Increased Fibrinolysis as a Specific Marker of Poor Outcome After Cardiac Arrest

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Objectives: Recent data suggest that early increased fibrinolysis may be associated with unfavorable prognosis in cardiac arrest. The current study aimed to assess whether there is an optimal fibrinolysis cutoff value as determined by thrombelastometry at hospital admission to predict poor outcome in a cohort of adult patients with out-of-hospital cardiac arrest.

Design: Prospective observational cohort study.

Setting: Emergency department of a 2,100-bed tertiary care facility in Vienna, Austria, Europe.

Patients: Patients with out-of-hospital cardiac arrest of presumed cardiac origin, subjected to targeted temperature management, who had achieved return of spontaneous circulation at admission were analyzed.

Interventions: None.

Measurements and Main Results: Fibrinolysis was assessed by thrombelastometry at the bedside immediately after hospital admission and is given as maximum lysis (%). The outcome measure was the optimal cutoff for maximum lysis at hospital admission to predict poor outcome (a composite of Cerebral Performance Category 3–5 or death) at day 30, assessed by receiver operating characteristic curve analysis. Seventy-eight patients (61% male, median 59 yr) were included in the study from March 2014 to March 2017. Forty-two patients (54%) had a poor 30-day outcome including 23 nonsurvivors (30%). The maximum lysis cutoff at admission predicting poor 30-day outcome with 100% specificity (95% CI, 90–100%) was greater than or equal to 20%. Tissue-type plasminogen activator antigen levels were likewise elevated in patients with poor neurologic outcome or death 52 ng/mL (interquartile range, 26–79 ng/mL) versus 29 ng/mL (interquartile range, 17–49 ng/mL; \( p = 0.036 \)).

Conclusions: Increased fibrinolysis at admission assessed by thrombelastometry specifically predicts poor outcome in cardiac arrest with presumed cardiac etiology. (Crit Care Med 2018; 46:e995–e1001)

Key Words: cardiac arrest; early prediction; fibrinolysis; point-of-care; thrombelastometry; outcome

BACKGROUND

The process of fibrinolysis is inevitable to regain microvesSEL patency and restore vital organ perfusion after intravascular clotting. Endothelial tissue-type plasminogen activator (t-PA) ensures clot dissolution by converting plasminogen into plasmin at the site of primary vascular damage averting permanent circulatory compromise and subsequent thrombotic organ failure. In contrast, primary hyperfibrinolysis occurs without preceding intravascular clotting and is associated with poor outcome in several critical conditions including trauma and sepsis (1, 2). In particular in traumatic coagulopathy, fibrinolysis has been investigated intensively and identified as an early and independent predictor of mortality (1, 3).

Although underlying mechanisms likely differ from that in trauma-associated fibrinolysis, which involves tissue injury and significant crystalloidal hemodilution (4), previous studies likewise reported an association between the presence of fibrinolysis and unfavorable prognosis in cardiac arrest (5, 6), with the highest fibrinolytic activity found in patients with early death.

Hypoperfusion resulting in release of endothelial t-PA (6) is considered one possible mechanism of fibrinolysis occurring during cardiopulmonary resuscitation (CPR) (7).
importance of hypoxia as a causal factor is best seen in the severe hyperfibrinolysis of young and previously healthy drowning patients where preceding activation of coagulation can be excluded (6). Hence, the extent of fibrinolysis at admission reflects prolonged or insufficient resuscitation efforts and may therefore provide reliable prediction of poor outcome (6).

In this context, previous studies have already identified fibrin degradation products, such as d-dimer, as an early indicator of unfavorable outcome in cardiac arrest (8, 9). D-dimer is a well-known marker of fibrinolysis and can be routinely assessed, but however lacks specificity, which makes the definition of a reliable predictive threshold unlikely.

Yet, thrombelastometry has proven useful for point-of-care detection of increased fibrinolysis in cardiac arrest (6, 7, 10).

The current study aimed to assess whether there is an optimal fibrinolysis cutoff value assessed by thrombelastometry to predict poor outcome in a preselected cohort of successfully resuscitated adult patients with out-of-hospital cardiac arrest.

