Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 46, No. 3, 2005
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2005.04.039

High-Volume Hemofiltration After Out-of-Hospital Cardiac Arrest

A Randomized Study

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OBJECTIVES The study examined the effect of isovolumic high-volume hemofiltration (HF) alone or combined with mild hypothermia (HT) on survival after out-of-hospital cardiac arrest (OHCA) with initial ventricular fibrillation or asystole.

BACKGROUND Global inflammation in response to whole-body ischemia-reperfusion is common after OHCA and may worsen the overall prognosis.

METHODS Sixty-one patients admitted between May 2000 and March 2002 in the intensive care units of two hospitals in France were randomized to one of three groups: control, HF (200 ml/kg/h over 8 h) or HF+HT (32°C for 24 h) induced by cooling the HF substitution fluid. Standard supportive care was provided in all three groups. The primary end point was survival with a follow-up time of six months. The effect of HF on death by intractable shock was the secondary end point.

RESULTS The six-month survival curves of the three groups were significantly different, with better survival in the HF group ($p = 0.026$) and in the HF+HT group ($p = 0.018$). After adjustment on baseline characteristics of cardiac arrest, HF (with or without HT) was associated with improved survival (logistic regression odds ratio, 4.4; 95% confidence interval [CI], 1.1 to 16.6). Compared to control group, the relative risk of death by intractable shock was 0.29 (95% CI, 0.09 to 0.91) in the HF+HT group and 0.21 (95% CI, 0.05 to 0.85) in the HF group.

CONCLUSIONS The HF may improve the overall prognosis after resuscitation from OHCA. Combination of HF with mild HT is feasible and should be evaluated in larger trials. (J Am Coll Cardiol 2005;46:432–7) © 2005 by the American College of Cardiology Foundation

Despite recent advances in the management of out-of-hospital cardiac arrest (OHCA) (1,2) the overall prognosis remains poor. Over the last few years, it has been shown that treatments, such as therapeutic hypothermia (HT) (32°C to 34°C), started after restoration of spontaneous circulation (ROSC), may be of value for a better outcome (3,4).

A post-resuscitation syndrome, characterized by hyperthermia, hypotension, and multiple organ failure (5) is probably the clinical expression of whole-body ischemia-reperfusion injury occurring after ROSC in animals and humans. Complement activation, cytokine release, expression of adhesion molecules, dysregulation of cytokine production by leukocytes, presence of endotoxin in plasma (6), and adrenal dysfunction (7) have been described after cardiac arrest. Thus, post-resuscitation syndrome shares many features with severe sepsis (6,7), a fact that suggests potential targets for new treatments. Systemic inflammation after OHCA was consistently present (6) and was associated with delayed vasodilation and death by multiple organ failure (8). However, in these studies, early hemodynamic failure was not predictive of a poor neurological outcome, and many patients with early hemodynamic dysfunction had a good neurological outcome. This opens up the possibility that treatments capable of decreasing early mortality related to intractable shock might result in a greater number of survivors with good neurological outcomes.

In experimental models of sepsis and ischemia-reperfusion injury (9), isovolumic high-volume hemofiltration (HF) (200 ml/kg/h over 8 h) using a synthetic high-cutoff membrane removes medium molecular-weight molecules responsible for ischemia-reperfusion injury (10) and improves myocardial performance, hemodynamics, and survival. This led us to hypothesize that HF may benefit patients who recover spontaneous circulation after OHCA. To evaluate this hypothesis, we conducted a randomized study assessing the potential benefits of HF used alone or in combination with mild HT in patients admitted after OHCA.

METHODS

Study design. Patients admitted consecutively between May 2000 and March 2002 to the intensive care units (ICUs) of two hospitals (Cochin Teaching Hospital, Paris; and Delafontaine General Hospital, Saint Denis, France)

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Manuscript received February 4, 2005; revised manuscript received March 18, 2005, accepted April 13, 2005.

Abbreviations and Acronyms

CI	= confidence interval
C3a	= complement compounds C3a
HF	= isovolumic high volume hemofiltration (200 ml/kg/h over 8 h)
HF+HT	= isovolumic high volume hemofiltration plus hypothermia (32°C for 24 h)
HT	= hypothermia
ICU	= intensive care unit
IL	= interleukin
OHCA	= out-of-hospital cardiac arrest
ROSC	= restoration of spontaneous circulation
TCC	= terminal complement complex

were potentially eligible for the study if they had cardiac arrest apparently related to heart disease. Additional inclusion criteria were age between 18 and 75 years, initial ventricular fibrillation or asystole, estimated interval of <10 min from cardiac arrest to initiation of cardiopulmonary resuscitation (no-flow interval), and interval of <50 min from initiation of cardiopulmonary resuscitation to ROSC (low-flow interval). Exclusion criteria were pregnancy, response to verbal commands after ROSC, or a terminal illness present before the cardiac arrest.

