

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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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 ultra-pure 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 m² 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.

End points. The primary end point was survival with a follow-up time of six months. To study the effect of HF (with or without hypothermia) on death by intractable shock, we chose as the secondary end point the rate of death by intractable shock in patients who had a favorable Glasgow coma scale (M5 or M6) or required sedation, making neurological evaluation impossible. Survival with a favorable neurological outcome was defined as a Pittsburgh cerebral-performance category of 1 (good recovery) or 2 (moderate disability) on the five-category scale (11); patients in these two categories have sufficient brain function to live independently.

Statistical analysis. Continuous variables, which were not normally distributed, were described as medians and interquartile ranges and categorical variables as counts and percentages. Differences between groups at baseline were analyzed using the Kruskal-Wallis method or chi-square test, as appropriate. The Kaplan-Meier method was used to establish the six-month survival plot, and probability values for survival comparisons were calculated using the log-rank statistic. For the secondary end point, the relative risk of death by intractable shock was determined for the HF group and the HF+HT group. Distributions of IL-6, C3a, and TCC were normalized by natural log transformation. After natural log transformation, the Shapiro-Wilk W test was used to test for normality, with p values >0.10 indicating a normal distribution. Then, between-group comparisons for IL-6, C3a, and TCC were tested by two-way analysis of variance using mixed model methodology, with group and time as the factors.

We used a multivariate logistic regression model to look for associations between HF and the primary and secondary end points after adjustment on classical baseline characteristics of cardiac arrest (no-flow interval, low-flow interval, and initial rhythm). For this analysis, both the HF and

HF+HT groups were pooled. Analyses were made using Stata 7 software (Stata Corp., College Station, Texas).

No data on the efficacy of high-volume HF after cardiac arrest were available for a sample size calculation. Before study initiation, sample size was estimated by assuming mortality rates of 75% in controls and 45% with HF. With alpha set at 0.05 and a power of 0.70, 30 patients were needed in each treatment group. We planned to include consecutive patients for three years. However, in February 2002, two studies reported benefits from therapeutic HT after cardiac arrest (3,4). This led us to halt the study in March 2002 out of concern that absence of therapeutic HT in the HF-only and control groups might be unethical.

RESULTS

During the study period, 244 patients were assessed for eligibility; 183 did not meet the inclusion criteria and 61 were included in the study. Reasons for noninclusion were a presumed noncardiac cause to the cardiac arrest in 82 patients; an estimated interval longer than 10 min from cardiac arrest to initiation of cardiopulmonary resuscitation in 71 patients; age above 75 years in 13 patients; response to verbal command after ROSC in 12 patients; and terminal illness in 5 patients. Baseline characteristics of the patients are shown in Table 1. At baseline, the patients in the three groups were similar, although a trend toward greater severity was seen in the HF group. Two patients (one in the HF group and one in the HF+HT group) died before the initiation of HF. These patients were not excluded from the analysis.

As indicated in Table 1, 4h after ICU admission, the median core temperature in the HF+HT group was 31.7°C (interquartile range 31.4°C to 32.5°C) and was always below 35°C, clearly lower than in the two other groups. After natural log transformation, the p values of the Shapiro-Wilk

