Vasopressin, Epinephrine, and Corticosteroids for In-Hospital Cardiac Arrest

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Background: Animal data on cardiac arrest showed improved long-term survival with combined vasopressin-epinephrine. In cardiac arrest, cortisol levels are relatively low during and after cardiopulmonary resuscitation. We hypothesized that combined vasopressin-epinephrine and corticosteroid supplementation during and after resuscitation may improve survival in refractory in-hospital cardiac arrest.

Methods: We conducted a single-center, prospective, randomized, double-blind, placebo-controlled, parallel-group trial. We enrolled 100 consecutive patients with cardiac arrest requiring epinephrine according to current resuscitation guidelines. Patients received either vasopressin (20 IU per cardiopulmonary resuscitation cycle) plus epinephrine (1 mg per resuscitation cycle) (study group; n=48) or isotonic sodium chloride solution placebo plus epinephrine (1 mg per resuscitation cycle) (control group; n=52) for the first 5 resuscitation cycles after randomization, followed by additional epinephrine if needed. On the first resuscitation cycle, study group patients received methylprednisolone sodium succinate (40 mg) and controls received saline placebo. Postresuscitation shock was treated with stress-dose hydrocortisone sodium succinate (300 mg daily for 7 days maximum, with gradual taper) (27 patients in the study group) or saline placebo (15 patients in the control group). Primary end points were return of spontaneous circulation for 15 minutes or longer and survival to hospital discharge.

Results: Study group patients vs controls had more frequent return of spontaneous circulation (39 of 48 patients [81%] vs 27 of 52 [52%]; $P=.003$) and improved survival to hospital discharge (9 [19%] vs 2 [4%]; $P=.02$). Study group patients with postresuscitation shock vs corresponding controls had improved survival to hospital discharge (8 of 27 patients [30%] vs 0 of 15 [0%]; $P=.02$), improved hemodynamics and central venous oxygen saturation, and more organ failure–free days. Adverse events were similar in the 2 groups.

Conclusion: In this single-center trial, combined vasopressin-epinephrine and methylprednisolone during resuscitation and stress-dose hydrocortisone in postresuscitation shock improved survival in refractory in-hospital cardiac arrest.

Trial Registration: clinicaltrials.gov Identifier: NCT00411879

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THE INCIDENCE OF IN-HOSPITAL cardiac arrest is 1 to 5 per 1000 patient admissions.[1] Survival to hospital discharge is approximately 20%.[1] Survival after refractory cardiac arrest, ie, refractory ventricular fibrillation/pulseless ventricular tachycardia or asystole/pulseless electrical activity, ranges from 5% to 15%.[2]

In nonsurvivors of cardiopulmonary resuscitation (CPR), the plasma vasopressin level is lower than in CPR survivors.[3] Vasopressin acts directly via V_1 receptors on vascular contractile elements. In cardiac arrest, vasopressin is released as adjunct vasopressor to epinephrine.[4] Recent animal data showed improved survival and postresuscitation neurologic status after treatment with vasopressin-epinephrine compared with epinephrine alone.[5] Combination treatment was associated with fewer postresuscitation cardiovascular complications and similar neurologic status relative to vasopressin alone.[5]

Relative to other stress states, cardiac arrest is associated with lower cortisol levels during and after CPR.[4,6,7] Return of spontaneous circulation is associated with plasma cytokine elevation,[4,6] endotoxemia,[4] coagulopathy,[4] and adrenal insufficiency contributing to postresuscitation shock.[4,7] Corticosteroid supplementation during and after CPR might confer benefits with respect to hemodynamics, intensity of postresuscitation systemic inflammatory response, and organ dysfunction.[4,7]

We hypothesized that, in refractory in-hospital cardiac arrest, treatment with combined vasopressin-epinephrine during CPR and corticosteroid supplementation during and after CPR, compared with epinephrine alone during CPR and no cor-

