Low Cerebral Oxygenation Levels during Resuscitation in Out-of-hospital Cardiac Arrest Are Associated with Hyperfibrinolysis

Anne Duvekot, M.D., Victor A. Viersen, M.D., Simone E. Dekker, M.D., Leo M. G. Geeraedts, Jr., M.D., Ph.D., Lothar A. Schwarte, M.D., Ph.D., Angelique M. E. Spoelstra-Man, M.D., Ph.D., Peter M. van de Ven, Ph.D., Charissa E. van den Brom, M.Sc., Ph.D., Monique C. de Waard, M.Sc., Ph.D., Stephan A. Loer, M.D., Ph.D., Christa Boer, M.Sc., Ph.D.

ABSTRACT

Background: The authors investigated whether patients with out-of-hospital cardiac arrest with an initial low cerebral oxygen level during cardiopulmonary resuscitation are more prone to develop hyperfibrinolysis than patients with normal cerebral oxygenation levels and which part of the fibrinolytic system is involved in this response.

Methods: In 46 patients, hyperfibrinolysis was diagnosed immediately upon emergency department admission using rotational thromboelastometry and defined as a lysis more than 15%. Simultaneously, initial cerebral tissue oxygenation was measured using near-infrared spectroscopy, and oxygen desaturation was defined as a tissue oxygenation index (TOI) of 50% or less. Blood sample analysis included markers for hypoperfusion and fibrinolysis.

Results: There was no difference in prehospital cardiopulmonary resuscitation duration between patients with or without hyperfibrinolysis. An initial TOI of 50% or less was associated with more clot lysis (91% [17 to 100%; n = 16]) compared with patients with a normal TOI (6% [4 to 11%]; n = 30; $P < 0.001$), with lower levels of plasminogen (151.6 ± 61.0 *vs.* 225.3 ± 47.0 μg/ml; $P < 0.001$) and higher levels of tissue plasminogen activator (t-PA; 18.3 ± 7.4 *vs.* 7.9 ± 4.7 ng/ml; $P < 0.001$) and plasminogen activator inhibitor-1 (19.3 ± 8.9 *vs.* 12.1 ± 6.1 ng/ml; $P = 0.013$). There were no differences in (activated) protein C levels among groups. The initial TOI was negatively correlated with t-PA ($r = -0.69$; $P < 0001$). Mortality rates were highest in patients with hyperfibrinolysis.

Conclusion: Activation of the fibrinolytic system is more common in out-of-hospital cardiac arrest patients with an initial cerebral tissue oxygenation value of 50% or less during resuscitation and is linked to increased levels of t-PA rather than involvement of protein C. **(Anesthesiology 2015; 123:820-9)**

OUT-OF-HOSPITAL cardiac arrest (OHCA) remains associated with a low rate of survival, despite advanced treatment algorithms.[1,2] The state of shock associated with OHCA is known to be accompanied by the activation of the coagulation system and disturbances in the fibrinolytic system.[3,4] We and others showed that a substantial proportion of OHCA patients develop endogenous excessive clot breakdown.[5–7] This hyperfibrinolytic state contributes to the development of disseminated intravascular coagulation in the absence of visible bleeding and is associated with poor outcome and increased risk for early mortality.[8–10]

We previously showed that the level of hyperfibrinolysis is associated with the severity of derangements in systemic markers of tissue hypoperfusion in OHCA patients, including base excess (BE), lactate, and pH values.[5] The underlying mechanism of hypoperfusion-associated hemostatic

What We Already Know about This Topic

- Out-of-hospital cardiac arrest (OHCA) remains associated with a low rate of survival, despite advanced treatment algorithms
- Recently, the level of cerebral oxygen saturation during resuscitation was acknowledged as novel outcome predictor in patients with cardiac arrest, but the association between cerebral tissue oxygenation levels and the prevalence of hyperfibrinolysis is unclear
- The objective of this study was to identify patients after OHCA with the highest risk of developing hyperfibrinolysis with particular emphasis on cerebral oxygenation levels

What This Article Tells Us That Is New

- Activation of the fibrinolytic system is more common in Out-of-hospital cardiac arrest patients with an initial cerebral tissue oxygenation value of 50% or less during resuscitation and is linked to increased levels of tissue plasminogen activator rather than involvement of protein C

This work has been presented at the International Symposium on Critical Bleeding, Copenhagen, Denmark, September 2–3, 2013.

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disturbances is however still under debate. In trauma patients, it has been suggested that the presence of tissue hypoperfusion is associated with changes in the thrombomodulin–protein C pathway, leading to protein C activation. This activation subsequently leads to anticoagulation by inactivation of factor V and VIII and increased fibrinolysis through an increase in tissue plasminogen activator (t-PA) and inactivation of fibrinolysis-inhibiting proteins such as plasminogen activator inhibitor- (PAI-1).[11,12] It is unknown whether the pathway of hypoperfusion-associated traumatic coagulopathy mechanisms is also responsible for the changes in coagulation observed in OHCA patients.

