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Clinical Paper

# Hyperfibrinolysis in out of hospital cardiac arrest is associated with markers of hypoperfusion☆

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ABSTRACT

*Aim of the study:* This study investigated the incidence of hyperfibrinolysis upon emergency department (ED) admission in patients with out of hospital cardiac arrest (OHCA), and the association of the degree of hyperfibrinolysis with markers of hypoperfusion.
*Methods:* From 30 OHCA patients, cardiopulmonary resuscitation (CPR) time, pH, base excess (BE), and serum lactate were measured upon ED admission. A 20% decrease of rotational thromboelastometry maximum clot firmness (MCF) was defined as hyperfibrinolysis. Lysis parameters included maximum lysis (ML), lysis onset time (LOT) and lysis index at 30 and 45 min (LI30/LI45). The study was approved by the Human Subjects Committee.
*Results:* Hyperfibrinolysis was present in 53% of patients. Patients with hyperfibrinolysis had longer median CPR times (36 (15–55) vs. 10 (7–18) min; $P = 0.001$), a prolonged activated partial thromboplastin time ($54 \pm 16$ vs. $38 \pm 10$ s; $P = 0.006$) and elevated D-dimers ($6.1 \pm 2.1$ vs. $2.3 \pm 2.0$ μg/ml; $P = 0.02$) when compared to patients without hyperfibrinolysis. Hypoperfusion markers, including pH ($6.96 \pm 0.11$ vs. $7.17 \pm 0.15$; $P < 0.001$), base excess ($-20.01 \pm 3.53$ vs. $-11.91 \pm 6.44$; $P < 0.001$) and lactate ($13.1 \pm 3.7$ vs. $8.0 \pm 3.7$ mmol/l) were more disturbed in patients with hyperfibrinolysis than in non-hyperfibrinolytic subjects, respectively. The LOT showed a good association with CPR time ($r = -0.76$; $P = 0.003$) and lactate ($r = -0.68$; $P = 0.01$), and was longer in survivors ($3222 \pm 34$ s) than in non-survivors ($1356 \pm 833$; $P = 0.044$).
*Conclusion:* A substantial part of OHCA patients develop hyperfibrinolysis in association with markers for hypoperfusion. Our data further suggest that the time to the onset of clot lysis may be an important marker for the severity of hyperfibrinolysis and patient outcome.


## 1. Introduction

Out-of-hospital cardiac arrest (OHCA) remains a significant cause of morbidity and mortality among the general population. Despite advances in cardiopulmonary resuscitation, the prognosis after OHCA remains very poor, with survival rates around 10% in Europe.[1]

Cardiac arrest and resuscitation are characterised by reduced cardiac output and blood flow, resulting in shock and tissue hypoperfusion.[2–4] Animal and human studies showed marked activation of inflammation and coagulation after cardiac arrest and resuscitation, resulting in intravascular coagulation, systemic formation of microthrombi and impairment of microcirculatory perfusion.[5–7] These changes may contribute to the development of ischemic injury and the post-resuscitation syndrome, which is further characterised by a systemic inflammation response, reperfusion injury, adrenal dysfunction, myocardial dysfunction and eventually organ failure.[8,9] In particular, an increased duration of cardiopulmonary resuscitation is associated with a rise in coagulation abnormalities and mortality.[8,10]

Recent studies have shown that markers of shock and hypoperfusion in trauma patients are frequently paralleled by hyperfibrinolysis, which in turn is associated with higher mortality rates.[11–13] One of the proposed mechanisms is that hypoperfusion-associated thrombin formation leads to systemic hyperfibrinolysis through the protein C pathway, but the underlying mechanisms are not well understood.[11,12,14] Secondly, hypoxia may lead to excessive release of tissue plasminogen activator (t-PA) and thereby contribute to the presence of hyperfibrinolysis.[15]

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Despite the close resemblance of systemic hypoperfusion as observed during trauma, sepsis or OHCA, there is only limited evidence showing that OHCA patients develop hyperfibrinolysis. Moreover, it has never been investigated whether fibrinolytic parameters, like the maximum lysis or lysis onset time, are indeed associated with markers for hypoperfusion. In the present study we therefore investigated whether cardiopulmonary arrest is associated with hyperfibrinolysis as diagnosed by rotational thromboelastometry, and hypothesised that the severity of hyperfibrinolysis is associated with the degree of shock and hypoperfusion.