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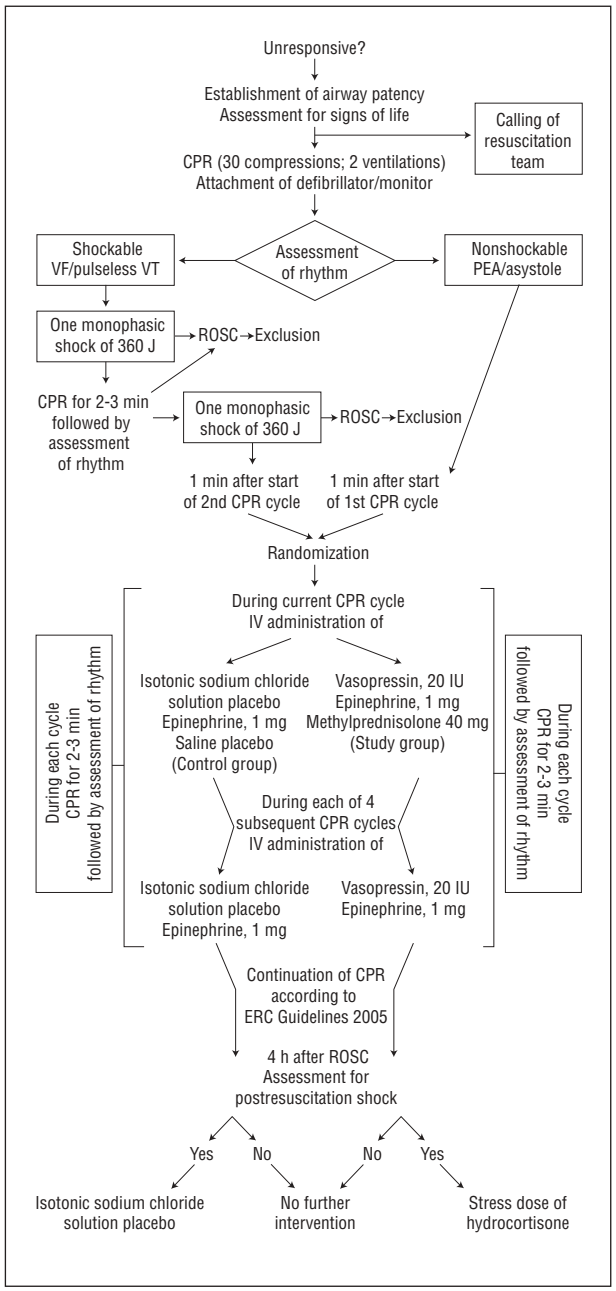

Figure 1. Schematic diagram of the cardiopulmonary resuscitation (CPR) procedures and study protocol. ERC indicates European Resuscitation Council; IV, intravenous; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; VT, ventricular tachycardia.

ticosteroid supplementation, may (1) facilitate return of spontaneous circulation, (2) attenuate postresuscitation systemic inflammatory response and cardiac arrest–associated organ injuries, and (3) improve survival to hospital discharge.

METHODS

PATIENTS

We conducted our study in the intensive/coronary care units (ICUs/CCUs), emergency department, general wards, and operating rooms of Evaggelismos Hospital, a tertiary care teaching hospital. The patient eligibility criterion was refractory cardiac arrest, defined as epinephrine requirement for ventricular fibrillation/ventricular tachycardia or asystole/pulseless electrical activity according to the European Resuscitation Council Guidelines for Resuscitation 2005.[8] Exclusion criteria were age younger than 18 years, terminal illness[2] or do-not-resuscitate status, cardiac arrest due to exsanguination, cardiac arrest before hospital admission, treatment with intravenous corticosteroids before the cardiac arrest, and previous enrollment in or exclusion from the current study. Consent was not obtained for the CPR-drug combination.[2] The patients and their families were informed about the trial.[9] Informed, written next-of-kin consent and nonwritten patient consent (whenever feasible) were obtained for stress-dose hydrocortisone sodium succinate in postresuscitation shock and for blood sampling to determine plasma cytokine levels. The Scientific Council of Evaggelismos Hospital approved the study.

STUDY DESIGN AND PROTOCOL

This was a single-center, prospective, randomized, double-blind, placebo-controlled, parallel-group clinical trial. Group allocation was conducted by the director of the hospital's pharmacy with the Research Randomizer (http://www.randomizer.org). Random numbers from 1 to 100 were generated in sets of 4. Each number of each set was unique and was assigned to 1 of the 100 consecutively enrolled patients as his or her code. Vasopressin and methylprednisolone were prepared by the hospital's pharmacy in identical, preloaded 5-mL syringes and placed along with epinephrine ampules in boxes bearing patient codes (for details, see the supplemental material available at http://www.mentzelopoulos-et-al.com). After patient randomization, a box was opened and study drugs were injected intravenously according to protocol. Drug injection was followed by 10 mL of isotonic sodium chloride solution.