Although hyperfibrinolysis has been acknowledged as an unfavorable complication of cardiac arrest, it is still unclear which patients are prone to develop a disturbed fibrinolytic state. Moreover, although we previously suggested that hyperfibrinolysis should be considered as an epiphenomenon of hypoxia and tissue hypoperfusion, the direct link between tissue oxygenation and the prevalence of hyperfibrinolysis has scarcely been investigated as most studies only focus on surrogate markers for inadequate tissue blood flow, such as arterial carbon dioxide partial pressure (pCO_2) or pH.[5,7]

Recently, the level of cerebral oxygen saturation during resuscitation was acknowledged as novel outcome predictor in patients with cardiac arrest,[13] but the association between cerebral tissue oxygenation levels and the prevalence of hyperfibrinolysis is unclear. The main objective of his study was therefore to further identify patients after OHCA with the highest risk of developing hyperfibrinolysis with particular emphasis on cerebral oxygenation levels. We hypothesized that OHCA patients with an initial low cerebral oxygen level during cardiopulmonary resuscitation (CPR) as measured upon emergency department (ED) arrival by near-infrared spectroscopy (NIRS) show a higher prevalence of hyperfibrinolysis than patients with normal oxygenation levels. We investigated whether excessive clot breakdown and alterations in plasma fibrinolytic markers are particularly present in case of cerebral tissue oxygenation levels of 50% or less during resuscitation as measured by NIRS. We further studied whether the association of cerebral oxygenation levels and initiation of the anticoagulant system is paralleled by activation of protein C.

Materials and Methods

Study Design

This prospective, single-center observational study was performed in the VU University Medical Center in Amsterdam, The Netherlands, between September 2012 and July 2013. The study was approved by the local Human Subjects Committee of the VU University Medical Center (METc VUmc, Amsterdam, The Netherlands) and registered in The Netherlands Trial Register (2012/119; NL39831.029.12). The data were not previously published, except for the correlation between the lysis onset time and t-PA levels in a subgroup of 13 patients by Dekker *et al.*[6]

Relatives of the patients provided written informed consent. Adult patients with out-of-hospital cardiac arrest (OHCA) undergoing CPR by an emergency medical service (EMS) upon hospital admission were eligible for the study inclusion. Hyperfibrinolysis was not the inclusion criterion for study admission. Exclusion criteria were the absence of a peripheral intravenous catheter, the use of anticoagulation medication (vitamin K antagonists, clopidogrel, or dabigatran), and a traumatic origin of cardiac arrest due to the risk of concomitant traumatic bleeding. None of the patients with OHCA received fibrinolytic therapy before hospital arrival. For data analysis, patients were *a priori* categorized according to the presence of an initial tissue oxygenation index (TOI) of 50% or less or greater than 50% and the presence of hyperfibrinolysis (EXTEM maximum lysis [ML] ≥15%) upon ED arrival.

Prehospital Management of OHCA in The Netherlands

In The Netherlands, EMS teams consist of ambulance paramedics who are trained as intensive care unit–certified nurses. Ambulance paramedics are not allowed to induce and maintain anesthesia and provide advanced life support in case of OHCA using oxygen administration by facemask or bag-valve-mask ventilation. Endotracheal intubation by ambulance paramedics is only allowed in comatose patients. Upon ED arrival of patients with OHCA, anesthesiologists induce anesthesia, perform endotracheal intubation, and start mechanical ventilation.

Mild Therapeutic Hypothermia Protocol

All surviving patients underwent therapeutic hypothermia according to the protocol upon admission at the intensive care department. Comatose patients after OHCA were treated with moderate therapeutic hypothermia irrespective of initial heart rhythm or presumed cause of OHCA. All patients were intubated and mechanically ventilated. Cooling was initiated in the ED with infusion of refrigerated NaCl 0.9% (4°C) with a maximum of 1 l. Upon arrival in the intensive care unit, an esophageal temperature probe was inserted for continuous temperature monitoring. Body and leg wraps were used for cooling, and an external temperature control unit adjusted the temperature of the water circulating through the wraps with a target temperature of 32.5°C (Medi-Therm, Gaymar; Stryker GmbH, Germany). Patients were deeply sedated with propofol and fentanyl. Moderate therapeutic hypothermia was maintained for 24 h, followed by rewarming with a maximum temperature increase of 0.65°C per hour. After rewarming, a neurologic examination was initiated to assess patient prognosis.

Near-infrared Spectroscopy

Near-infrared spectroscopy measurements and concurrent blood sample drawings were immediately performed upon arrival of the patient at the ED. Local cerebral oxygen saturation was determined using NIRS (Covidien, The Netherlands)

and expressed as the TOI in percentages. NIRS measures the presence of oxygenated and deoxygenated hemoglobin in the underlying tissue through locally placed electrodes.

Population and Metabolic Characteristics

Age, sex, cause of cardiac arrest, the time span between the emergency call and arrival of the EMS at the OHCA location, the duration of CPR provided by the EMS in the prehospital period, the duration of CPR after ED arrival, the number of patients who received an endotracheal tube by the EMS in the prehospital period, and the primary observed heart rhythm were documented at the time of arrival in our hospital. The time span between the emergency call and arrival of the EMS at the OHCA location and the prehospital CPR duration by the EMS were documented for 13 patients (76.4%) with hyperfibrinolysis and 24 patients (82.8%) without hyperfibrinolysis. Metabolic parameters were determined by standard blood gas analysis and consisted of BE, arterial oxygen partial pressure (pO_2), pCO_2, lactate, and pH values. Furthermore, mortality was assessed and defined as death within 24 h after hospital admission and as death before hospital discharge.