## 2. Methods

### 2.1. Patient population

The present study comprised a prospective observational clinical study that included patients admitted to the shock room of the emergency department (ED) after out of hospital cardiac arrest (OHCA) who were monitored by rotational thromboelastometry according to standard clinical routine. The study was performed according to the regulations of the Human Subjects Committee. Patients aging 18 years and older who had a witnessed out-of-hospital cardiac arrest that was not related to trauma were included in the study. Exclusion criteria were the inability to drawn blood samples, previous haemostatic abnormalities, traumatic arrest, pregnancy, cardiac arrest from septic shock, the use of heparin or warfarins and/or suspected (massive) pulmonary embolism.

### 2.2. Study parameters

Data included patient characteristics, the transportation time between arrest and arrival at the emergency department, initial heart rhythm on site recorded by the ambulance paramedic, the duration of chest compressions, the heart rhythm upon arrival at the emergency department, haemoglobin, haematocrit, arterial oxygen partial pressure ($pO_2$), arterial carbon dioxide partial pressure ($pCO_2$), base excess (BE), pH and serum lactate.

### 2.3. Blood sampling

Blood sampling was performed as soon as possible after patient admission to the emergency department. Blood sampling took place either before or after return of spontaneous circulation (ROSC) from a single arterial puncture, which is routine practice in our trauma centre. All coagulation tests were performed within 30 min after blood sampling.

### 2.4. Coagulation parameters

All routine coagulation tests were performed in the haemostasis laboratory of the VU University Medical Centre using standardised measurements. Samples were centrifuged for 10 min at 4000 rpm and subsequently centrifuged for another 5 min at 12,000 rpm. The routine coagulation tests consisted of the prothrombin time (PT) using calcium thromboplastin, the activated partial thromboplastin time (aPTT) using cefaline/microcrystaliline and platelet count. The aPTT and PT tests were performed using a STA-R instrument® (Roche Diagnostics FmbH, Basel, Switzerland).

Rotational thromboelastometry (TEM International, Munich, Germany) consisted of a 60-min registration of the EXTEM test (measurement of thromboplastin-induced activation of the coagulation). ROTEM parameters included the clotting time (CT), clot formation time (CFT), maximum clot firmness (MCF), maximum lysis (ML), lysis time (LT) and lysis onset time (LOT) (Fig. 1).

### 2.5. Definition of hyperfibrinolysis

Hyperfibrinolysis was defined as a maximum lysis of the clot of >20% within 60 min following initiation of rotational thromboelastometry in the EXTEM channel. The maximum lysis index (ML) is the difference between the maximum MCF and the lowest MCF due to fibrinolysis and is described as percentage. The lysis onset time (LOT) is the time from the start of the reaction to the point that a lysis of 20% from the MCF is reached. The lysis index at 30 and 45 min (LI30 and LI45, respectively) represent the remaining clot firmness amplitude at 30 and 45 min after the start of the reaction relative to the maximal clot firmness. The lysis time (LT) is the time from when the MCF is reached until maximum lysis.

### 2.6. Statistical analysis

Data were stored in the hospital electronic medical database (Mirador® iSOFT Nederland). Statistical analysis was performed using the SPSS statistical software package 17.0 (IBN, New York, USA). Descriptive statistics were calculated for all parameters and included mean, median with standard deviation, frequencies or median with interquartile range. Statistical differences between patients with or without hyperfibrinolysis were calculated using a Student's *T*-test or Mann–Whitney *U* test. Pearson correlations were used to determine the association between several laboratory values and fibrinolytic parameters. A *P*-value of 0.05 or less was considered as statistically significant.