Table 1. Baseline Characteristics of the Patients

Characteristic	Control Group (n = 19)	HF Group (n = 20)	HF+HT Group (n = 22)	p Value
Age, yrs	58 [53-64]	52 [47-59]	56 [50-70]	0.18
Female gender, n (%)	4 (21)	4 (20)	4 (18)	0.97
Arrest witnessed, n (%)	19 (100)	20 (100)	22 (100)	0.99
History of coronary heart disease, n (%)	2 (11)	6 (30)	3 (14)	0.22
Interval between collapse and first attempt at resuscitation (min)	4 [2-8]	5 [2-10]	4 [2-7]	0.79
Interval between first attempt at resuscitation and restoration of spontaneous circulation (min)	14 [10-15]	25 [10-38]	16 [8-25]	0.11
Asystole as the initial cardiac rhythm, n (%)	5 (26)	5 (25)	6 (27)	0.98
Number of shocks	3 [1-5]	3 [1-7]	3 [1-4]	0.38
Dose of epinephrine during resuscitation	1 [0-3]	6 [0-11]	3 [0-4]	0.09
Hypotension requiring continuous epinephrine on hospital admission, n (%)	4 (21)	8 (40)	6 (27)	0.41
Acute myocardial infarction, n (%)	9 (56)	9 (45)	9 (41)	0.38
Temperature at ICU admission (°C)	35.7 [34.9-36.3]	36.0 [35.3-36.5]	36.0 [34.7-36.3]	0.60
Temperature 4 h after ICU admission (°C)	37.4 [37.1-38.4]	37.3 [36.0-37.9]	31.7 [31.5-32.4]	0.0001

Continuous variables are reported as (medians) and [interquartile ranges]. Categorical variables are reported as counts and percentages.

HF = high-volume hemofiltration; HT = hypothermia; ICU = intensive care unit.

Table 2. Biochemical Data

Variable	Time	Control Group	HF Group	HF+HT Group
IL-6 (pg/ml)	ICU admission	71 [47-128]	116 [63-331]	85 [41-577]
	4 h	38 [28-152]	248 [40-3,668]	43 [40-576]
	8 h	35 [19-77]	151 [33-1594]	42 [34-117]
	12 h	26 [18-54]	55 [16-154]	24 [21-1,275]
	30 h	24 [18-32]	17 [13-79]	30 [20-93]
C3a (ng/ml)	ICU admission	345 [268-535]	524 [313-1,054]	531 [332-830]
	4 h	228 [186-371]	371 [224-578]	301 [280-565]
	8 h	213 [141-374]	347 [215-464]	228 [186-371]
	12 h	203 [106-357]	223 [163-356]	236 [183-523]
	30 h	171 [85-288]	253 [163-371]	282 [186-396]
TCC (ng/ml)	ICU admission	737 [590-2,157]	1048 [489-2,497]	815 [428-865]
	4 h	785 [349-1,109]	1384 [932-2,747]	718 [659-1,151]
	8 h	458 [214-865]	840 [546-1,663]	512 [433-668]
	12 h	433 [248-693]	630 [344-970]	437 [403-874]
	30 h	471 [263-649]	725 [498-1,076]	588 [500-790]

Variables are reported as medians [interquartile ranges]. Two-way analysis of variance p for the group effect: 0.33 for interleukin (IL)-6; 0.17 for complement components C3a (C3a); 0.51 for terminal complement complex (TCC).
HF = high-volume hemofiltration; HT = hypothermia; ICU = intensive care unit.

W test were 0.90 for IL-6, 0.88 for C3a, and 0.91 for TCC, indicating a normal distribution. No significant differences across groups for the biochemical data (IL-6, C3a, and TCC) obtained during the first 30 h (data are shown in Table 2).

Figure 1 shows the survival curves of the three groups, with a better survival in the HF ($p = 0.026$) and HF+HT ($p = 0.018$) groups, compared to the control group. The six-month survival rates were 32% in the HF+HT group (7 of 22 patients), 45% in the HF group (9 of 20 patients), and 21% (4 of 19 patients) in the control group ($p = 0.28$). The neurological outcome was favorable in all six-month survivors. The hospital survival rate was very similar in the two groups treated with HF (HF group: 9 of 20 patients, 45%; and HF+HT group: 10 of 22 patients, 45%) and was nonsignificantly higher than the rate of the control group (5 of 19 patients, 26%, $p = 0.16$).