CPR Interventions

Adult inpatients with cardiac arrest induced by ventricular fibrillation/ventricular tachycardia not responsive to 2 defibrillations separated by 2 to 3 minutes of CPR[8] or patients with asystole/pulseless electrical activity were randomized to receive either combined vasopressin (20 IU per CPR cycle; Monarch Pharmaceuticals, Bristol, Tennessee) and epinephrine (1 mg per CPR cycle; Demo, Athens, Greece) (study group), or isotonic sodium chloride solution placebo and epinephrine (1 mg per CPR cycle) (control group), for the first 5 CPR cycles after randomization. Forty milligrams of methylprednisolone sodium succinate (Pfizer, Athens, Greece) and isotonic sodium chloride solution placebo were administered during the first CPR cycle after randomization to study group and control group patients, respectively. If return of spontaneous circulation was not achieved on completion of the experimental treatment, CPR was continued according to current guidelines.[8] Our protocol is schematically presented in **Figure 1**. Experimental drug stability in the syringes was confirmed by high-performance liquid chromatography (see the online supplemental material). Advanced life support was conducted according to current standards[8] (also described in the online supplemental material).

Postresuscitation Shock

At 4 hours after resuscitation, surviving study group patients with postresuscitation shock received stress-dose hydrocortisone sodium succinate (300 mg daily for 7 days maximum, and gradual taper; Pfizer).[10] Hydrocortisone was available in vials

containing 100 mg of hydrocortisone sodium succinate powder. Each daily dose was diluted in 100 mL of isotonic sodium chloride solution at the hospital's pharmacy and administered to study group patients as a continuous infusion. On vasopressor cessation or on day 8 after cardiac arrest, the daily hydrocortisone sodium succinate dose was consecutively reduced to 200 mg and 100 mg and then discontinued (see the online supplemental material). Control group patients with postresuscitation shock received daily infusions of 100 mL of isotonic sodium chloride solution placebo. Isotonic sodium chloride solution infusion bags bore the patient codes.

DEFINITIONS

Circulatory failure was defined as inability to maintain mean arterial pressure greater than 70 mm Hg without using vasopressors after volume loading.[10] *Respiratory failure* was defined as a ratio of arterial oxygen partial pressure to inspired oxygen fraction of 200 mm Hg or less. *Coagulation failure* was defined as a platelet count of $50 \times 10^3/\mu L$ or less. *Hepatic failure* was defined as serum bilirubin concentration of 6 mg/dL (to convert to micromoles per liter, multiply by 17.104) or less. *Renal failure* was defined as serum creatinine level of 3.5 mg/dL (to convert to micromoles per liter, multiply by 88.4) or greater and/or requirement of renal replacement therapy. *Neurologic failure* was defined as a Glasgow Coma Score of 9 or less.

After resuscitation, cardiac arrest–induced cardiac and microcirculatory dysfunction lasts approximately 24 hours.[6] Postresuscitation shock was defined as sustained (>4 hours), new postarrest circulatory failure or postarrest need for at least a 50% increase in any prearrest vasopressor/inotropic support targeted to maintain mean arterial pressure above 70 mm Hg.

DOCUMENTATION AND PATIENT FOLLOW-UP

Attempts at CPR were documented according to the Utstein style.[9] Additional data comprised periarrest arterial pressure, gas exchange, electrolyte and lactate levels, vasopressor/inotropic support, and intravenous fluids given. Daily follow-up was conducted by 4 blinded investigators (N.K., S.G., A.P., and A.S.). Follow-up to day 60 after cardiac arrest included medication, organ or system failures, and ventilator-free days. Morbidity and complications throughout ICU/CCU and hospital stay and times to ICU/CCU and hospital discharge were also recorded. Encoded patient data were entered into a database by 2 investigators (N.K. and S.G.) and independently cross-checked by another 2 investigators (A.P. and A.S.). Data were independently scrutinized by a steering committee.

PLASMA CYTOKINE CONCENTRATIONS

Venipuncture blood samples were obtained on day 0 (at 6 hours after randomization) from the last 35 surviving patients with postresuscitation shock; additional blood samples were obtained on days 1, 3, and 7 after randomization. Serum concentrations of tumor necrosis factor, interleukin (IL)-1β, IL-6, IL-8, and IL-10 were measured by an enzyme-linked immunosorbent assay (Quantikine; R&D Systems Europe Ltd, Abingdon, England) according to manufacturer instructions.

STUDY END POINTS

Primary end points were return of spontaneous circulation for 15 minutes or longer and survival to hospital discharge, defined as presence of an attending physician discharge order to home or to a rehabilitation facility. Secondary end points were arterial pressure during and 15 to 20 minutes after CPR, intensity of postarrest systemic inflammatory response, number of organ failure–free days until completion of follow-up, and cerebral performance according to the Glasgow-Pittsburgh scale at hospital discharge (see online supplemental material for details on determination of end points).