## 3. Results

### 3.1. Patient characteristics

The study included 30 patients with witnessed out of hospital cardiac arrest that were admitted to the emergency department of the VU University Medical Center after witnessed out-of-hospital cardiac arrest between November 2009 and May 2010. Three patients were excluded due to suspected pulmonary embolism, eight patients were not included since no blood sample could be drawn and one patient was included due to missing coagulation data. The remaining 30 patients were $66 \pm 15$ years old and 64% were male. The mean time from witnessed cardiopulmonary arrest to emergency department arrival was $42 \pm 13$ min. The mean duration of cardiopulmonary resuscitation was $27 \pm 22$ min. The number of patients with first rhythm ventricular fibrillation was 53%.

Table 1 shows the characteristics of patients without or with hyperfibrinolysis. In the total study group, 16 patients out of 30 patients (53%) developed hyperfibrinolysis. The median chest compression time (ALS) and median time to first cardiac output was higher in patients with hyperfibrinolysis (36 (15–55) min and 44 (33–58) min, respectively) than patients without hyperfibrinolysis (10 (7–18) min and 16 (13–28) min, respectively). Patients with hyperfibrinolysis had signs of disseminated intravascular coagulopathy as indicated by the higher aPTT ($54 \pm 16$ s vs. $38 \pm 10$ s) and D-dimers ($6.1 \pm 2.1$ μg/ml vs. $2.3 \pm 2.0$ μg/ml) when compared to patients without hyperfibrinolysis, respectively.

Hyperfibrinolysis was associated with markers of hypoperfusion as indicated by pH, base excess, lactate, $pO_2$ and $pCO_2$ (Table 1). In particular, base excess ($-11.91 \pm 6.44$ vs. $-20.01 \pm 3.53$; $P < 0.001$) and lactate ($8.0 \pm 3.7 \pm 13.1 \pm 3.7$; $P = 0.001$) levels differed significantly between patients without or with hyperfibrinolysis, respectively.

**Table 1**
Characteristics of patients without or with hyperfibrinolysis.

| | No hyperfibrinolysis | Hyperfibrinolysis | *P* |
|---|---|---|---|
| *N* | 14 | 16 | |
| Age (years) | 65 ± 18 | 68 ± 13 | ns |
| Resuscitation parameters | | | |
| Median transportation time (min) | 44 (34–49) | 38 (32–53) | ns |
| Median CPR time (min) | 10 (7–18) | 36 (15–55) | 0.001 |
| Median time to 1st output (min) | 16 (13–28) | 44 (33–58) | 0.007 |
| Coagulation parameters | | | |
| Haemoglobin (mmol/l) | 8.3 ± 1.0 | 8.5 ± 1.2 | ns |
| Haematocrit | 0.41 ± 0.05 | 0.43 ± 0.06 | ns |
| aPTT (s) | 38 ± 10 | 54 ± 16 | 0.006 |
| INR | 1.55 ± 1.03 | 2.04 ± 1.42 | ns |
| Platelet count ($10^{-9}$)* | 217 ± 92 | 186 ± 90 | ns |
| Fibrinogen (g/l) | 3.4 ± 1.0 | 1.9 ± 1.4 | ns |
| D-dimers (μg/ml) | 2.3 ± 2.0 | 6.1 ± 2.1 | 0.02 |
| Markers for hypoperfusion | | | |
| pH | 7.17 ± 0.15 | 6.96 ± 0.11 | <0.001 |
| BE | −11.91 ± 6.44 | −20.01 ± 3.53 | <0.001 |
| Lactate (mmol/l) | 8.0 ± 3.7 | 13.1 ± 3.7 | 0.001 |
| Median $pO_2$ (kPa) | 237 (127–405) | 92 (54–124) | 0.001 |
| Median $pCO_2$ (kPa) | 44 (35–52) | 59 (46–78) | 0.03 |

Values are presented as mean ± SD or median with interquartile range. CPR, cardiopulmonary resuscitation; aPTT, activated partial thromboplastin time; INR, international normalised ratio in the prothrombin time; BE, base excess; $pO_2$, arterial oxygen pressure; $pCO_2$, arterial carbon dioxide pressure; ns, not significant.
* $P < 0.05$ was considered as statistically different.