Definition of Cerebral Oxygen Desaturation

Cerebral oxygen desaturation was defined as an initial TOI of 50% or less upon ED arrival. This definition was based on observations by others showing that even short episodes below this threshold are associated with cognitive and neurological injury, increased hospitalization, and poor outcome.[14,15]

Blood Sample Analysis

Blood samples were immediately drawn upon admission to the ED and used for rotational thromboelastometry (ROTEM; TEM International, Germany) and platelet aggregometry (Chrono-log CH592A whole blood aggregometry; Stago BNL, The Netherlands). ROTEM measures the dynamics of blood clot formation and transfers this information into a graphic, showing clot growth, clot strength, and clot breakdown. Whole blood aggregometry was used to measure the platelet function by determining the electrical impedance in whole blood samples and was defined by the area under the curve (AUC). One milliliter of 1:1 NaCl diluted blood was activated by 10 μl of 1 mM adenosine diphosphate (ADP; Chrono-Log Corporation; Stago BNL). The ROTEM and Chrono-log tests were performed within 20 min after blood withdrawal.

ROTEM tests included the EXTEM test (extrinsic coagulation). Markers for coagulation included clotting time, clot formation time, and maximum clot formation. Other coagulation parameters were activated partial thromboplastin time (aPTT), prothrombin time (PT), platelet count, fibrinogen (Clauss test), and D-dimer concentration, which were performed by the Central Laboratory for Clinical Chemistry.

Definition of Hyperfibrinolysis

Clot lysis was determined using the ML during the EXTEM test. Hyperfibrinolysis was defined as an ML of 15% or greater within 1 h after the initiation of the thromboelastometric measurement or complete absence of clot formation.

Blood Plasma Analysis

Blood plasma was stored in a freezer at −80°C until blood sample assays were performed by enzyme-linked immunosorbent assay (Bio-Connect Diagnostics B.V., The Netherlands). Thrombin–antithrombin (TAT) III complex was assayed as a coagulation marker. Enzyme-linked immunosorbent assay tests for fibrinolytic markers included t-PA, plasminogen, PAI-1, thrombin activatable fibrinolysis inhibitor (TAFI), protein C, and activated protein C (APC).

Statistical Analysis

Data were entered in an SPSS database (SPSS Statistics 20.0; IBM, USA). The study was originally powered to detect a difference of 20% in mean TOI between the hyperfibrinolysis and nonhyperfibrinolysis group assuming an SD of 25% (two-sided testing at a significance level of 5% and a desired power of 80%). Presence of hyperfibrinolysis was assumed to be 50% based on Viersen *et al.*,[5] yielding a desired sample size of 25 per group. We planned to include a small number of additional patients (approximately 20%) to anticipate some dropout of patients.

The study hypothesis was based on comparison of mean TOI between groups with and without hyperfibrinolysis using a two-sided independent-samples *t* test. Data were represented as mean ± SD, median with interquartile range, or frequencies. The positive predictive value and negative predictive value of a TOI of 50% or less or greater than 50% for the absence or presence of hyperfibrinolysis (EXTEM ML <15% or ≥15%) were calculated from cross-tabulation. Means (or medians) of coagulation and fibrinolysis markers were compared between groups (EXTEM ML <15% compared with ≥15% or TOI ≤50% compared with >50%) using an independent-samples *t* test in case of a normal-distribution or a Mann–Whitney test in case data were not normally distributed. Linear regression was used to adjust estimated differences in means and *P* values for possible confounding by prehospital CPR time. The linear regression models contained the grouping variable and prehospital CPR time. For association between continuous variables (TOI and markers), partial correlations were calculated adjusting for differences in prehospital CPR time. *P* value less than 0.05 was considered as statistically significant.

Results

From September 2012 until July 2013, 57 patients with OHCA admitted to the ED of VU University Medical Center were enrolled in the study; of whom, 11 patients were excluded due to a trauma-related cardiac arrest or the use of anticoagulant medication. Table 1 represents the patient

Table 1. Hemodynamic, Respiratory, and Metabolic Parameters of Patients with or without Hyperfibrinolysis upon ED Admission

	Hyperfibrinolysis	No Hyperfibrinolysis	*P* Value
N	17	29	
Age (yr)	61 ± 12	66 ± 15	0.33
Sex (males) (%)	53	69	0.28
Cause of OHCA (%)			0.52
MI/coronary stenosis	47.0	58.6	
Pulmonary embolism	5.9	6.9	
Cardiomyopathy	11.8	6.9	
Arrhythmias	17.7	17.2	
SAB	0.0	6.9	
Other	17.7	3.4	
Delay between emergency call and EMS team arrival (min)	7 ± 3*	9 ± 6†	0.43
Duration of prehospital CPR by EMS team (min)	49 ± 18*	41 ± 20†	0.25
Duration of CPR after ED arrival (min)	20 (6–40)‡	4 (1–12)§	*0.02*‖
Prehospital intubation by EMS (%)	88	69	0.17
Initial TOI upon ED arrival (%)	35.1 ± 24.4	65.2 ± 13.3	*<0.001*‖
Heart rate (beats/min)	84 ± 33	91 ± 24	0.52
pO_2 (mmHg)	174 ± 148	195 ± 131	0.63
pCO_2 (mmHg)	71 ± 25	44 ± 12	*<0.001*‖
pH	6.95 ± 0.20	7.25 ± 0.15	*<0.001*‖
Base excess (mM)	−16.0 ± 6.1	−7.7 ± 5.9	*<0.001*‖
Lactate (mM)	11.7 ± 4.1	6.8 ± 3.4	*<0.001*‖
24-h mortality (%)	53	6	*0.001*

Data represent frequencies, mean ± SD, or median with interquartile range. Differences between groups were analyzed using a chi-square test for categorical variables or a Student *t* test or Mann–Whitney U test to compare mean or median values, respectively. Entries in italics are statistically significant values.

