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Protein C activation during cardiopulmonary resuscitation following out-of-hospital cardiac arrest

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The deficiency of protein C, a vitamin-K-dependent glycoprotein that regulates hemostasis by inactivating factors Va and VIIIa and potentiates fibrinolysis by neutralizing a circulating plasminogen activator inhibitor, has been implicated in a number of acquired pathological conditions associated with the activation of the coagulation mechanism and fibrin formation [1].

To investigate the hypothesis that human cardiac arrest and cardiopulmonary resuscitation accelerate protein C activation, we measured serial levels of protein C activity and protein C antigen concentration (protein C antigen) in 27 patients who suffered an out-of-hospital cardiac arrest. The patients were classified into three groups, survivors (n = 12) who had a return of spontaneous circulation (ROSC), nonsurvivors (n = 9) who had a ROSC but expired within 24 h, and the patients who died (n = 16) without any achievement of ROSC.

Blood samples were collected using an arterial catheter immediately after the patients' arrival at the Emergency Department (time point 1). The second blood sample was drawn when the cardiopulmonary resuscitation (CPR) was discontinued due to death (patients who died) or at 30 min after arrival (time point 2). In the case of ROSC, third and the fourth samples were collected at 60 min and 24 h, respectively, after the arrival at the Emergency Department (time points 3 and 4). Immediately thereafter, the blood was put into prechilled individual tubes containing 3.8% sodium citrate (1:9, v/v) and centrifuged at 3000 rpm for 10 min at 4°C. The plasma was stored at −80°C. Protein C activity was measured by the activated partial thromboplastin time (APTT) clotting time method (protein C clot Bw, Behringwerke, Marburg, Germany). Protein C antigen was measured by the latex photometric immunoassay (Lpiaace—PC, Diaiatron, Tokyo, Japan). Protein C activity was determined in all of the patients but the protein C antigen was determined in only 24 of the patients.

There were statistical differences in the initial ECG rhythms, in the total CPR times, and in the doses of epinephrine between the three groups (Table 1).

The upper panels in Fig. 1 show the protein C activity measurements. On arrival, many patients already had markedly low levels of protein C activity. A further significant decrease in protein C activity was found at 30 min after their arrival at the Emergency Department, and we also found that the levels of protein C activity were statistically different among three groups (survivors: 74.7% ± 5.0%; nonsurvivors: 66.5% ± 7.4%; patients who died: 54.5% ± 4.5%). This difference suggests that the longer the CPR time, the higher the dose of epinephrine in the nonsurvivors and the patients who died may have had greatly accelerated thrombin generation [2] followed by marked protein C consumption. In the survivors, protein C activity continued to show low values until 24 h after their arrival at the Emergency Department (69.1% ± 7.8%) and three of the four patients who showed protein C activity below the normal range expired in the hospital. There was a weak but significant correlation between the protein C activity and the total cardiopulmonary resuscitation time (r^2 = 0.109, P = 0.0455). Changes in the protein C antigen were significantly similar to those of the protein C activity. No definite correlation could be found between protein C activity, protein C antigen, and the total infusion volume during CPR (P = 0.8725 and P = 0.5701, respectively), indicating that hemodilutional effects did not occur during CPR. Impaired liver synthesis may be one of the mechanisms responsible for the reduced plasma protein C [1] at time point 4 in the survivors.

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Table 1. Characteristics of the patients and Emergency Medical Service System

	ROSC			
	Survivor ($n = 12$)	Nonsurvivor ($n = 9$)	Death ($n = 16$)	P
Age (years)	64.5 ± 5.1	68.6 ± 5.1	67.6 ± 2.8	0.9812
Male/Female	9/3	6/3	13/3	0.7154
Initial rhythm at ED (Vf/asystole/other)	5/2/5	1/7/1	4/11/1	0.0221
Total CPR time (min)	32.5 ± 3.3	40.0 ± 4.7	55.8 ± 2.5	0.0001
Epinephrine (mg)	3.2 ± 1.6	5.7 ± 1.8	8.3 ± 0.5	0.0002

Values except integer and P values are expressed as mean ± standard error of the mean.
ROSC, return of spontaneous circulation; ED, Emergency Department; Vf, ventricullar fibrillation; CPR, cardiopulmonary resuscitation.