METHODS

Study Population
Eligible for inclusion were adults (≥18 yr) with out-of-hospital cardiac arrest of presumed cardiac origin, subjected to targeted temperature management, who had achieved return of spontaneous circulation (ROSC) at admission to the ICU section of the emergency department at the Medical University of Vienna. Exclusion criteria comprised thrombolytic therapy and application of intravascular cooling or extracorporeal bypass device, as both may affect fibrinolytic activity. All patients were treated with therapeutic hypothermia at a target temperature range of 33°C ± 1°C. Patients were cooled using cooling pads (Emcoools Flex.Pad, Emcools AG, Pfaffstetten, Austria) (11) or water-circulating gel-coated pads (Arctic Sun 5000 Temperature Management System; Medivance, Louisville, CO) with or without cold fluids. Target temperature between 32°C and 34°C was maintained for 24 hours after first achievement of less than 34°C. Rewarming was performed at a rate of 0.25–0.5°C per hour. Body temperature was recorded with an esophageal and bladder probe.

Resuscitation-related variables were analyzed and reported according to Utstein recommendations as described previously (12). The primary endpoint was a composite of poor neurologic function or death, defined as a Cerebral Performance Category (CPC) of 3–5 (severe cerebral disability; coma or vegetative state; or brain death, respectively) at day 30 post resuscitation (13). Neurologic function at 30 days was assessed by study fellows through structured face-to-face interview with the patient or by means of structured telephone interview with the patient, the relatives, treating physicians, or nursing home members. Study fellows assessing outcome were all blinded to results obtained by rotational thrombelastometry (ROTEM).

Sustained ROSC was defined as recovery of spontaneous circulation for more than 20 minutes. No- and low-flow intervals were defined as the time from collapse to initiation of CPR and the time from CPR initiation to sustained ROSC, respectively.
with a 95% CI. Potentially missing data for demographic variables were not imputed. Between-group comparisons were performed using the Mann-Whitney \( U \) test for continuous variables or the chi-square test/Fisher exact test for nominal variables. We performed exact bivariable logistic regression to estimate the effect on poor neurologic function or death at day 30 of ML and remaining candidate predictors, which were judged to be clinically plausible, including age, no-flow time, low-flow time, pH, lactate, d-dimer levels, sex, CPC prior to cardiac arrest, arrest site, witness status, presence or absence of bystander resuscitation, initial rhythm, epinephrine dose administered during resuscitation, and the rate of sustained ROSC at admission. Results are given as odds ratios/median unbiased estimates with 95% CI and are available in Supplemental Table 4 (Supplemental Digital Content 1, http://links.lww.com/CCM/D848).

The optimal cutoff for ML to predict poor 30-day outcome was assessed by computing a receiver operating characteristic curve. Specificity and sensitivity were calculated with 95% CI. The Kaplan-Meier method was used to describe survival according to the optimal cutoff for ML.

Generally, a two-sided \( p \) value of less than 0.05 was considered statistically significant. We used IBM SPSS Statistical Software, Version 22.0 (IBM Corp., Armonk, NY) and Stata Statistical Software: Release 15 (StataCorp., College Station, TX) for statistical analysis and GraphPad Prism Version 7.00 for Windows (GraphPad Software, La Jolla, CA) to draw figures.

**RESULTS**

Seventy-eight patients (median age 59 yr; 47–69; 78% male) were included in the study. Results from thrombelastometry at admission and all data for the primary outcome were available. Median core temperature at admission was 35.3°C (34.8–35.8°C). Fibrinolysis exceeding the normal reference value of 15% was present in 36% of patients (28/78; 95% CI, 25–48%). The rate of overt DIC was 4% overall (3/78; 95% CI, 1–11%). In total, 54% of patients (42/78) had a poor 30-day outcome including 23 nonsurvivors (30%). Kaplan-Meier estimates of survival to day 30 according to ML cutoff of greater than or equal to 20% are available with the supplement (Supplemental Fig. 2, Supplemental Digital Content 1, http://links.lww.com/CCM/D848).