### 3.2. Relation hyperfibrinolysis parameters and markers of hypoperfusion

In patients with hyperfibrinolysis, the lysis index of the EXTEM at 30 and 45 min estimated 72 ± 43% and 56 ± 42%, respectively. The lysis onset time was 1798 ± 970 s, with a lysis time of 1487 ± 1159 s. Overall, the lysis onset time ranged from 514 to 2947 s. The maximum lysis was 64 ± 39%. Fig. 2 show the association of the lysis onset time with cardiopulmonary resuscitation (CPR) time (panel A), base excess (panel B) and lactate levels (panel C). The lysis onset time showed a good correlation with the CPR time and lactate levels. Lactate, and not base excess, was overall associated with the maximum lysis ($r = 0.52$; $P = 0.04$), LI30 ($r = -0.61$; $P = 0.01$) and LI45 ($r = -0.87$; $P < 0.001$).

### 3.3. Patient outcome

In the total group, 19 patients (63%) died after hospital admission. The study was not powered to compare mortality in patients with or without hyperfibrinolysis. Overall, mortality in patients with or without hyperfibrinolysis estimated 69% and 57%, respectively. Patients with hyperfibrinolysis who died showed a shorter lysis onset time (1356 ± 833 s) when compared to survivors with hyperfibrinolysis (3222 ± 34 s; $P = 0.044$).

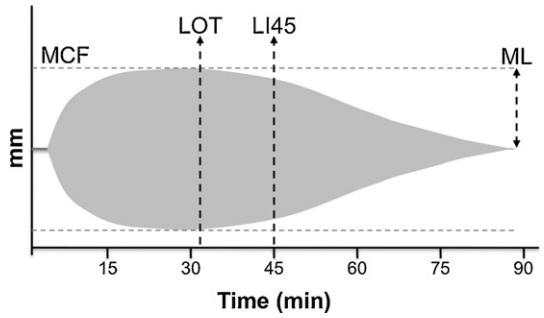


**Fig. 1.** ROTEM lysis parameters: MCF, maximum clot formation, LOT, lysis onset time, LT, lysis time, LI30, lysis index at 30 min, LI45, lysis index at 45 min, ML, maximum lysis.

## 4. Discussion

This is the first clinical study showing hyperfibrinolysis using rotational thromboelastometry in a majority of the patients admitted after witnessed out of hospital cardiac arrest. Hyperfibrinolysis was associated with profound disseminated intravascular coagulopathy compared to patients without hyperfibrinolysis. The most interesting marker for hyperfibrinolysis was the lysis onset time, which was related to the cardiopulmonary resuscitation time and lactate levels. A delayed start of hyperfibrinolysis was less frequently associated with markers for hypoperfusion and mortality. Our study shows that a significant part of out of hospital cardiac arrest patients develop hyperfibrinolysis, in particular in case of signs of hypoperfusion. This supports the hypothesis that hyperfibrinolysis may be induced by shock and hypoperfusion solely, without the presence of trauma or massive blood loss.