STATISTICAL ANALYSIS

Initial rhythm is asystole in 75% to 80% of the refractory cardiac arrests occurring in our hospital. Sample-size calculation (G*Power version 3.0.8; Heinrich Heine University, Düsseldorf, Germany) was based on a possible, drug-related, overall 3.1-fold improvement in survival to hospital discharge of the study group vs the control group. Survival improvement was expected mainly for patients with asystole.[9] Thus, our overall prediction was equivalent to an experimental treatment–induced 3.8-fold rise in the survival of patients with asystole. This corresponds to an improvement of 22.6% relative to a recently reported vasopressin-induced 3.1-fold rise in survival after asystolic cardiac arrest.[9] Predicted overall survival of the control group was 5%.[2] Calculated χ^2 effect size was 0.34. For an α value of .05 and a power of 0.80, the estimated sample size was 68 (ie, 34 patients per group). The inclusion of 100 patients resulted in a safety margin of 32 of 68 (47%).

An intention-to-treat analysis was conducted with SPSS version 12.0 statistical software (SPSS Inc, Chicago, Illinois). Data are reported as mean (SD), median (interquartile range [IQR]), or number (percentage), unless otherwise specified. Distribution normality was tested by the Kolmogorov-Smirnov test. Dichotomous and categorical variables were compared by the χ^2 or Fisher exact test. Continuous variables were compared by a 2-tailed, independent-samples *t* test or the Mann-Whitney exact test.

In postresuscitation shock, we used linear mixed-model analysis to determine the overall effects of group, time, and their interaction (group × time) on log-transformed plasma cytokine concentrations throughout the first 7 days after randomization. The effects of group, time, and group × time on (1) average daily central venous oxygen saturation and arterial blood lactate (measured every 12 hours), mean arterial pressure (recorded every 3 hours), and infusion rates of vasopressors; (2) daily fluid balance; and (3) hemoglobin concentration (measured every 24 hours) were also analyzed for the first 10 days after randomization. Fixed-effects significance was determined by the *F* test. Model selection was based on the minimum values of −2 restricted log-likelihood and Akaike information criteria. Between-group comparisons at individual, consecutive time points were conducted with the independent-samples *t* test; *P* values were not corrected for multiple comparisons.

Survival was analyzed by the Kaplan-Meier method, and survival data were compared by (1) the Fisher exact test to determine any nonrandom association between group and survival to hospital discharge and (2) the log-rank test to test the null hypothesis that the probability of death did not differ between the study and control groups throughout patient follow-up. Univariate and multivariate backward-stepwise Cox regression analysis was used to identify independent predictors of death and to determine the respective proportional hazards and their 95% confidence intervals. Variable entry and removal criteria were 0.05 and 0.10, respectively. Reported *P* values are 2 sided. Statistical significance was set at $P < .05$.

RESULTS

From June 8, 2006, to March 16, 2007, there were 139 potentially eligible patients with cardiac arrest. Overall survival to hospital discharge was 37 of 139 patients