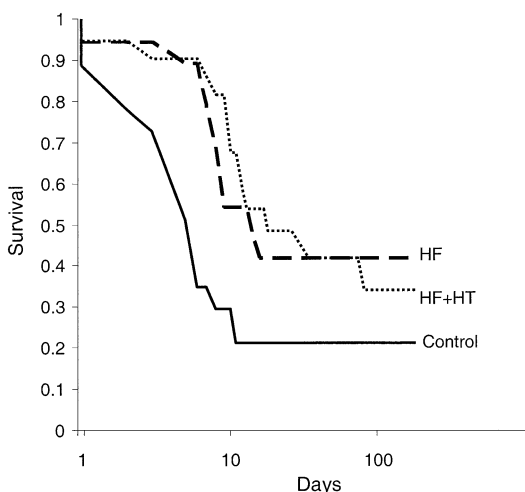


Figure 1. Kaplan-Meier survival curves in each group (log-rank $p = 0.018$). Patients treated with hemofiltration (HF) only ($p = 0.026$) or hemofiltration with hypothermia (HF+HT) ($p = 0.018$) differed significantly from patients in the control group.

The rate of death by intractable shock (secondary end point) was 14% in the HF+HT group (3 of 22 patients), 10% in the HF group (2 of 20 patients), and 42% (9 of 19 patients) in the control group ($p = 0.009$). Thus, the relative risk of death by intractable shock was 0.29 (95% confidence interval [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. After adjustment on classical baseline characteristics of cardiac arrest (no-flow interval, low-flow interval, and initial rhythm), the multivariate logistic-regression model showed a significant association between high-volume hemofiltration and both the primary end point (odds ratio for six-month survival 4.4; 95% CI 1.1 to 16.6) and the secondary end point (odds ratio for death by intractable shock 0.15, 95% CI 0.03 to 0.69).

Hypokalemia (<3.5 mmol/l) was observed in 10 patients during HF (5 each in the HF and HF+HT groups) and was corrected by adding potassium-chloride to the substitution fluid. Hypophosphatemia (<0.70 mmol/l) occurred in 20 patients (9 in the HF group and 12 in the HF+HT group) and was corrected by intravenous infusion of disodium phosphate, 8 mmol/h, during HF. During the first 24 h in ICU, ventricular tachycardia occurred in 6 patients in the HF+HT group, in 2 patients in HF group, and 3 patients in the control group ($p = 0.31$).

DISCUSSION

In this prospective randomized study, HF after ICU admission for OHCA was associated with better six-month survival and a decreased risk of death from early intractable shock. Although it is well established that prolonged ischemia results in tissue and organ damage, reperfusion-induced injury may also be harmful. In our previous studies, we found that patients who were successfully resuscitated after cardiac arrest exhibited a systemic inflammatory response syndrome as early as 3 h after the ROSC (6). We

also found an increase in plasma endotoxin levels consistent with gut ischemia/reperfusion injury (6). Patients with a systemic inflammatory response often experience cardiogenic and distributive shock leading to multiple organ failure and death within five days of the cardiac arrest (8). In contrast, after OHCA, late mortality is primarily ascribable to brain damage (12). However, early hemodynamic instability may compromise cerebral blood flow, thereby worsening the brain damage.

Experimental and clinical studies on the hemodynamic effects of HF have suggested that the efficacy of HF may be increased by early use (13) and that high doses may be useful in patients with sepsis syndrome (14). Consequently, the HF dose used in this trial (200 ml/kg/h) was based on results by Grootendorst et al. (9) who studied the efficacy of HF on gut ischemia-reperfusion injury. However, when used for long periods these high doses may markedly decrease the plasma levels of phosphorus and trace elements such as selenium and may compromise myocardial performance. Therefore, in our study, the duration of HF was limited to 8 h, on the basis of our previous study showing early onset of the systemic inflammatory response syndrome after OHCA (6).

