Journal of the American College of Cardiology
© 2005 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 46, No. 1, 2005
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2005.03.046

Coagulopathy After Successful Cardiopulmonary Resuscitation Following Cardiac Arrest

Implication of the Protein C Anticoagulant Pathway

Christophe Adrie, MD,* Mehran Monchi, MD,† Ivan Laurent, MD,† Suzan Um, BS,‡ S. Betty Yan, PhD,‡ Marie Thuong, MD,* Alain Cariou, MD,§ Julien Charpentier, MD,§ Jean François Dhainaut, MD§

Saint Denis, Massy, and Paris, France; and Indianapolis, Indiana

OBJECTIVES We investigated coagulation abnormalities in out-of-hospital cardiac arrest (OHCA) patients, with special attention to the protein C anticoagulant pathway.

BACKGROUND Successfully resuscitated cardiac arrest is followed by a systemic inflammatory response and by activation of coagulation, both of which may contribute to organ failure and neurological dysfunction.

METHODS Coagulation parameters were measured in all patients admitted after successfully resuscitated OHCA.

RESULTS At admission, 67 patients had a systemic inflammatory response with increased interleukin-6 and coagulation activity (thrombin-antithrombin complex), reduced anticoagulation (antithrombin, protein C, and protein S), activated fibrinolysis (plasmin-antiplasmin complex), and, in some cases, inhibited fibrinolysis (increased plasminogen activator inhibitor-1 with a peak on day 1). These abnormalities were more severe in patients who died within two days (50 of 67, 75%) and were most severe in patients dying from early refractory shock. Protein C and S levels were low compared to healthy volunteers and discriminated OHCA survivors from nonsurvivors. Furthermore, a subgroup of patients had a transient increase in plasma-activated protein C at admission followed by undetectable levels. This, along with an increase in soluble thrombomodulin over time, suggests secondary endothelial injury and dysfunction of the protein C anticoagulant pathway similar to that observed in severe sepsis.

CONCLUSIONS Major coagulation abnormalities were found after successful resuscitation of cardiac arrest. These abnormalities are consistent with secondary down-regulation of the thrombomodulin-endothelial protein C receptor pathway. (J Am Coll Cardiol 2005;46:21–8) © 2005 by the American College of Cardiology Foundation

Sudden death from coronary heart disease before reaching the hospital occurs in about 225,000 people annually in the U.S. The overall survival rate is low, ranging from 4% to 33% depending on the efficacy of the chain of survival (1,2). In successfully resuscitated patients admitted to the intensive care unit (ICU), the prognosis remains poor, and life-threatening disturbances known as "post-resuscitation disease" may lead to multiple organ dysfunction and jeopardize neurological recovery (3). Shock often develops several hours after hospital admission. It is characterized by low cardiac output and is usually reversible within 24 h, suggesting post-resuscitation myocardial dysfunction associated with peripheral vasodilation (4). Early death by multiple organ failure is associated with low cardiac output lasting longer than 24 h; however, the hemodynamic status does not predict the neurological outcome (4). Reperfusion failure, ischemia-reperfusion injury, and cerebral injury may be responsible for an overwhelming systemic inflammatory response associated with elevated plasma cytokines, presence of circulating endotoxin, leukocyte dysregulation, and adrenal dysfunction, a picture similar to that observed in severe sepsis (5,6). Moreover, a similar systemic inflammatory response has been described in severe cardiogenic shock with multiple organ failure (7) or a need for mechanical circulatory support (8).

Cardiopulmonary resuscitation (CPR) and a return to spontaneous circulation are associated with marked activation of blood coagulation, without adequate concomitant activation of endogenous fibrinolysis (9,10). This suggests that intravascular fibrin formation and microvascular thrombosis after cardiac arrest may contribute to organ dysfunction, including neurological impairment. Consistent with this hypothesis, thrombolytic therapy after CPR improved survival in experimental models of induced cardiac arrest (11,12) and allowed the return of spontaneous circulation after failed initial CPR (13).

Inflammatory and procoagulant host responses are closely linked not only to infection, but to all inflammatory processes (14). Inflammatory cytokines activate coagulation and inhibit fibrinolysis, whereas the procoagulant thrombin stimulates multiple inflammatory pathways (14). Activated protein C is an endogenous protein that enhances fibrino-

From the *Intensive Care Unit, Delafontaine Hospital, Saint Denis, France; †Intensive Care Unit, Jacques Cartier Hospital, Massy, France; ‡Lilly Research Laboratories, Eli Lilly Company, Indianapolis, Indiana; and §Medical Intensive Care Medicine, Cochin Hospital, University of Paris V, Paris, France. Suzan Um and Dr. Yan are employees of Eli Lilly and Company, and Dr. Dhainaut has served as a consultant for Eli Lilly and Company. However, this study was a research collaboration effort and was not funded by Lilly.

Manuscript received October 9, 2004; revised manuscript received February 24, 2005, accepted March 15, 2005.

