Resuscitation 84 (2013) 454–459

Contents lists available at SciVerse ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

Hyperfibrinolysis is common in out-of-hospital cardiac arrest Results from a prospective observational thromboelastometry study☆

H. Schöchl[a,b,*], J. Cadamuro[c], S. Seidl[d], A. Franz[d], C. Solomon[a], C.J. Schlimp[a], B. Ziegler[d]

[a] Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Vienna, Austria
[b] Department of Anaesthesiology and Intensive Care Medicine, AUVA Trauma Centre, Salzburg, Austria
[c] Department of Laboratory Medicine, University Hospital SALK, Salzburg, Austria
[d] Department of Anaesthesiology, Intensive Care and Perioperative Medicine, Salzburg University Hospital, Salzburg, Austria

ARTICLE INFO

Article history:
Received 14 June 2012
Accepted 15 August 2012

Keywords:
Out-of-hospital cardiac arrest
CPR
ROTEM
Hyperfibrinolysis

ABSTRACT

Background: Cardiocirculatory arrest (CCA) activates procoagulant pathways. It has also been reported to inhibit fibrinolysis, resulting in fibrin deposition and further impairment of blood flow. Until now, no studies have used whole-blood viscoelastic tests to characterize coagulation and the impact of fibrinolysis in out-of-hospital cardiac arrest (OHCA).
Methods: Patient with established OHCA who underwent cardiopulmonary resuscitation (CPR) were enrolled. Blood samples were obtained immediately after placement of an intravenous line at the scene, for full blood cell count, standard coagulation tests and rotational thromboelastometric (ROTEM®) analyses. Patients with return of spontaneous circulation (ROSC) were compared to non-ROSC patients.
Results: Fifty-three patients (median age 67 years, interquartile range: 56–73 years) were included in the study. ROSC was established in 25 patients. Prothrombin time index (PTI) was significantly lower and activated partial thromboplastin time (aPTT) was significantly prolonged in non-ROSC patients compared to ROSC patients. Clotting time (CT) in the extrinsically activated ROTEM test (EXTEM) was significantly longer in non-ROSC versus ROSC patients. For the remaining EXTEM parameters, there were no significant differences between ROSC and non-ROSC patients. Hyperfibrinolysis (maximum lysis > 15% according to ROTEM test results) was observed in 19 patients (35.8%). There was no difference between ROSC and non-ROSC patients in the incidence of hyperfibrinolysis.
Conclusions: PTI, aPTT and EXTEM CT revealed significant differences between ROSC and non-ROSC patients. Hyperfibrinolysis according to ROTEM test results was much more common than previously assumed. Routine use of fibrinolytic therapy in all patients with prolonged CPR cannot therefore be recommended.

1. Introduction

Hypoperfusion and stasis in the course of cardiocirculatory arrest (CCA) are associated with marked activation of procoagulant pathways and a pronounced inflammatory response.[1] Enhanced tissue factor expression results in distinct thrombin generation, followed by an increase in plasminogen activator inhibitor (PAI-1) activity and subsequent inhibition of fibrinolysis.[2–4] This imbalance causes intravascular fibrin deposition, microthrombosis, and insufficient fibrin removal; it is assumed to be an important contributor to multi organ dysfunction syndrome and the "no reflow" phenomenon following successful cardiopulmonary resuscitation (CPR).[1,5,6]

To characterize alterations of the coagulation system in the course of CCA, standard coagulation tests (prothrombin time PT, alternatively prothrombin time index PTI, and activated partial thromboplastin time, aPTT) and extended coagulation analyses (e.g. levels of thrombin–antithrombin complex, D-dimers, tissue plasminogen activator, plasmin–antiplasmin complexes, plasmin activator inhibitor) have been used.[2,3,5] These tests are performed in plasma rather than whole blood, whereby blood cells such as platelets, erythrocytes and monocytes are removed by

Abbreviations: aPTT, activated partial thromboplastin time; CCA, cardiocirculatory arrest; CPR, cardiopulmonary resuscitation; CT, clotting time; CFT, clot formation time; EXTEM, extrinsically activated ROTEM test; HF, hyperfibrinolysis; IQR, interquartile range; MCE, maximum clot elasticity; MCF, maximum clot firmness; ML, maximum lysis; LI, lysis index; OHCA, out-of-hospital cardiac arrest; PT, prothrombin time; PTI, prothrombin time index; ROSC, return of spontaneous circulation; ROTEM, rotational thromboelastometry; VET, viscoelastic test.

☆ A Spanish translated version of the abstract of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2012.08.318.

* Corresponding author at: Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Donaueschingenstr. 13, 1200 Vienna, Austria.
Tel.: +43 662 6580 2577.
E-mail address: Herbert.schoechl@auva.at (H. Schöchl).

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http://dx.doi.org/10.1016/j.resuscitation.2012.08.318

centrifugation. However, blood cells play a pivotal role in coagulation and subsequent fibrinolysis.[7] In contrast to standard coagulation tests, viscoelastic coagulation tests (VETs) are performed in whole blood. This enables the contribution of blood cells to the coagulation process to be included in the evaluation.[8]

Viscoelastic coagulation analysers such as thromboelastometry (ROTEM®, TEM international, Munich, Germany) and thrombelastography (TEG®, Haemonetics Corp., Braintree, MA, USA) have gained increasing interest in clinical settings such as liver transplant,[9] trauma,[10] cardiovascular surgery,[11] and postpartum hemorrhage.[12] Viscoelastic coagulation analysers can be used as point-of-care devices and provide a comprehensive overview of the whole coagulation process. This includes information on the initiation of coagulation, the speed of clot formation and clot strength.[13] Furthermore, VETs provide rapid information on premature dissolution of the clot (hyperfibrinolysis, HF).