* n = 13 patients. † n = 24 patients. ‡ n = 15 patients. § n = 18 patients. ‖ $P < 0.05$ compared with patients without hyperfibrinolysis.

CPR = cardiopulmonary resuscitation; ED = emergency department; EMS = emergency medical service; MI = myocardial infarction; OHCA = out-of-hospital cardiac arrest; pCO_2 = arterial carbon dioxide partial pressure; pO_2 = arterial oxygen partial pressure; SAB = subarachnoidal bleeding; TOI = tissue oxygenation index.

characteristics and information about CPR times. The mean age of the remaining 46 patients was 64 ± 14 yr, and 63% of the patients were male. Coronary stenosis with or without myocardial infarction was the most frequent cause for cardiac arrest. There were no differences with respect to the etiology of OHCA among groups.

CPR and Metabolic Characteristics

Figure 1A shows a flow diagram for patients included in the study. Blood sampling and NIRS measurements were immediately initiated upon arrival of the patient at the ED while CPR was continued. Figure 1B shows the variation in available prehospital transportation and CPR times for 13 patients with and 24 patients without hyperfibrinolysis. There was no difference in the time span between the emergency call and arrival of the EMS at the location of OHCA for patients with or without hyperfibrinolysis (7 ± 3 *vs.* 9 ± 6 min, respectively; $P = 0.43$). The duration of CPR by the EMS in the prehospital period was similar among groups (49 ± 18 *vs.* 41 ± 20 min for patients with or without hyperfibrinolysis, respectively; $P = 0.25$). CPR times after ED arrival was longer in patients with hyperfibrinolysis (20 [6 to 40] *vs.* 4 [1 to 12] min; $P = 0.02$). In 57% of all the patients, ventricular fibrillation was the primarily observed heart rhythm.

The initial TOI upon ED admission was lower in patients with hyperfibrinolysis compared with patients without hyperfibrinolysis (35.1 ± 24.4% *vs.* 65.2 ± 13.3%, respectively; $P < 0.001$).

Heart rate and pO_2 values after return of spontaneous circulation were not different between groups. However, upon ED admission, patients with hyperfibrinolysis showed higher pCO_2 and lower pH values, a more disturbed BE and higher lactate levels, which are indicative for hypoventilation, hypoxia, and metabolic acidosis, than patients without hyperfibrinolysis.

Figure 2 shows two examples of the restoration of the initial TOI during CPR in the first 30 min after ED admission. While patient A (fig. 2A) showed an increase in cerebral oxygen saturation during CPR from 15 to 70%, the TOI did not markedly increase in patient B (fig. 2B) during CPR. Cerebral hemoglobin saturation improved during in-hospital resuscitation in 100% and 67% of the patients with an initial TOI greater than 50% or TOI 50% or less, respectively. There was a moderately positive correlation between the initial TOI and BE (fig. 3A; $r = 0.48$; $P = 0.001$), a moderately negative correlation with lactate (fig. 3B; $r = -0.57$; $P < 0.001$), and a moderately positive relation with pH (fig. 3C; $r = 0.63$; $P < 0.001$).

Hemostatic Characteristics

Table 2 summarizes the coagulation and fibrinolytic characteristics of patients with or without hyperfibrinolysis. The aPTT and PT values were prolonged in all patients after

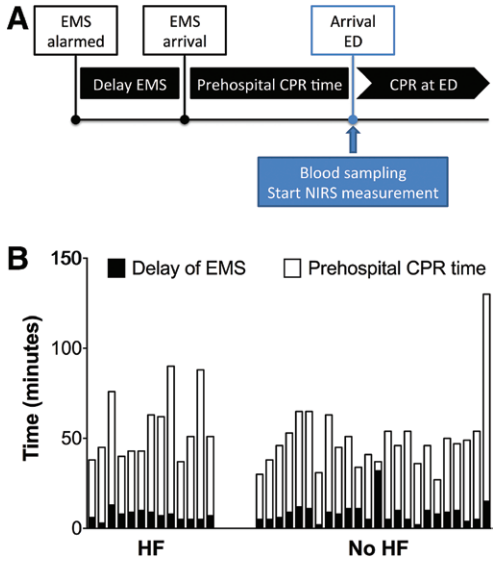

Fig. 1. Schematic representation of the patient flow in the prehospital period and after admission to the emergency department (ED; *A*). Blood sampling and near-infrared spectroscopy (NIRS) measurements were immediately initiated upon ED arrival. Cardiopulmonary resuscitation (CPR) time after ED admission was not of influence on the results of the blood analyses or the initial tissue oxygenation index as assessed by NIRS. (*B*) The variation in the time span between the emergency call and emergency medical service (EMS) team arrival at the location of out-of-hospital cardiac arrest and the duration of prehospital CPR by the EMS for patients with hyperfibrinolysis (HF; n = 13) or without HF (n = 24; table 1).

OHCA, independent of the presence of hyperfibrinolysis. After adjustment for prehospital CPR duration, patients with hyperfibrinolysis showed a lower platelet count (mean difference, −0.22 [95% CI, −0.41 to −0.02]; $P = 0.03$) and an increased D-dimer concentration (mean difference, 1.00 [95% CI, 0.09 to 1.92]; $P = 0.03$) upon ED admission when compared with patients without hyperfibrinolysis.