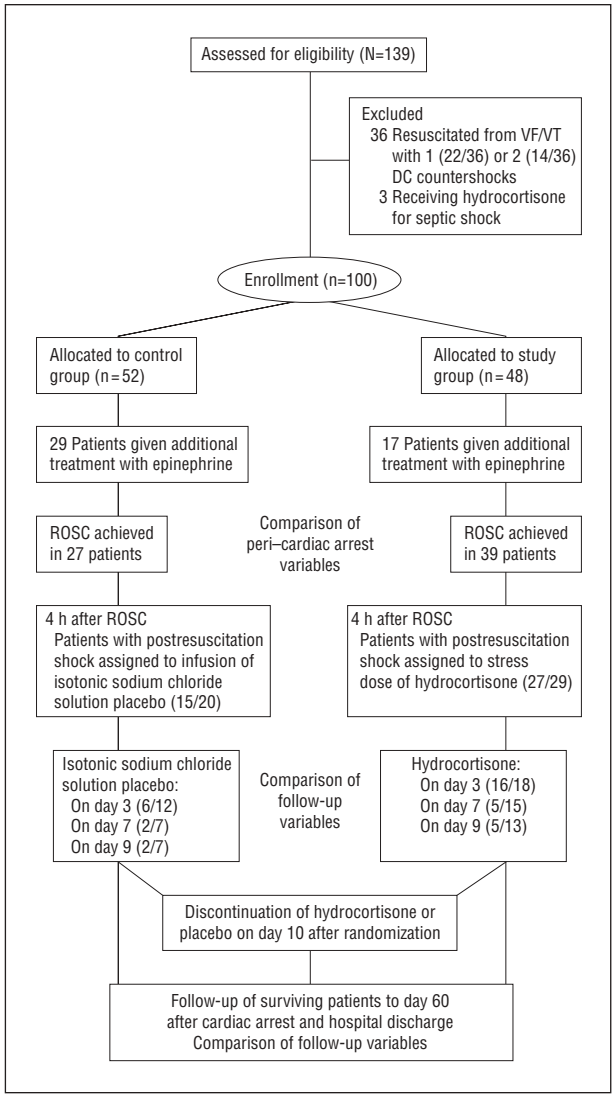

Figure 2. Study flowchart. DC indicates direct current; ROSC, return of spontaneous circulation; and VF/VT, ventricular fibrillation/ventricular tachycardia. Numbers in parentheses are number of patients with postresuscitation shock receiving isotonic sodium chloride solution placebo or hydrocortisone sodium succinate/total number of surviving patients at that time point.

Table 1. Patient Characteristics Before Cardiac Arrest and Causes of Cardiac Arrest

Characteristic	Control Group (n=52)	Study Group (n=48)
Age, mean (SD), y	69.2 (17.7)	65.4 (17.6)
Male, No. (%)	29 (56)	30 (63)
BMI, mean (SD)	25.3 (4.7)	27.3 (8.6)
Pre–cardiac arrest hospital stay, mean (SD), d	3.4 (4.2)	3.9 (3.5)
Cardiovascular history, No. (%)		
Hypertension	33 (63)	31 (65)
Coronary artery disease	18 (35)	21 (44)
Diabetes mellitus	15 (29)	14 (29)
Cardiac conduction disturbances	5 (10)	4 (8)
Cardiac arrhythmia	4 (8)	4 (8)
Valvular heart disease	4 (8)	4 (8)
Peripheral vascular disease	8 (15)	11 (23)
Other chronic comorbidity, No. (%)[a]	33 (63)	32 (67)
Hospital admission cause, No. (%)[b]		
Acute cardiovascular disease	26 (50)	20 (42)
Acute respiratory disease	7 (13)	8 (17)
Acute renal disease	4 (8)	1 (2)
Acute digestive disease	3 (6)	4 (8)
Acute neurologic disease	1 (2)	6 (13)
Malignant neoplasm	6 (12)	7 (15)
Trauma	5 (10)	9 (19)
Other	2 (4)	3 (6)
Cause of cardiac arrest, No. (%)[c]		
Acute coronary syndrome	12 (23)	12 (25)
Cardiogenic shock	4 (8)	5 (10)
Lethal arrhythmia	3 (6)	2 (4)
Hypoxemia-pulmonary edema	7 (13)	2 (4)
Cardiac tamponade	1 (2)	0 (0)
Hypoxemia-pneumonia	10 (19)	8 (17)
Hypoxemia-COPD exacerbation	2 (4)	1 (2)
Pulmonary embolism	6 (12)	10 (21)
Septic shock	4 (8)[d]	3 (6)[e]
Electrolyte disturbances	6 (12)	2 (4)
Tension pneumothorax-hemothorax	1 (2)	3 (6)
Hypovolemia	3 (6)	3 (6)
Other	1 (2)	4 (8)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease.

[a] Includes chronic respiratory, neurologic, digestive, renal, and musculoskeletal disease; malignant neoplasm; and immunosuppression.

[b] Some patients had more than 1 cause of hospital admission; "other" causes included 2 cases of peritonitis and 1 case each of severe dehydration, pheochromocytoma, and amyloidosis.

[c] In some patients, more than 1 major disturbance precipitated the cardiac arrest; "other" causes included 2 cases of drug toxic effects and 1 case each of vagotonic arrest, intracerebral hemorrhage, and tension hydrothorax.

[d] Three patients died during the initial resuscitation attempt. One patient was successfully resuscitated but had a second and fatal cardiac arrest after 4 hours.

[e] One patient died during the initial resuscitation attempt. Two patients were successfully resuscitated but had a second and fatal cardiac arrest within the following 8 hours.

(26.6%). Thirty-nine patients were excluded and 100 patients (52 in the control group and 48 in the study group) were enrolled (**Figure 2**). Patient encoding was disclosed to one of us (S.D.M.) on April 9, 2007 (hospital discharge date for the last surviving patient). Data from the first 50 patients enrolled were independently analyzed by the steering committee on December 13, 2006. This interim analysis established study safety and proper working of randomization.