When acute myocardial infarction was the suspected cause of OHCA, patients were first admitted to the cardiac catheterization laboratory for coronary angiography, which was performed according to standard techniques. As described previously (2), when a recent coronary-artery occlusion was found, coronary angioplasty was attempted, unless the infarct-related artery was too small or the operator considered the procedure to be technically impossible. The patients were then transferred to the ICU.

A three-lumen central venous catheter was routinely inserted at admission. Each patient had a femoral artery catheter for arterial blood pressure monitoring and repeated blood sample collection. Blood samples (4 ml) were collected on sodium citrate and ethylene-diamine-tetra-acetate at ICU admission (H0) and after 4, 8, 12, and 30 h. Blood samples were immediately centrifuged at 1,500 g for 10 min at 4°C, and the plasma was then stored at −70°C until assays of interleukin (IL)-6, complement components C3a (C3a), and the terminal complement complex (TCC). The IL-6 concentrations were determined using the ELISA kit from BioSource Systems (Camarillo, California), and the TCC and C3a levels were determined by using ELISA kits from Technoclone GmbH (Vienna, Austria).

A bladder catheter with a temperature probe was inserted routinely to monitor urinary output and core temperature. All patients were sedated using intravenous midazolam (0.1 mg/kg/h initially) and morphine (0.1 mg/kg/h initially) during the first 24 h in the ICU. Patients treated with hypothermia were also given the neuromuscular blocker pancuronium (1 to 4 mg/h).

The protocol was reviewed and approved by the ethics committee of the Cochin Teaching Hospital (approval no. 1657). As all patients were comatose, informed written consent was obtained as soon as possible from the patient's next-of-kin; however, according to French law treatment trials for immediate life-threatening situations, consent was not required to begin treatment. Patients who awoke with little or no neurological impairment were informed of their inclusion in the trial and asked whether they agreed to provide written informed consent.

Treatment protocol. The study was designed as a prospective, randomized trial to compare three treatment strategies after OHCA: the control group received standard supportive care including mechanical ventilation, volume expansion, and vasopressive drugs, as needed; the other two groups received the same supportive treatment plus either HF alone (HF group) or HF combined with HT (HF+HT group). At the time of our study, there were no published data supporting a beneficial role for HT after cardiac arrest; thus, HT was not used in the control group.

Before the study, a computer-generated 1/1/1 randomization sequence was prepared for each center. Patients were screened by an investigator immediately after the first call from the emergency responders (fire squadron or mobile medical team). Those subjects who met the inclusion criteria were randomly allocated to treatment using sealed opaque envelopes. This strategy was aimed at reducing the interval between OHCA onset and HF initiation, as 45 min are needed to prepare and prime HF circuits. All randomized patients were analyzed, on an intention-to-treat basis.

HF. The HF was achieved with a Gambro AK200-Ultra machine (Gambro, Lund, Sweden) producing a sterile ultrapure substitution fluid (endotoxin <0.25 U/ml), which was infused into the bloodstream (on-line HF) before the filter (predilution mode). According to experimental data (9), an ultrafiltration rate of 200 ml/kg/h (limited to 12.5 l/h) was used for 8 h. The ultrafiltrate was replaced by the same volume of bicarbonate-buffered (35 mmol/l) on-line produced fluid (zero-balance HF). The membrane used for HF was a 2.1 m^2 high-flux biocompatible polyamide dialyzer (POLYFLUX 21S, Gambro, Hechingen, Germany).

Vascular access for HF was via two single-lumen venous catheters (8-F, 20 cm, Vygon, Ecouen, France) inserted in two different veins (femoral or jugular veins), allowing high blood-flow rates (450 to 600 ml/min) with a minimal risk of recirculation. Anticoagulation was limited to an initial intravenous injection of 20 mg of enoxaparin.

In the HF group, the temperature of the replacement fluid was set at 37°C. In the HF+HT group, the temperature of the fluid was set at 30°C (the lowest temperature allowed by the AK200U machine) and was decreased to 15°C by placing ice packs around the infusion line. When the target core temperature of 32°C was reached, the ice packs were removed and a fluid temperature of 30°C was used for the remaining HF time. At the end of HF, mild therapeutic HT (32°C to 33°C) was maintained by external cooling for 16 h, when passive rewarming was started.