Primary fibrinolysis is a local tissue phenomenon that supports blood clot breakdown. Under physiological conditions, fibrinolysis is activated by urokinase or tissue plasminogen activator (tPA) that is released by the damaged endothelium. Urokinase and tPA are inhibited by plasminogen activator inhibitor (PAI) 1 or 2. After conversion of plasminogen to plasmin, plasmin is primary inhibited by alpha-2-antiplasmin, while thrombin activatable fibrinolysis inhibitor (TAFI) further inhibits fibrinolysis itself.[15–17] Secondary fibrinolysis refers to an abnormal clot breakdown under pathophysiological circumstances, like trauma or disturbances in tissue perfusion, which may confer to hyperfibrinolysis. One of the proposed mechanisms underlying excessive fibrinolysis is the activation of protein C, which subsequently inhibits PAI-1 and TAFI.[10,12,14] Moreover, hypoxia induces a systemic release of t-PA, leading to excessive fibrinolysis.[15,18,19] Our findings warrant closer evaluation of levels of t-PA, activated protein C, plasminogen, PAI and TAFI in OHCA patients in order to understand the pathophysiology of hyperfibrinolysis during cardiopulmonary arrest.

Cardiac arrest and resuscitation have previously been shown to be associated with activation of coagulation and inflammation that closely resembled the changes observed in sepsis. Adrie et al. showed that patients who were successfully resuscitated after cardiopulmonary arrest had a systemic inflammatory response with activation of coagulation, reduction of anticoagulation, activation of

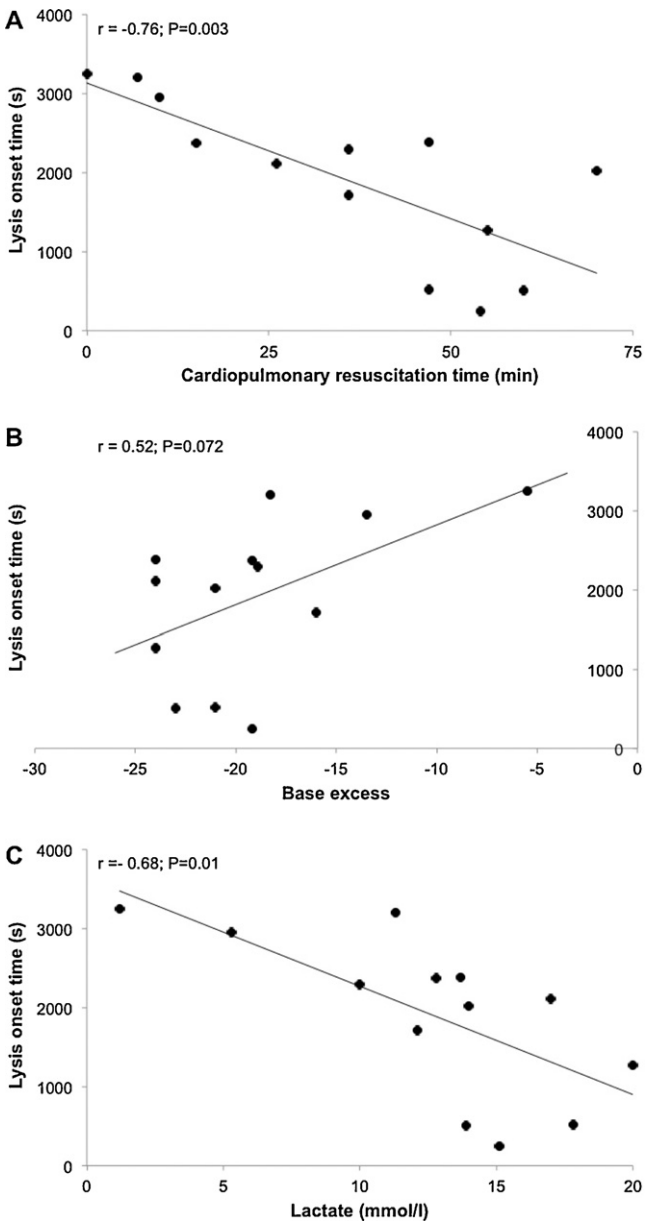


**Fig. 2.** Pearson correlations (*r*) between lysis onset time and cardiopulmonary resuscitation time (panel A), base excess (panel B) and lactate levels (panel C). *P*-values are shown in the figures.