Until now, no study has investigated the potential role of whole-blood VETs in patients with out-of-hospital cardiac arrest (OHCA). Therefore, we conducted a study investigating thromboelastometric findings in patients with OHCA and subsequent CPR. We compared routine coagulation tests with thromboelastometric findings. The hypothesis was that ROTEM measurements provide a more comprehensive overview of coagulation status following OHCA than standard coagulation tests.

2. Methods

After approval by the local Ethics Committee of the State of Salzburg (E 1143-09), the study took place in Salzburg, Austria between January 2010 and April 2011. The study was performed according to the ethical rules of the local Ethics Committee; the requirement for signed informed consent was waived. No previous thromboelastometric data from patients with CCA were available. Therefore, the study was considered as explorative.

Patients were enrolled into the study when emergency physicians were dispatched to victims with established OHCA. OHCA was defined as the absence of spontaneous breathing and palpable pulse, and unresponsiveness to stimuli, upon examination by the emergency team. Patients were enrolled when CPR was started, independent of the time from collapse to the start of CPR. Exclusion criteria were: age under 18 years, pregnancy, traumatic cardiac arrest and participation in any other clinical study.

Return of spontaneous circulation (ROSC) was defined as measurable blood pressure and pulse for more than 1 h, independent of catecholamine infusion. Successful resuscitation was defined as discharge alive from the hospital independent of neurological deficits. At the beginning of the study, resuscitation was performed according to the 2005 guidelines of the European Resuscitation Council.[14] The resuscitation protocol was amended in November 2010 after publication of an updated version of these guidelines.[15]

Demographic data and ECG findings at the scene were collected from the medical report of the emergency physician in charge. Standard coagulation test results were obtained from the laboratory data management system. Thromboelastometric (ROTEM®, TEM international GmbH, Munich, Germany) measurements were reviewed from the database which stores data from the device and were prospectively collected.

Blood samples, taken for full blood cell count and for both ROTEM analysis and standard coagulation tests, were drawn immediately after intravenous line placement by the emergency physician. No medication was administered before blood samples were collected. The first 2 mL of blood were discarded. The blood samples were processed within 2 h.

For blood cell count, 3 mL of blood was collected in tubes containing 1.6 mg mL^{-1} K3-EDTA (S-Monovette®, Sarstedt AG & Co., Nümbrecht, Germany). For both standard coagulation tests and ROTEM analyses, 3 mL of blood was placed in tubes containing 0.3 mL buffered 3.2% trisodium citrate, giving a volume ratio of 1:10 (S-Monovette®, Sarstedt AG & Co., Nümbrecht, Germany).

2.1. ROTEM analyses

ROTEM analyses were performed within 2 h after blood sampling. This is in accordance with stability analyses published by Lang et al.[16] Whole blood was extrinsically activated with recombinant tissue factor (ex-tem® reagent). To provide sufficient data on HF, the duration of the analysis was 60 min. The following variables were measured: clotting time (CT [expressed as seconds], the time from start of measurement until formation of a clot with an amplitude of 2 mm, normal range: 37–79 s); clot formation time (CFT [expressed as seconds], time from end of CT [amplitude of 2 mm] until a clot firmness of 20 mm is achieved, normal range 30–110 s); alpha angle (expressed as°, the angle between the center line and a tangent to the curve through the 2-mm amplitude point, reflecting rate of clot development, normal range for EXTEM: 63–71°); and maximum clot firmness (MCF [expressed as mm], the final strength of the clot resulting from the interaction of fibrin, activated platelets and factor XIII, normal range: 50–72 mm). The maximum clot elasticity (MCE) was also calculated as follows: MCE = (MCF − 100)/(100 − MCF) [no dimension].

The following lysis parameters were measured with the ROTEM device: maximum lysis (ML [expressed as %], the maximum reduction of clot firmness during the analysis, defined by the ratio between the lowest amplitude after reaching MCF and the MCF value, normal range: <15%, HF defined as ML > 15%); lysis index at 30, 45 and 60 min (LI30, 45, 60 [expressed as %], clot firmness 30, 45 and 60 min after CT as a percentage of MCF, indicating the speed of fibrinolysis, normal range: 94–100%); and lysis onset time (expressed as seconds, time from start of the analyses to the time point where a 20% reduction in clot strength from the MCF is reached [no normal value as there is usually no lysis]).

2.2. Standard coagulation tests

In parallel, the following standard laboratory analyses were performed: PTI (expressed as percentage of normal PT, normal range: 70–130%); aPTT (expressed as seconds, normal range: 26–40 s); and fibrinogen concentration (measured by the Clauss method [optical read-out], expressed as g L^{-1}, normal range: 1.6–4.0 g L^{-1}).

The following reagents were used: PTI (Thromborel S; Siemens, Marburg, Germany), aPTT (Pathromtin SL; Siemens), fibrinogen concentration (Mulitfibren U; Siemens – using a fully automated blood coagulation analyzer [BCS-XP system, Siemens]). Blood samples were analyzed on the Sysmex XE-2100 device (Sysmex Cooperation, Kobe, Japan).

2.3. Statistical analysis

As no previous data on this type of coagulation testing in patients suffering from OHCA were available, the study was considered to be explorative. Therefore, sample size could not be calculated formally. Demographic and clinical data were presented as mean ± standard deviation or median and range (minimum, maximum or interquartile range [IQR], as indicated) for continuous variables, and as percentages for categorical variables. For continuous variables, adherence to the normal distribution was analyzed using the Kolmogorov–Smirnov test. To detect differences between the patient groups, either the Student's *t*-test or the Mann–Whitney *U* test was performed, depending on the underlying distribution.