While nine patients died due to multiple organ failure, in 14 patients a decision to withdraw life-sustaining therapy was made by treating physicians after determination of unfavorable neurologic prognosis. Characteristics of the study patients according to 30-day outcome (CPC) are shown in Table 1.

The admission ML cutoff predicting poor outcome with 100% specificity (95% CI, 90–100) was greater than or equal to 20% (sensitivity 41%; 95% CI, 26–58%) (Fig. 1). The corresponding positive and negative predictive values were 100% and 59%, respectively. The receiver operating characteristic curve of ML for prediction of poor 30-day outcome as well as specificity, sensitivity, and cumulative frequency distributions of covariables are given with the supplement (Supplemental Figs. 3 and 4, Supplemental Digital Content 1, http://links.lww.com/CCM/D848).

Patients presenting with a ML greater than or equal to 20% (17/78, 22%; 59% male) were older (median 64 yr [IQR, 56–71 yr] vs 56 yr [46–67 yr]; \( p = 0.004 \)) and tended to have a higher frequency of nonshockable rhythm (35% vs 15%; \( p = 0.09 \)), had on average a 83% longer low-flow time (44 min [35–58 min] vs 24 min [15–36 min]; \( p < 0.001 \)), slightly higher lactate (8.3 mmol/L [6–14 mmol/L] vs 6.9 mmol/L [4–10 mmol/L]; \( p < 0.001 \)), 2.7-fold higher d-dimer (20 μg/mL [10–37 μg/mL]; \( p < 0.001 \)), and more

**TABLE 1. Characteristics of the Study Patients According to 30-Day Outcome**

| Variables                          | Total (n = 78) | Good Outcome (n = 36) | Poor Outcome (n = 42) | \( p \) |
|------------------------------------|---------------|-----------------------|-----------------------|-------|
| Male sex, n (%)                    | 61 (78)       | 31 (86)               | 30 (71)               | 0.12a |
| Age, yr                            | 59 (47–69)    | 52 (44–62)            | 63 (54–71)            | 0.004a|
| Comorbid diseases, n (%)           |               |                       |                       |       |
| Coronary artery disease            | 17 (22)       | 7 (19)                | 10 (24)               | 0.64a |
| Hypertension                       | 32 (41)       | 17 (47)               | 15 (36)               | 0.30a |
| Chronic heart failure              | 10 (13)       | 4 (11)                | 6 (14)                | 0.75c |
| Diabetes mellitus                  | 16 (21)       | 3 (8)                 | 13 (31)               | 0.01a |
| Smoker                             | 31 (40)       | 17 (47)               | 14 (33)               | 0.21a |
| Hyperlipidemia                     | 22 (28)       | 11 (31)               | 11 (26)               | 0.67a |
| CPC prior to cardiac arrest, n (%) |               |                       |                       | 0.50c |
| CPC 1                              | 76 (97)       | 36 (100)              | 40 (95)               |       |
| CPC 2                              | 2 (3)         | 0                     | 2 (5)                 |       |

(Continued)
TABLE 1. (Continued). Characteristics of the Study Patients According to 30-Day Outcome