Abbreviations and Acronyms

AT	= antithrombin
CPR	= cardiopulmonary resuscitation
ICU	= intensive care unit
IL	= interleukin
LOD	= Logistic Organ Dysfunction score
OHCA	= out-of-hospital cardiac arrest
PAI	= plasminogen activator inhibitor
PAP	= plasmin-antiplasmin complex
SAPS II	= Simplified Acute Physiology score
sTM	= soluble thrombomodulin
TAT	= thrombin-antithrombin complex

lysis, limits thrombin generation, and modulates inflammation. It is converted from its inactive precursor, protein C, by thrombin coupled to thrombomodulin. On the other hand, thrombin can have multiple proinflammatory properties; it activates endothelial cells to express P-selectin, promotes neutrophil and monocyte adhesion, induces endothelial platelet-activating factor formation, and acts as a chemoattractant for polymorphonuclear neutrophils (15). Administration of activated protein C significantly reduces mortality in patients with severe sepsis, a disease of systemic inflammatory activation (16).

In this study, we investigated the inflammation and coagulation responses in patients who were successfully resuscitated after an out-of-hospital cardiac arrest (OHCA). We directed special attention to the protein C pathway.

METHODS

Patients after OHCA, patients with severe sepsis, and healthy volunteers. This study was performed according to the ethical rules of our institutions (Cochin Hospital, Paris, France, and Delafontaine Hospital, Saint Denis, France), and informed consent was obtained from the next-of-kin of all patients. Cardiac arrest was defined as absence of spontaneous respiration, palpable heartbeat, and responsiveness to stimuli. Consecutive patients older than 16 years of age who were successfully resuscitated after OHCA were prospectively included in the study. Successful resuscitation was defined as recovery of blood pressure and pulse for more than 1 h, with or without a continuous catecholamine infusion. Both the Simplified Acute Physiology score (SAPS II) (17) and the Logistic Organ Dysfunction (LOD) score (18) were calculated. We recorded oral anticoagulants and/or antiplatelet agents given before or after admission, as well as prophylactic heparin therapy. Outcomes identified three groups of patients: survivors, all of whom were conscious; patients who died within four days from early refractory shock with multiple organ failure; and patients who died later from neurological dysfunction with or without a need for initial inotropic support (4–6). Patients were excluded from the study if they received thrombolytic therapy or therapeutic heparin. We also excluded patients with end-stage liver disease identified on the basis of clinical evidence or medical history. To check the validity of our biomarker assay methods, we studied two control groups, one composed of patients with severe sepsis meeting American College of Chest Physicians/Society of Critical Care Medicine consensus criteria (19) and studied within two days of ICU admission, and the other composed of healthy volunteers.

Blood samples. Citrated blood samples (4 ml) were collected and immediately centrifuged at 1,500 *g* for 10 min. The plasma was stored at −80°C until analysis. Blood collection was performed at ICU admission (day 0) and daily for the next 7 days (days 1 to 7). In a subset of 16 patients, additional blood samples were collected on days 0, 1, and 2 for measuring plasma endogenous activated protein C. Blood samples were drawn into citrated tubes containing the reversible serine protease inhibitor benzamidine, which blocks the irreversible inhibition of activated protein C by endogenous plasma protease inhibitors (20).

Assays. The following assays were performed using an STA Compact coagulation analyzer (Diagnostica Stago, Asnières, France) with Diagnostica Stago test kits. Activated partial thromboplastin time (STA-PTT A), prothrombin time (STA-Neoplastine Cl plus), protein C (Staclot Protein C), and free protein S (Staclot Protein S) were measured using coagulation-based activity assays. D-dimer levels were measured immunoturbidimetrically with the STA Liatest D-DI latex immunoassay. Antithrombin (AT) (Stachrom ATIII) and plasminogen activator inhibitor (PAI)-1 (Stachrom PAI) levels were quantitated using chromogenic activity assays. Soluble thrombomodulin (sTM) (Asserachrom Thrombomodulin, Diagnostica Stago), thrombin-antithrombin complex (TAT) (Enzygnost TAT micro, Dade Behring, Marburg, Germany), plasmin-antiplasmin complex (PAP) (PAP micro ELISA, DRG International Inc., Mountainside, New Jersey), and interleukin (IL)-6 (Quantikine Human IL-6 kit, R & D Systems, Minneapolis, Minnesota) antigen levels were measured by enzyme immunoassays. Plasma-activated protein C levels were measured using immunocapture-amidolytic assays, as previously described by Gruber and Griffin (20). Normal ranges and abbreviations for each of the biomarkers are reported in the Appendix.

Statistical analysis. Continuous data were expressed as medians and interquartile ranges. Undetectable levels (levels below the detection threshold) were assigned the value 0. Because of the high mortality rate within the first few days in the ICU, the statistical analysis of circulating markers was confined to the first two days. Differences between groups were evaluated using Mann-Whitney *U* tests or chi-square tests. Relationships between two continuous variables were analyzed using Spearman's rank correlation tests. Repeated measures analysis of variance was used to compare the time-course of coagulation markers between survivors and nonsurvivors. For this analysis, levels of coagulation parameters were normalized by natural log transformation. After natural log transformation, the Shapiro-Wilk W test was