Cutoff | AUC | Se (%) | Sp (%) | PPV (%) | NPV (%) |
|-------|--------|-----|--------|--------|---------|---------|
| R, min | 10.5 | 0.823 | 78.9 | 79.2 | 21.1 | 20.8 |
| K, min | 5.7 | 0.895 | 84.2 | 83.2 | 15.8 | 16.7 |
| Alpha angle, ° | 43.9 | 0.846 | 77.1 | 78.9 | 21.1 | 22.9 |
| MA, mm | 45.4 | 0.888 | 77.1 | 89.5 | 10.5 | 22.9 |
| Coagulation index | –7.1 | 0.891 | 81.3 | 89.5 | 10.5 | 18.8 |

AUC: area under the receiver operating characteristic curve; R: reaction time; K: kinetic time; MA: maximal amplitude; Se: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value.

Normal reference range of TEG parameters: R (5–10) min, K (1–3) min, Alpha angle (55–78)°, MA (50–70) mm, Coagulation index (-3 to 3).

Table 4. Univariate and multivariate analysis to identify predictors of heatstroke-associated DIC.

| Characteristics | OR (95% CI) | P | OR (95% CI) |
|-----------------|-------------|---|-------------|
| MA (≥45.4 mm < 54.4 mm) | 28.5 (5.7–143.4) | <0.001 | 9 (1.2–69.2) | 0.035 |
| K (≥5.7 mm < 57 mm) | 26.7 (6.3–113.5) | <0.001 | 6.1 (0.9–39.2) | 0.058 |
| R (≥10.5 mm < 10.5 mm) | 1.1 (1.0–1.2) | 0.003 | – | – |
| Alpha angle (≥43.9 mm) | 12.6 (3.5–45.9) | <0.001 | – | – |
| APTT, s | 1.0 (1.0–1.1) | 0.009 | – | – |
| TT, s | 1.2 (1.0–1.4) | 0.017 | – | – |
| Temperature, °C | 1.8 (1.1–3.0) | 0.03 | – | – |
| Classification | 1.7 (0.5–6.0) | 0.407 | – | – |
| Hemoglobin, g/L | 1.0 (0.9–1.0) | 0.013 | – | – |
| Creatine kinase, U/L | 1.0 (1.0–1.0) | 0.011 | – | – |
| MODS | 0.2 (0.2–0.2) | 0.192 | – | – |

Multivariate analysis included logistic regression and forward elimination. OR: odds ratio; MA: maximal amplitude; R: reaction time; K: kinetic time; APTT: activated partial thromboplastin time; TT: thrombin time.

** Significant value (p < 0.05).
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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the 908th Hospital of Chinese Logistical Support Force (approval number: LC 20200006).

Disclosure statement

The authors declare that they have no competing interests.

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Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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