| Variables                                                                 | Total (n = 78) | Good Outcome (n = 36) | Poor Outcome (n = 42) | p     |
|--------------------------------------------------------------------------|----------------|-----------------------|-----------------------|-------|
| **Cause of cardiac arrest, n (%)**                                       |                |                       |                       | 0.65a |
| Cardiac                                                                  | 75 (96)        | 35 (97)               | 40 (95)               |       |
| Unknown                                                                  | 3 (4)          | 1 (3)                 | 2 (5)                 |       |
| **Location of cardiac arrest, n (%)**                                     |                |                       |                       | 0.81a |
| Place of residence                                                       | 40 (51)        | 19 (53)               | 21 (50)               |       |
| Public place                                                             | 38 (49)        | 17 (47)               | 21 (50)               |       |
| Witnessed, n (%)                                                         | 64 (82)        | 32 (89)               | 32 (76)               | 0.15a |
| Basic life support, n (%)                                                | 56 (72)        | 27 (75)               | 29 (69)               | 0.56a |
| Shockable rhythm, n (%)                                                  | 62 (80)        | 34 (94)               | 28 (67)               | 0.002a|
| Cumulative dose of epinephrine, mg (IQR)                                 | 3 (1–5)        | 1 (0–4)               | 3 (2–5)               | < 0.001b|
| Sustained return of spontaneous circulation at admission, n (%)          | 70 (90)        | 34 (94)               | 36 (86)               | 0.28c |
| **Body temperature, °C, median (IQR)**                                   | 35.3 (34.8–35.8) | 35.5 (35.0–35.8) | 35.1 (34.4–35.7) | 0.10b |
| **No-flow interval, min, median (IQR)**                                  | 0 (0–3)        | 0 (0–0)               | 0 (0–1)               | 0.20b |
| **Low-flow interval, min, median (IQR)**                                 | 27 (16–43)     | 21 (10–34)            | 37 (24–50)            | < 0.001b|
| **pH (7.35–7.45)d, median (IQR)**                                       | 7.16 (7.05–7.25) | 7.24 (7.15–7.3) | 7.1 (7.02–7.17) | < 0.001b|
| **Lactate, mmol/L (< 1.8)d, median (IQR)**                               | 7.4 (5–10)     | 5.6 (3.2–7.3)         | 8.7 (6.3–11.5)        | < 0.001b|
| **Troponin T, ng/L (< 15)d, median (IQR)**                               | 161 (42–10,000) | 201 (47–10,000) | 106 (35–10,000) | 0.48b |
| **D-dimer, μg/mL (< 0.5)d, median (IQR)**                                | 8 (3–17)       | 4 (2–8)               | 14 (8–21)             | < 0.001b|
| **Platelets, 10^9/L (150–350)d, median (IQR)**                          | 209 (169–246)  | 214 (185–245)         | 205 (165–261)         | 0.78b |
| **Prothrombin time, % (> 70)d, median (IQR)**                            | 79 (66–91)     | 78 (62–87)            | 79 (70–92)            | 0.21b |
| **Fibrinogen, mg/dL (200–400)d, median (IQR)**                          | 282 (237–322)  | 287 (242–320)         | 270 (237–341)         | 0.66b |
| **Overt Disseminated Intravascular Coagulation†, n (%)**                 | 3 (4)          | 3 (7)                 | 0                     | 1.0c  |
| **Maximum lysis, % (≤ 15%)d, median (IQR)**                             | 10 (4–20)      | 6 (3–10)              | 11 (5–96)             | < 0.001b|
| **Maximum lysis > 15%, n (%)**                                           | 28 (36)        | 2 (6)                 | 26 (62)               | < 0.001b|
| **Maximum lysis ≥ 20%, n (%)**                                           | 17 (22)        | 0                     | 17 (41)               | < 0.001b|
| **Tissue-type plasminogen activator, ng/mL (2–8)d†, median (IQR)**      | 34 (21–54)     | 27 (14–43)            | 43 (23–66)            | 0.01b |
| **Plasminogen activator inhibitor 1, IU/mL (1–7)d†, median (IQR)**      | 0.76 (0–3.30)  | 1.00 (0.07–2.65)      | 0.72 (0–3.34)         | 0.79b |
| **Prothrombin fragments (F1 + 2), pmol/L (69–229)‡, median (IQR)**      | 1,141 (516–1,201) | 1,165 (638–1,201) | 1,068 (403–1,201) | 0.38b |
| **Coronary angiography, n (%)**                                          | 63 (81)        | 30 (83)               | 33 (79)               | 0.60a |
| **Rearrest after admission, n (%)**                                      | 6 (8)          | 2 (6)                 | 4 (14)                | 0.68c |

CPC = Cerebral Performance Category, IQR = interquartile range.

*χ^2* test.

U test.

Fisher exact test.