fibrinolysis and in some cases inhibition of fibrinolysis.[10] In particular, hyperfibrinolysis was associated with increased early mortality, but the authors did not look further into the association between the degree of shock and the level of hyperfibrinolysis.[10] In agreement with their study, we found that about 50% of the patients with cardiopulmonary arrest developed hyperfibrinolysis.[10] Moreover, we found a good correlation between chest compression time and lactate with the onset time of hyperfibrinolysis, suggesting an association between hypoperfusion and excessive fibrinolysis in OHCA patients. However, even though mean pH, BE and lactate levels were higher in the group of patients with hyperfibrinolysis, patients in the non-hyperfibrinolysis group also suffered from severe metabolic acidosis. Further studies are necessary to unravel the involvement of endothelial activation, t-PA release and the inhibition of PAI and TAFI in order to gain more insight in the cause of hyperfibrinolysis in patients with cardiac arrest.

This is the first study that uses rotational thromboelastometry to diagnose hyperfibrinolysis in the patients with cardiopulmonary arrest. Hyperfibrinolysis is not detectable by classical haemostatic testing such as the aPTT or PT. Schöchl et al. were the first to show that trauma patients with hyperfibrinolysis as measured by thromboelastometry were at higher risk for unfavourable outcome.[11] Interestingly, they also detected hyperfibrinolysis in a small group of patients with isolated traumatic brain injury in the absence of extracranial haemorrhage, suggesting that excessive bleeding is no prerequisite for hyperfibrinolysis.[20] As the number of hospitals with point-of-care coagulation testing increases, more insight might be obtained of the association between out of hospital cardiac arrest and hyperfibrinolysis.

There is currently no consensus with respect to the validity of the fibrinolytic parameters provided by rotational thromboelastometry. Moreover, it is unclear whether the level or the onset time of fibrinolysis is more important to determine the severity level of hyperfibrinolysis. Most studies use the maximum lysis index (ML), which shows the extent of lysis as percentage of the maximum clotting amplitude (MCF) after 60 min of runtime. In particular, Schöchl et al. used a categorical classification for late, intermediate and fulminant hyperfibrinolysis.[11] The solely use of the ML may lead to an underestimation of the degree of hyperfibrinolysis in cases where a maximum lysis is reached before 60 min of runtime. We therefore used the lysis onset time (LOT) as the point where the decline in clot firmness starts. Theoretically, this parameter seems most appropriate for determining the degree of hyperfibrinolysis as it provides a measure for hyperfibrinolysis for every patient with clot lysis within 60 min of ROTEM runtime. Moreover, in contrast to the maximum lysis, the LOT has no maximum. The choice for the LOT in our study matches with previous ex vivo research by Nielsen et al., who showed a relation between increasing tPA concentrations and the time to clot disintegration.[21] Further studies are necessary to validate the use of the lysis onset time to quantify the degree of hyperfibrinolysis.

Our investigation did not include body temperature registrations of included patients. As hypothermia may deteriorate coagulation, our findings might be confounded in case of low body temperature. Part of our study population received prehospital fluids up to 500 ml, but these data were also not included in our study database. It is however not expected that the fluid administration did affect the time to hyperfibrinolysis in our study population. This study was not powered to determine differences in outcome between patients with or without hyperfibrinolysis, and no conclusions may be drawn from these data regarding final outcome. However from the seven patients with unfavourable outcome in the emergency room, six patients showed hyperfibrinolysis. On one hand, this may suggest that excessive fibrinolysis is associated with early death, although larger studies are warranted to support this concept. On the other hand, a state of hyperfibrinolysis may theoretically be beneficial in patients in severe shock by maintaining vascular patency and end-organ perfusion. The question remains whether hyperfibrinolysis in patients with cardiopulmonary arrest is an evolutionary end-of-life indicator or a physiological phenomenon to prevent further ischemic and thromboembolic injury and ensure end-organ perfusion under stressful conditions.

## Disclosures

None of the authors have disclosures.

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## Conflict of interest statement

None of the authors have a conflict of interest.

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