Platelet function of patients with and without hyperfibrinolysis is shown in figure 4. ADP-induced platelet function was significantly reduced in patients with hyperfibrinolysis as indicated by a lower AUC. There was no difference in the AUC between surviving and nonsurviving patients, respectively (24 [11 to 36] *vs.* 12 [3 to 37] AUC; $P = 0.48$), within 24 h after cardiac arrest.

Figure 5 represents the relative number of patients with hyperfibrinolysis (fig. 5A), the median D-dimer concentration (fig. 5B), and the median ML (fig. 5C) in case of an initial TOI less than or greater than 50%. The prevalence of hyperfibrinolysis was 75.0% in patients with a TOI of 50% or less and 16.7% in patients with normal cerebral oxygenation levels ($P < 0.001$).

The positive predictive value of a TOI of 50% or less for the presence of hyperfibrinolysis was 75% (12 of 16 cases), and the negative predictive value of a TOI of greater than 50% for the absence of hyperfibrinolysis was 86% (25 of 29 cases). In case of cerebral oxygen desaturation, the occurrence of hyperfibrinolysis was higher as reflected by the increased D-dimer levels (14.0 μg/l [3.4 to 41.2 μg/l] *vs.* 6.0 μg/l [2.0 to 10.3 μg/l]; $P = 0.01$) and a higher ML (91% [17 to 100%] *vs.* 6% [4 to 11%]; $P < 0.001$).

Coagulation and Fibrinolysis Markers in Patients with Cerebral Oxygen Desaturation

Table 3 shows the differences in TAT complex, t-PA, plasminogen, PAI-1, TAFI, protein C, and APC for patients with or without an initial TOI of 50% or less adjusted for the duration of prehospital CPR. Patients with cerebral oxygen desaturation showed lower plasminogen levels, whereas t-PA and PAI-1 were increased in these patients. TAT and TAFI were similar in patients with or without cerebral oxygen desaturation. Remarkably, we found no differences in protein C and APC levels among groups. The initial TOI showed a good negative correlation with t-PA (fig. 6A; $r = -0.69$; $P < 0001$) and moderate positive correlation with plasminogen ($r = 0.53$; $P = 0.001$; fig. 6). After correction for duration of prehospital CPR, the partial correlations were −0.61 (95% CI, −0.83 to −0.28; $P = 0.001$; n = 29) for t-PA and 0.51 (95% CI, 0.20 to 0.74; $P = 0.006$; n = 29) for plasminogen.

Relation of Hyperfibrinolysis and Patient Outcome

Twenty-four hour mortality was significantly higher in 17 patients with hyperfibrinolysis compared with 29

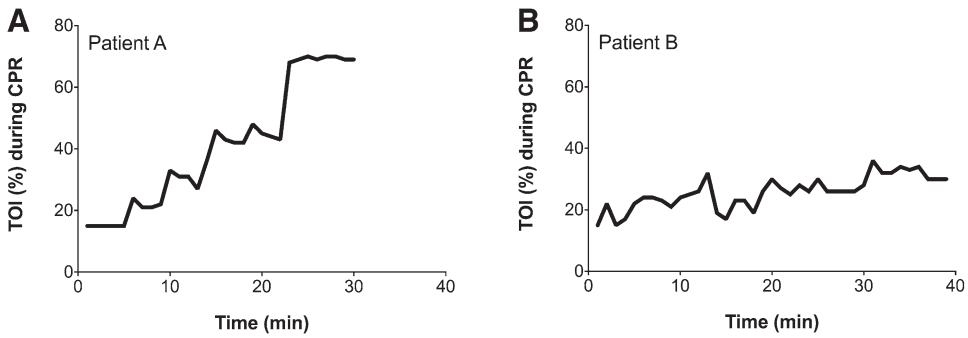

Fig. 2. Typical examples of the course of the tissue oxygenation index (TOI) in out-of-hospital cardiac arrest patients during cardiopulmonary resuscitation (CPR) within the first 30 min after admission upon the emergency department, with (*A*) or without (*B*) restoration of cerebral oxygen saturation.