Reference range/upper limit of normal.

*A disseminated intravascular coagulation (DIC) score ≥ 5 is compatible with overt DIC (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/CCM/D848).

The study included only patients with presumed cardiac cause of cardiac arrest who had achieved return of spontaneous circulation at hospital admission. Laboratory variables and core temperature were assessed immediately after admission. Body temperature was recorded with an esophageal and bladder probe. Missing data were as follows: no flow time, n = 1; initial rhythm, n = 2; prothrombin time, n = 3; lactate levels, n = 2; epinephrine, n = 2; pH, n = 3; temperature at admission, n = 2.
The prevalence of increased fibrinolysis (ML > 15%) in our study is in good agreement with previous findings (10). However, we were interested in the optimal cutoff for fibrinolysis to specifically predict poor outcome. The greater than or equal to 20% cutoff value that predicted poor outcome with 100% specificity found in the current study corresponds well to the cutoff for increased fibrinolysis recently observed in healthy volunteers (18).

From previous research, we interpret fibrinolysis as a marker of tissue hypoperfusion due to prolonged resuscitation efforts or poor-quality CPR performance and consecutive accumulation of t-PA (6). This hypothesis is mainly based on data obtained from patients with drowning-related out-of-hospital cardiac arrest (OHCA), who are characterized by severely prolonged no- and low-flow intervals along with massive bleeding at hospital admission (6). Their bleeding phenotype was accompanied by increased t-PA levels and absent clotting signature in thrombelastometry, which were reversed by adding aprotinin in vitro. A subsequent forearm-ischemia model conducted in healthy volunteer confirmed the increase of t-PA levels following interruption of arterial blood flow. Further previous studies likewise reported high plasma fibrinolytic activity in cardiac arrest patients with early death (5) and a good correlation between t-PA levels and markers of hypoperfusion (7). In accordance, patients with ML greater than or equal to 20% had significantly higher t-PA levels at admission. Levels of the t-PA inhibiting protein PAI-1 were comparatively low in patients with and without increased fibrinolysis, which is in agreement with current literature (19). This relates to the lack of a storage compartment for PAI-1—in contrast to t-PA stored in endothelial cells—which forbids a readily available release upon hypoxic conditions. Upon acute t-PA release, PAI-1 is consumed (20, 21), and therefore it seems plausible that its activity is low in the very early phase after arrest. PAI-1 levels have been found to likewise increase only within 6 hours after acute hypoxia, contributing to the fibrinolytic shutdown in the subacute phase of the postcardiac arrest syndrome (5, 22).

Low-flow times and lactate levels in the current study were significantly higher in patients with a ML greater than or equal to 20%, which supports the above findings. Likewise, the rate of nonshockable rhythm tended to be higher, which may suggest longer preceding no-flow intervals before initiation of CPR in these patients. No-flow times did not differ significantly between groups, but are, however, usually only estimates with low reliability.

We suggest that fibrinolysis is mainly triggered by hypoperfusion which could also explain the low negative predictive value of ML found in the current study. It is conceivable that patients with prolonged no-flow times but high-quality CPR performance—and thus, hypothetically, rapid clearance of t-PA—suffer poor neurologic recovery despite lack of fibrinolysis at admission. The quality of CPR performance is, however, difficult to assess routinely.

An alternative or possibly contributing mechanism of increased fibrinolysis in cardiac arrest may be thrombin-related plasmin activation following blood exposure to...
interstitial tissue factor through hypoxic endothelial damage. Along these lines, Adrie et al (5) found a significant association between thrombin levels and organ dysfunction after successful resuscitation. Thrombin may also contribute to delayed t-PA (23) and/or urokinase-type plasminogen activator (24) release from endothelial cells.

In our study, patients’ prothrombin fragments were markedly elevated in both, patients with and without increased fibrinolysis, suggesting early thrombin generation in cardiac arrest. Yet, although thrombin-mediated coagulopathy likely becomes important hours or days after successful resuscitation, possibly as part of the postcardiac arrest syndrome, its contribution to increased fibrinolysis detected by thrombelastometry very early after successful resuscitation is questionable. Furthermore, in tissue factor/thrombin-driven coagulopathy, we would expect substantial consumption of clotting factors and platelets resulting in what is referred as DIC with fibrinolytic phenotype (25).