In this study, we found no significant effect of HF on IL-6, C3a, or TCC levels. Other investigators have also reported hemodynamic improvement with HF but no significant changes in plasma cytokines (15). However, serum endothelin-1 concentrations were significantly reduced by HF (15). Endothelin-1 is now considered as a polyfunctional cytokine with a proinflammatory effect. Plasma concentrations of endothelin-1 were negatively correlated with most indices of cardiac function and with mean arterial blood pressure. This supports the hypothesis that other soluble mediators may be implicated in hemodynamic failure in humans after OHCA. Another hypothesis suggested that the effectiveness of HF is related to a cutting effect on the peaks of these soluble mediators (16). Unfortunately, we have not determined the plasma peaks of endothelin-1.

One limitation of our study lies in the nature of the standard care used in the control group. Our study was conducted before the publication of studies showing beneficial effects of mild therapeutic HT after OHCA (3,4). Thus, our controls did not receive therapeutic HT. When the study was designed, we believed that patients admitted after a cardiac arrest needed a very fast cooling to benefit from HT. We believed that the best method for cooling these patients is intravenous injection of a high amount of cold fluid and for this reason, the study included a group with HT and HF. In fact, the core temperature decrease in the HF+HT group seemed to occur faster than in the two studies of external cooling (3,4). The patients in our HF+HT group received up to 12.5 l of cold fluid intravenously per h, ensuring a rapid drop in core temperature. The above-mentioned studies (3,4) included only patients with nonperfusing ventricular tachycardia or ventricular fibrillation as the initial cardiac rhythm, and severity was greater in

our study population, which included 16 (26%) patients with asystole. The survival rate in resuscitated patients with asystole as the initial cardiac rhythm in Europe is about 3%, far lower than in patients with ventricular tachycardia or ventricular fibrillation (17). Nevertheless, the survival rate in our control group (26%) was the same as in the control group of the Australian study (3), indicating that high-quality standard care was provided to our patients.

However, without patient hypothermia, a better survival in the HF group was observed. The increased survival rate in the HF group without HT supports our working hypothesis that HF may improve overall survival, possibly by improving early hemodynamic stability. Thus, HF may hold promise as a complement to therapeutic HT in patients admitted after OHCA, even those with initial asystole. Both HF and HT may have different but complementary therapeutic targets, with HF reducing early hemodynamic instability and HT protecting against neurological impairment.

Another limitation of our study was that blinding to the assigned treatment was not feasible. However, we believe that full support was not inappropriately withdrawn from any of our patients, as all treatment limitation decisions were reached by consensus among ICU staff members, regardless of the study group.

The third limitation of our study was the small number of patients. We planned to include 90 patients during three years of this study, in the absence of previous data on the efficacy of HF on our primary and secondary outcomes in patients admitted after OHCA. However, publication of the two studies reporting a benefit of therapeutic HT after cardiac arrest led us to stop the enrollment, for ethical considerations, after the inclusion of only 61 patients. The small sample size may have limited our ability to compare improvements and adverse effects in the two HF-treated groups.

The fourth limitation of our study pertains to the generalizability of our findings to other ICUs. In many ICUs, hemofiltration is now available. However, we used a high hemofiltration dose (200 ml/kg/h) that requires special equipment. Use of high doses (up to 12.5 l/h) may be difficult without an online-produced solution.

Our study provides the first evidence that HF is clinically beneficial in patients without renal failure. The yearly incidence of OHCA in the general population of the European Union is about 9.5 per 10,000 inhabitants, and the relative risk in individuals with cardiovascular disease is about 10 (17). About 10% of these patients meet the inclusion criteria for therapeutic hypothermia studies and 15% meet those used in our study, in which we included patients with initial asystole. Thus, early high-dose hemofiltration may be of value in patients admitted after OHCA and may constitute another step toward improving the outcome of these patients.

CONCLUSIONS

Early HF after OHCA may decrease the risk of death from intractable shock and improve the final outcome. However, definite conclusions must await larger randomized clinical trials testing the combination of HF with HT in a larger cohort of OHCA survivors (11).

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