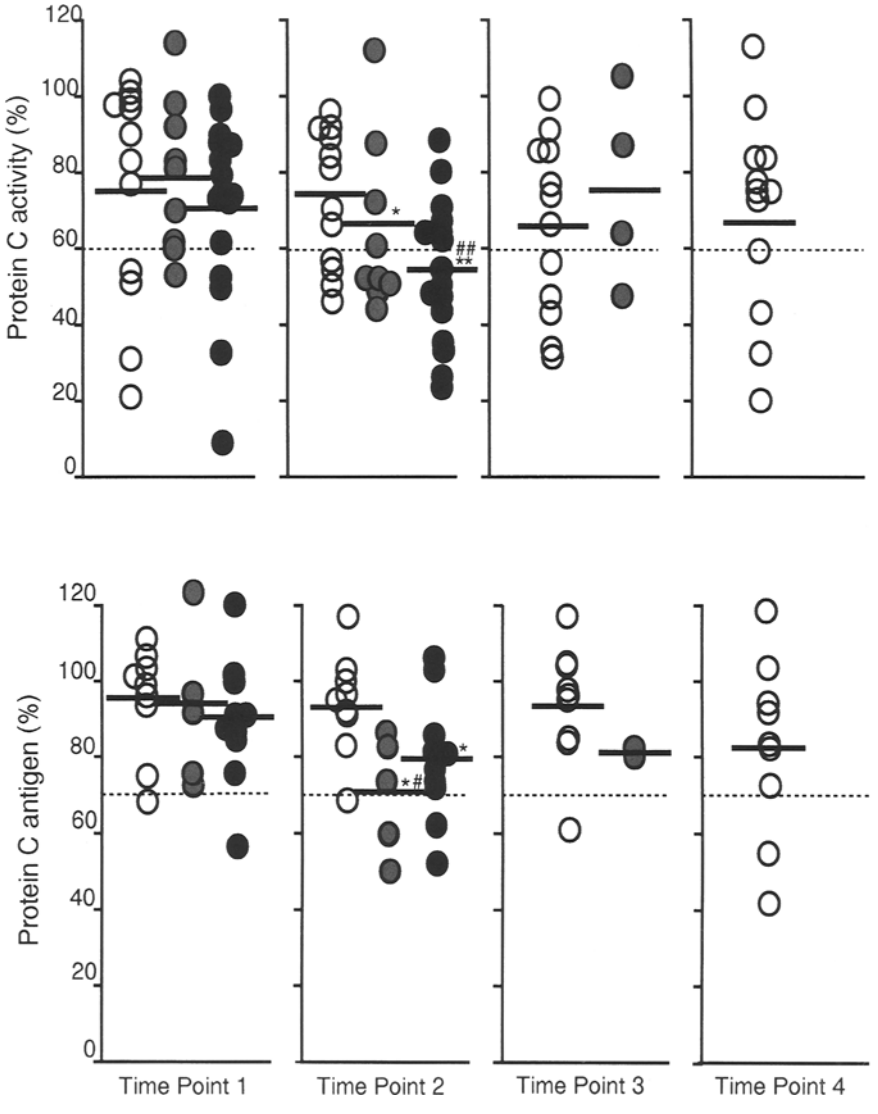

Fig. 1. Scatterplots showing changes in protein C activity (*top*) and protein C antigen concentration (*bottom*) in patients with out-of-hospital cardiac arrest. *Open circle*, survivors; *stippled circle*, nonsurvivors; *solid circle*, patients who died. *Horizontal bars* indicate the mean value for the group. *Dotted lines* indicate the lower limit of the normal range. Following the Kruskal–Wallis one-way analysis of variance, the Mann–Whitney *U*-test or the Wilcoxon signed-ranks test were used. $^{*}P < 0.05$, $^{**}P < 0.01$ *vs* Time Point 1; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ *vs* survivors

An alternative mechanism for the reduced protein C is the rapid removal of protein C from circulation after activation by the thrombin–thrombomodulin complex [1]. Ischemia due to cardiac arrest accelerates blood coagulation [3] and there is frequent evidence of disseminated intravascular coagulation following cardiopulmonary arrest [4]. Recently, Böttiger et al. demonstrated that there is an extreme activation of blood coagulation and fibrin formation which is not balanced by the activation of fibrinolysis after an out-of-hospital cardiac arrest and subsequent CPR in humans [5]. Thus, the reduction of the protein C levels in this study may be due to massive thrombin formation which activates protein C and results in a rapid removal of protein C from the circulation. In other words, human cardiac arrest and CPR activate the protein C pathway. Accordingly, our study implies that protein C activation following cardiac arrest, in combination with massive fibrin formation and impairment of fibrinolysis [5], contributes to post-resuscitation syndrome and also affects patient outcome.

In summary, we have demonstrated in this pilot study that human cardiac arrest induces significant decreases in protein C activity and in protein C antigen. The decreases suggest protein C pathway activation during CPR following out-of-cardiac arrest.

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