Consumptive coagulopathy, however, was very rare in our study patients, and the rate of overt DIC at admission did not differ between patients with and those without increased fibrinolysis. The low prevalence of overt DIC in our study patients, however, is in striking contrast to data from a retrospective Asian study, which reported overt DIC rates of 33% in resuscitated cardiac arrest with greater than 90% hospital mortality (26). As we analyzed a highly preselected subset of patients, the results of the two studies are difficult to compare. Yet, it would be of interest whether these differences result from different resuscitation policies (including termination-of-care rules) and whether overt DIC simply represents a premortem sign.

Another possible contributor to the impairment of coagulation may be hypothermia, but, however, a substantial impact on increased fibrinolysis in our patients seems unlikely. Median body temperature at admission was above 35°C, which is in agreement with recent literature (27), and did not differ significantly between patients with and without ML greater than or equal to 20%. Furthermore, previous studies did not report patterns of increased fibrinolysis under intentional hypothermia (28–31).

We were further interested in whether exogenous epinephrine may contribute to the extent of increased fibrinolysis in cardiac arrest. Catecholamines are known to promote release of t-PA from the endothelium (32), and the amount of epinephrine given during resuscitation has previously been linked to poor outcome regardless of the length of resuscitation (33). In the current study, there was an insignificant trend of higher cumulative epinephrine doses in patients who presented with ML greater than or equal to 20%. In regression analysis, however, the dosage of epinephrine administered had no effect on mortality after adjustment for ML greater than or equal to 20, which may suggest no causative relationship. Whether exogenous epinephrine directly contributes to fibrinolysis or simply reflects longer resuscitation efforts, and thus prolonged preceding hypoperfusion remains speculative and might be answered in a further study. Furthermore, yet, no data are available on the interaction between endogenous catecholamine levels and fibrinolysis in cardiac arrest. Our own recent data derived from a subset of 1,188 cardiac arrest patients underlie the outcome-predictive role of sympathoadrenergic activation following resuscitation indicated by both, increased short- and long-term mortality in cardiac arrest along with the amount of immature peripheral neutrophils at admission (34).

It is unclear whether this simply reflects the gradual extent of stress to the body following resuscitation or whether endogenous catecholamines may have a role in subsequent alterations of the coagulation and fibrinolytic system, as it has been described in trauma and septic patients (35, 36). In addition to increased fibrinolysis caused by stress-mediated sympathoadrenergic catecholamine release, neutrophil elastase has been linked as trigger for fibrinolysis in trauma (25). However, to date, no comparable data are available on the contribution of neutrophil elastase to promote fibrinolysis in cardiac arrest.

Some limitations need to be considered while interpreting the results. The current prospective observational study analyzed a strictly preselected cohort of OHCA patients including only those with presumed cardiac cause of cardiac arrest, who had achieved ROSC at admission, and were subjected to targeted temperature management. The possibly associated selection bias has to be considered, and study results need to be interpreted with appropriate caution.

Furthermore, it has to be mentioned that there is currently no widely accepted “gold standard” assay available for detection of systemic fibrinolysis. A possible risk of bias relating to the lack of a reference standard must be taken into account. Future studies determining thrombelastometry thresholds for increased fibrinolysis in OHCA need to validate their findings against standardized methods for detection of fibrinolysis, which may become available in the future (37). Further investigations also need to confirm the predictive performance of a greater than or equal to 20% ML cutoff found in this study.

CONCLUSIONS
Increased fibrinolysis at admission may be interpreted as cumulative surrogate marker for hypoperfusion and hypoxia, that is, the duration of no-flow time and resuscitation quality. The current study provides a predictive cutoff value for a readily available bedside marker with 100% positive predictive value for poor outcome, which could be of interest for both treating physicians and relatives.

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