Table 1 displays baseline patient characteristics and causes of cardiac arrest. Study group patients vs control group patients had significantly higher rates of return of spontaneous circulation for 15 minutes or longer (39 of 48 patients [81%] vs 27 of 52 [52%]; $P=.003$) (**Table 2**). In the study group, average mean arterial pressure during CPR (determined only in the ICU/CCU among patients with an arterial line in place) and 15 to 20 minutes after CPR (determined in all CPR survivors) was higher by 32.1% ($P=.009$) and 25.9% ($P=.02$), respectively (**Table 3**).

At 4 hours after resuscitation, 27 of 29 surviving study group patients and 15 of 20 surviving controls had postresuscitation shock and were assigned to stress-dose hydrocortisone and isotonic sodium chloride solution placebo, respectively (Figure 2). Within 12 hours after cardiac arrest, all surviving patients were in the ICU or CCU. Survival to hospital discharge was significantly

Table 2. Documentation of CPR Procedures

	Control Group (n=52)	Study Group (n=48)	*P* Value
Location of cardiac arrest, No. (%)			
Ward	25 (48)	21 (44)	.69
ICU or CCU	14 (27)	17 (35)	.39
Emergency department	10 (19)	8 (17)	.80
Operating room	3 (6)	2 (4)	>.99
Initial rhythm, No. (%)			
Ventricular fibrillation/tachycardia	7 (13)	7 (15)	>.99
Asystole	31 (60)	30 (63)	.84
Pulseless electrical activity	14 (27)	11 (23)	.82
Witnessed arrest, No. (%)	43 (83)	38 (79)	.80
Time to ALS initiation in witnessed arrest, mean (SD), min	1.1 (1.0)	1.0 (0.9)	.56
ALS duration, mean (SD), min	31.2 (29.9)	25.1 (23.6)	.27
Not intubated at arrest, No. (%)[a]	36 (69)	34 (71)	>.99
No. of cardiopulmonary resuscitation cycles, mean (SD)[b]	8.0 (7.5)	6.4 (5.6)	.26
No. of defibrillations, mean (SD)	0.7 (1.9)	0.5 (1.2)	.47
Rate of ROSC ≥15 min, No. (%)	27 (52)	39 (81)	.003
Medication, mean (SD)[c]			
Vasopressin, IU	0.0 (0.0)	73.3 (30.1)	. . .
Epinephrine, mg	7.8 (7.0)	6.3 (5.8)	.26
Methylprednisolone sodium succinate, mg	0.0 (0.0)	40.0 (0.0)	. . .
Atropine sulfate, mg	2.9 (0.6)	2.7 (0.9)	.26
Amiodarone hydrochloride, median (range), mg	0.0 (0.0-300.0)	0.0 (0.0-300.0)	.27
Bicarbonate, mean (SD), mmol	27.7 (32.3)	25.3 (32.0)	.71
Calcium, mean (SD), mmol	5.2 (10.4)	4.4 (11.2)	.68
Magnesium, mean (SD), mmol	0.7 (3.9)	0.5 (2.9)	.61
Reverse tissue plasminogen activator, median (range), mg	0.0 (0.0-100.0)	0.0 (0.0-100.0)	.73
Crystalloids, median (IQR), mL	120 (80-200)	100 (60-190)	.14
Colloids, median (range), mL	0 (0-1000)	0 (0-2000)	.59
Packed red blood cells, median (range), U	0.0 (0.0-5.0)	0.0 (0.0-5.0)	.81
Fresh frozen plasma, median (range), U	0.0 (0.0-2.0)	0.0 (0.0-0.0)	.50
Temporary pacing, No. (%)	2 (4)	3 (6)	.67

Abbreviations: ALS, advanced life support; CCU, coronary care unit; CPR, cardiopulmonary resuscitation; ICU, intensive care unit; IQR, interquartile range; ROSC, return of spontaneous circulation; ellipses, not applicable.

[a] In all cases the trachea was successfully intubated on the first attempt and within the first 3 minutes of onset of ALS; in both groups, approximately 30% of the patients were already intubated before the occurrence of the cardiac arrest.

[b] The average (SD) duration of CPR cycles was 3.9 (0.4) minutes and was determined from the recorded time intervals between the intermittent administrations of the study drugs during the first 5 cycles following randomization or of epinephrine after the first 5 cycles following randomization (see also Figure 1).