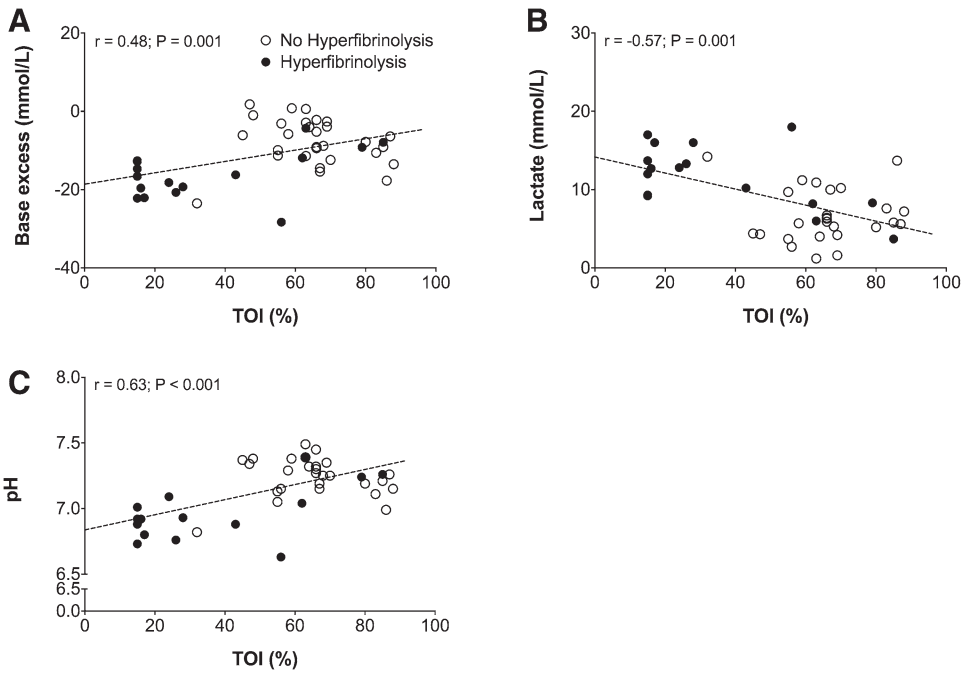

Fig. 3. The tissue oxygenation index (TOI) upon emergency department admission showed a moderately positive correlation with base excess (*A*) and pH (*C*) and a moderately negative correlation with lactate (*B*) in patients with (*black circles*) or without (*white circles*) hyperfibrinolysis.

Table 2. Hemostatic Characteristics of Patients with or without HF upon Emergency Department Admission

	Mean Values		Adjusted for Duration of Prehospital CPR	
	HF	No HF	Mean Difference (95% CI)*	*P* Value
N	17	29		
Hemoglobin (g/l)	8.6 ± 1.2	8.4 ± 1.0	0.24 (0.57 to 1.05)	0.55
aPTT (s)	77 ± 71	82 ± 71	2.52 (–56.9 to 62.0)	0.93
PT (INR)	1.40 ± 0.25	1.37 ± 0.57	0.02 (–0.40 to 0.44)	0.93
Platelet count (10^9/l)	202 ± 67	240 ± 48	–0.22 (–0.41 to –0.02)†	*0.03*
Fibrinogen (g/l)	3.3 ± 1.3	4.0 ± 1.2	–0.89 (–2.03 to 0.25)	0.12
D-dimer concentration (μg/l)	12 (4–35)	6 (2–9)	1.00 (0.09 to 1.92)†	*0.03*

Data represent mean ± SD or median with interquartile range. Entries in italics are statistically significant values.

* Mean in HF group minus mean in no-HF group. † Difference in means of log-transformed values.

aPTT = activated partial thromboplastin time; CPR = cardiopulmonary resuscitation; HF = hyperfibrinolysis; INR = international normalized ratio; PT = prothrombin time.

patients without hyperfibrinolysis (53 *vs.* 6%, respectively; $P = 0.001$). Only 19% of all patients with hyperfibrinolysis survived until hospital discharge compared with 70% of the patients without hyperfibrinolysis ($P = 0.001$).

Discussion

This is the first study showing that hyperfibrinolysis occurs most prominently in OHCA patients experiencing low cerebral oxygen saturation levels during CPR. Moreover, patients with cerebral oxygen desaturation showed diminished platelet function, increased t-PA and PAI-1 levels, and a reduction in plasminogen levels compared with patients with an initially normal TOI. Interestingly, we could not find evidence for alterations in protein C and APC levels in patients with signs of hypoperfusion as observed in trauma patients with signs of tissue hypoperfusion.[11,12,16] Finally, although this study was not powered to make definite conclusions about patient outcome, in accordance with others, we observed higher mortality rates in patients with hyperfibrinolysis.[5,7,8]

Although the presence of hyperfibrinolysis might be considered as an epiphenomenon of hypoxia and tissue hypoperfusion rather than a stand-alone phenomenon, its presence may be of added value in determining the prognosis of OHCA patients based on initial pO_2 values, pH, BE, and lactate.[13,17] The level of metabolic acidosis in our patients was associated with the level of hyperfibrinolysis, and the presence of hyperfibrinolysis might alarm physicians with respect to the severity of disease.

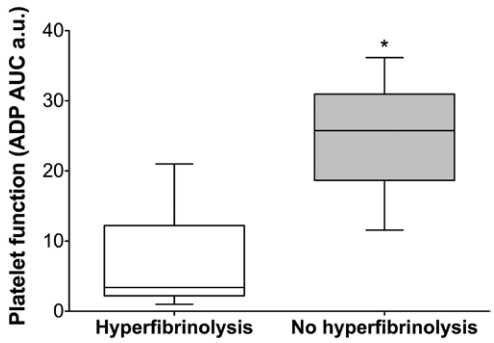

Fig. 4. Adenosine diphosphate (ADP)–induced platelet function analysis using impedance aggregometry in patients with or without hyperfibrinolysis upon emergency department admission. Data represent median with interquartile range. *P = 0.01 patients with *versus* patients without hyperfibrinolysis. a.u. = arbitrary units; AUC = area under the curve.