[c] All drugs were injected exclusively intravenously either via a central venous catheter (patients in an ICU or CCU) or via a 14-, 16-, or 18-gauge peripheral venous catheter. A functional intravenous line was present before the cardiac arrest in all but 2 controls and 3 study group patients. In all 5 of these cases, an intravenous line was started within 1 minute after the confirmation of asystole.

higher in the study group than in the control group (9 of 48 [19%] vs 2 of 52 [4%]; *P*=.02 by Fisher exact test) (**Figure 3**A; *P*=.003 by log-rank test). Multivariate Cox regression analysis showed that independent risk factors for death were assignment to study group and completion of a full postarrest course of hydrocortisone according to protocol (relative risk, 0.15; 95% confidence interval, 0.06-0.38; *P*<.001), periarrest lactate level (see also Table 3, footnote *e*) (1.07; 1.02-1.11; *P*=.003), and successful resuscitation after 3 or fewer CPR cycles (0.49; 0.29-0.83; *P*=.008). Post hoc analysis showed that rapid (ie, requiring ≤3 CPR cycles) successful resuscitation was more frequent in the study group than in the control group (22 of 48 [46%] vs 11 of 52 [21%], *P*=.01).

Full follow-up data were obtained for all CPR survivors. In those who survived for 4 hours or longer, prescribed medication was similar, except that vasopressor use throughout follow-up was significantly lower in the study group (*P*=.002) (see the online supplemental materials). Median (IQR) days free of all organ failure were 0.0 (0.0-36.0) and 0.0 (0.0-0.0) in the study group and control group, respectively (*P*=.27). Postarrest morbidity, complications, and causes of death were similar in both groups (**Table 4**). For the 11 long-term survivors, ICU/CCU and hospital discharge occurred at a mean (SD) of 37.6 (27.4) and 58.8 (31.2) days after arrest, respectively.

FOLLOW-UP IN POSTRESUSCITATION SHOCK

Study group patients with postresuscitation shock vs corresponding controls had significantly improved survival to hospital discharge (8 of 27 [30%] vs 0 of 15 [0%]; *P*=.02 by Fisher exact test) (Figure 3B; *P*=.01 by log-rank test), a trend toward significantly more all–organ failure–free days (median [IQR], 0.0 [0.0-32.0] vs 0.0 [0.0-0.0]; *P*=.06), and significantly more renal failure–free days (3.0 [1.0-59.0] vs 0.0 [0.0-5.0]; *P*=.03). Study group patients who completed a full course of hydrocortisone according to protocol (n=12) vs corresponding controls (n=6) had significantly more days free of all organ failure and circulatory, neurologic, hepatic, renal, coagulation, and respiratory failure (*P*=.001 to *P*=.04) (Figure 3C).

Table 3. Physiologic Variables During and 15 to 20 Minutes After CPR[a]

Variable	Control Group (n=52)	Study Group (n=48)	*P* Value
During CPR			
Systolic arterial pressure, mm Hg[b]	74.6 (21.2)	105.9 (28.5)	.002
Mean arterial pressure, mm Hg[b]	54.5 (16.5)	72.0 (17.9)	.009
Diastolic arterial pressure, mm Hg[b]	44.5 (14.5)	55.0 (14.4)	.05
Pa_{O_2}, mm Hg[c]	91.9 (57.6)	109.1 (111.3)	.47
Pa_{CO_2}, mm Hg[c]	56.2 (16.8)	55.6 (32.6)	.94
Arterial pH[c]	7.07 (0.17)	7.06 (0.20)	.80
Potassium ion, mEq/L[c]	5.6 (1.2)	5.4 (1.8)	.65
Sodium ion, mEq/L[c]	144.6 (10.2)	140.0 (10.8)	.08
Calcium ion, mEq/L[c]	2.2 (1.2)	2.0 (0.6)	.18
Glucose, mg/dL[c]	262.9 (75.0)	286.6 (183.1)	.55
After return of spontaneous circulation			
Systolic arterial pressure, mm Hg[d]	106.1 (34.6)	131.2 (50.4)	.03
Mean arterial pressure, mm Hg[d]	73.8 (23.6)	92.9 (35.4)	.02
Diastolic arterial pressure, mm Hg[d]	57.7 (20.0)	73.8 (29.3)	.02
Heart rate, beats/min[d]	117.9 (26.3)	112.4 (29.8)	.45
Pa_{O_2}, mm Hg[d]	142.4 (89.6)	193.7 (137.2)	.07
Pa_{CO_2}, mm Hg[d]	46.2 (17.6)	42.8 (22.3)	.52
Arterial pH[d]	7.25 (0.15)	7.22 (0.18)	.49
Potassium ion, mEq/L[d]	4.7 (1.0)	4.7 (1.4)	.96
Sodium ion, mEq/L[d]	141.9 (10.2)	142.8 (11.4)	.73
Calcium ion, mEq/L[d]	2.2 (1.6)	2.2 (1.2)	.67
Glucose, mg/dL[d]	278.3 (83.3)	281.9 (144.1)	.91
Peri–cardiac arrest lactate, mg/dL[e]	91.9 (46.8)	89.2 (52.3)	.78
Infusions			
Norepinephrine, μg/kg/min[d,f]	0.5 (0.4)	0.5 (0.4)	.92
Dobutamine, median (IQR), μg/kg/min[d,f]	0.0 (0.0-10.0)	0.0 (0.0-4.0)	.44
Epinephrine, median (IQR), μg/kg/min[d,f]	0.0 (0.0-0.0)	0.0 (0.0-0.1)	.47
Intravenous fluids, median (IQR), mL[g]	130 (110-230)	130 (90-330)	.39