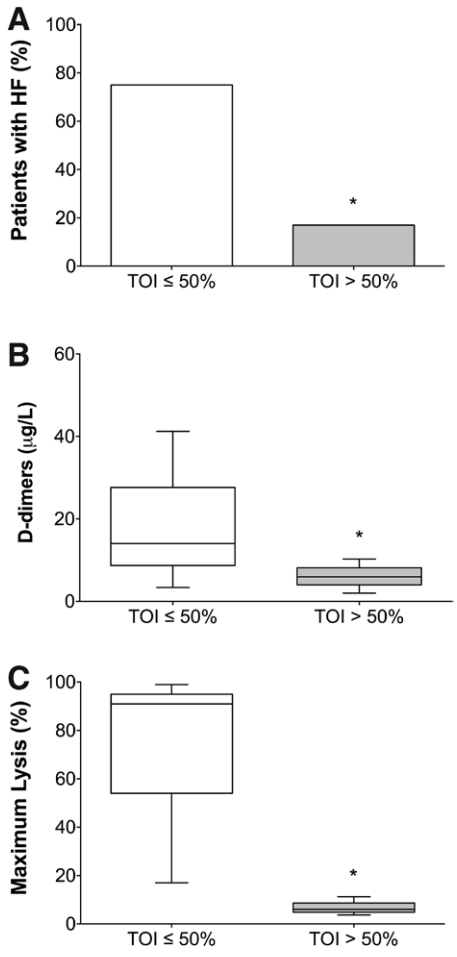

Fig. 5. Relative number of patients with hyperfibrinolysis (HF; *A*), the median D-dimer concentration (*B*), and the median maximum lysis (*C*) in patients with an incidence of cerebral oxygen desaturation (tissue oxygenation index [TOI] <50%) compared with patients with normal TOI values. *P < 0.001 *versus* patients with HF.

It however remains questionable whether there are therapeutic strategies available that reduce the unfavorable impact of a hyperfibrinolytic state on body hemostasis. Although the use of fibrinolytic therapeutics in case of a suspected prothrombotic profile might worsen the coagulation state of OHCA patients, antifibrinolytic therapy may counteract the reaction of the body to maintain microcirculatory perfusion. The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) collaborators showed that prophylactic use of tranexamic acid in patients at risk for bleeding with hyperfibrinolysis reduced the risk of death and warranted the widespread use of antifibrinolytics in patients with severe traumatic injury, with the highest benefit in patients who received early therapy to prevent exsanguination.[18,19] The lack of analogy between the trauma population and patients with OHCA resides in the presence of bleeding, and the findings presented by the CRASH-2 collaborators can therefore not easily be extrapolated to our study population.

Naturally, prolonged CPR times reflect an extended ineffective circulation, which causes a substantial decrease in cerebral oxygen desaturation. Failure of circulatory restoration after cardiac arrest is therefore a major indicator of prognosis and survival. Interestingly, we found no differences in CPR duration by an EMS team before blood sampling and initiation of NIRS measurements between patients presented with or without hyperfibrinolysis. Moreover, the etiology of OHCA in patients with or without hyperfibrinolysis was similar, with the highest prevalence of coronary stenosis with or without myocardial infarction. The latter suggests that the prothrombotic profile associated with cardiac ischemia was not a distinct risk factor for the development of hyperfibrinolysis.

There is growing interest in the usefulness of cerebral NIRS monitoring during resuscitation in patients with cardiac arrest, in particular with respect to its predictive value regarding patient outcome.[20–23] Our study confirms that effective CPR is directly reflected by improvement of cerebral oxygen saturation measured by NIRS. Due to biological variation among patients, most studies use the relative decrease in tissue oxygenation levels from baseline values to diagnose local ischemia.[14] However, this method is not applicable in cardiac arrest patients due to the lack of baseline values. On the basis of the existing literature, we therefore considered a TOI of less than 50% as a sign of cerebral ischemia and tissue hypoperfusion.[13,14,22,23] Predicting return of spontaneous circulation based on TOI appears to be more adequate than using static and invasively collected blood pH, lactate, and carbon dioxide levels.[13,17,20,22] Moreover, the TOI during the first 24 h after admission to the intensive care department was significantly increased in survivors compared with nonsurvivors.[23] We, however, have to take into account that the observed low TOI values might be influenced by disturbed autoregulation of cerebral blood flow in combination with changes in systemic blood pressure, leading to an overestimation of cerebral blood flow.[24,25]

Table 3. Coagulation and Fibrinolytic Markers in Patients with Cerebral Oxygen Desaturation

	Mean Values		Adjusted for Duration of Prehospital CPR	
	TOI >50%	TOI ≤50%	Mean Difference (95% CI)	*P* Value
N	22	13		
Thrombin–antithrombin (ng/ml)	29.5 ± 11.4	20.0 ± 11.2	4.75 (–14.7 to 5.24)	0.34
t-PA (ng/ml)	7.9 ± 4.7	18.3 ± 7.4	–8.67 (–14.0 to –3.36)	*0.002*
Plasminogen (μg/ml)	225.3 ± 47.0	151.6 ± 61.0	72.5 (35.0 to 109.9)	*<0.001*
PAI-1 (ng/ml)	12.1 ± 6.1	19.3 ± 8.9	–8.05 (–14.8 to –1.35)	*0.02*
TAFI (ng/ml)	17.0 ± 7.2	16.5 ± 9.6	2.59 (–3.51 to 8.69)	0.39
Protein C (μg/ml)	0.18 ± 0.02	0.20 ± 0.05	–0.015 (–0.048 to 0.019)	0.38
Activated protein C (ng/ml)	64.5 ± 30.1	65.7 ± 20.2	–8.22 (–32.7 to 16.2)	0.50

Entries in italics are statistically significant values.

CPR = cardiopulmonary resuscitation; PAI-1 = plasminogen activator inhibitor-1; TAFI = thrombin activatable fibrinolysis inhibitor; TOI = tissue oxygenation index; t-PA = tissue plasminogen activator.

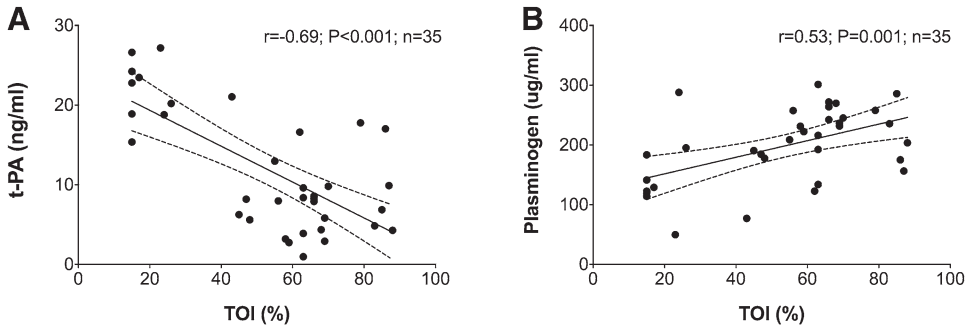

Fig. 6. Association of the tissue oxygenation index (TOI) upon emergency department admission with tissue plasminogen activator (t-PA; *A*) and plasminogen (*B*). The *lines* represent the linear regression line with 95% CI.

Fibrinolysis is a phenomenon that, under normal physiological circumstances, sustains a balance between clot formation and clot breakdown. Locally induced activation of t-PA or urokinase by the injured endothelium leads to the conversion of plasminogen into plasmin, which subsequently degrades fibrin clots. The fibrinolytic activity is regulated by, among others, PAI-1 and PAI-2, α-2-antiplasmin, and TAFI.[26] The occurrence of excessive fibrinolysis after hypoxia and shock in patients after trauma and cardiac arrest has been previously described by others and involves PAI-1 and TAFI inhibition upon protein C activation.[11,12,15,27–29] Protein C activation leads to consumption of PAI-1 and subsequent deinhibition of t-PA, resulting in initiation of clot breakdown.[30,31] Normally, protein C and its activated form (APC) are present in a 2:1 concentration in blood plasma, but in case of increased thrombin levels, protein C is converted to its activated fibrinolytic form and may exert anticoagulant effects.[31] APC is not the primary activator of fibrinolysis. However, in the studies reported by Brohi *et al.*,[11,12] APC is frequently mentioned as a common denominator of coagulopathy with hyperfibrinolysis during a state of hypoperfusion. Because cardiac arrest is characterized by severe hypoperfusion without confounding factors such as sepsis or bleeding, we considered this disease state as an ultimate model to confirm whether hyperfibrinolysis is mediated by an APC-mediated mechanism. Although our data are associative by nature, we could not confirm this assumption and showed that OHCA-related hyperfibrinolysis is paralleled by an increase in t-PA. Because protein C levels were a secondary endpoint in the current study, our findings however warrant future studies focusing on the pathophysiologic mechanisms underlying the initiation of hyperfibrinolysis in OHCA patients.

Despite similar aPTT and PT values in patients with or without hyperfibrinolysis, hyperfibrinolysis was associated with a reduction in platelet count and ADP-induced platelet function. In trauma patients, a reduction in platelet function was associated with increased mortality rates,[32] whereas others reported that cardiac arrest is associated with hyperfunctional platelets.[33,34] We found a moderately negative correlation between t-PA and platelet aggregation, suggesting that patients with the highest t-PA concentrations showed the largest impairment of platelet function (data not shown), but it cannot be excluded whether reduced platelet function is due to the primary disease of the patient (*e.g.*, myocardial ischemia). However, the association of hyperfibrinolysis with reduced platelet function in the absence of anticoagulant treatment hints toward alterations in platelet function in patients with activation of the anticoagulant system.[35] Although not demonstrated in this study, it is important to keep in mind that a thrombosis-related etiology of cardiac arrest, such as acute coronary syndrome or a massive pulmonary embolism, themselves can enhance the fibrinolytic system in contrast to nonthrombotic origins of arrest such as rhythmical disturbances leading to heart failure.

Our findings should be assessed in light of the included patient population and the single-center and observational character of our study. Patients were only included for further analysis if they had a nontraumatic cause of cardiac arrest and when they were not on anticoagulant or antiplatelet medication. Based on previous findings by our group[5] we *a priori* hypothesized that hyperfibrinolysis is more prevalent in patients with low initial cerebral tissue oxygenation, and we could confirm our hypothesis. We are aware of the relatively small nature of the current study and the risk of a type I error for the observed associations and emphasize that this may limit the generalizability of the study findings. However, our observations are unique and complimentary to previously published observations by our group and others.[5–7] Although we found higher 24-h mortality rates in patients with hyperfibrinolysis compared with patients without hyperfibrinolysis, this study was not designed to assess outcome differences between patients with or without alterations in anticoagulant pathways.

Treatment algorithms after OHCA are still a topic of discussion, and there is no consensus about the most beneficial strategy. Future studies should evaluate whether measuring and subsequently increasing cerebral oxygen saturation in the acute setting by EMSs improves final patient outcome, in particular as this may indirectly be beneficial for the patient hemostasis, partly due to the prevention of hyperfibrinolysis. Our findings also warrant caution, as the combination of endogenous hyperfibrinolysis in combination with thrombolytic therapy may lead to uncontrolled bleeding and worse outcome. Whether prevention of hyperfibrinolysis may finally contribute to improved patient outcome after cardiac arrest should be a subject of future studies.

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Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Boer: Department of Anesthesiology, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands. c.boer@vumc.nl. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. Anesthesiology's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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