Abbreviations: CPR, cardiopulmonary resuscitation; IQR, interquartile range.

SI conversion factors: To convert potassium and sodium to millimoles per liter, multiply by 1; calcium to millimoles per liter, multiply by 0.5; glucose to millimoles per liter, multiply by 0.0555; lactate to millimoles per liter, multiply by 0.111.

[a] Data are mean (SD) unless otherwise specified.

[b] Data are from 14 control group and 17 study group intensive care unit or coronary care unit patients who had an arterial line in place before the occurrence of the cardiac arrest. Invasive blood pressure measurements were averaged over 1 or 2 consecutive CPR cycles during the first 5 to 15 minutes of CPR, and resulting mean values were analyzed.

[c] Data are from 40 control group and 26 study group patients who received more than 3 CPR cycles.

[d] Data are from 27 control group and 39 study group patients who were successfully resuscitated. Invasive blood pressure measurements were averaged during a 5-minute period (15 to 20 minutes after the return of spontaneous circulation). Noninvasive blood pressure measurements were taken every 60 seconds during the aforementioned 5-minute period and averaged. Only mean values of blood pressure measurements were analyzed.

[e] Arterial blood gas analysis–derived lactate concentrations during CPR or 15 to 20 minutes after the return of spontaneous circulation. Thirty-three patients were successfully resuscitated after more than 3 CPR cycles. In these patients, arterial blood gas analysis was performed both during and after resuscitation, and the average of the 2 lactate concentration values was used in the present analysis.

[f] Data are from individual average infusion rates recorded during a 5-minute period (15 to 20 minutes after the return of spontaneous circulation).

[g] Refers to cumulative administered volume of crystalloids, colloids, packed red blood cells, and fresh frozen plasma from the onset of CPR to 15 minutes after return of spontaneous circulation.

Linear mixed-model analysis showed significant effects of group on log-transformed plasma IL-6 levels ($P<.001$), central venous oxygen saturation ($P<.001$), and mean arterial pressure ($P<.001$). There was a significant effect of group × time on central venous oxygen saturation ($P=.007$). There was a time-dependent decrease in arterial blood lactate levels ($P<.001$), daily norepinephrine infusion rate ($P=.004$), and positivity of daily fluid balance ($P=.001$) (see the online supplemental material).

Plasma IL-6 level was significantly lower in the study group than in the control group throughout the first week after randomization ($P=.002$ to $P=.02$). Six hours after randomization, plasma tumor necrosis factor level was significantly lower ($P=.04$), and plasma IL-1β level exhibited a trend toward significantly lower values ($P=.06$) in the study group (Figure 3D). Central venous oxygen saturation and mean arterial pressure were significantly higher in the study group than in the control group throughout the first 10 days ($P<.001$ to $P=.04$) and at days 2, 4, and 10 ($P=.006$ to $P=.03$) after randomization, respectively (Figures 3E and 3F). Arterial oxygen saturation, hemoglobin concentration, and dobutamine and epinephrine daily infusion rates were similar in the 2 groups (data not shown).

ADDITIONAL ANALYSES

Additional analyses are presented in the online supplementary material at http://www.mentzelopoulos-et-al.com. Prearrest physiologic disturbances and medication had similar distributions in the 2 groups. Four study group patients (8%) and 4 controls (8%) with acute coro-

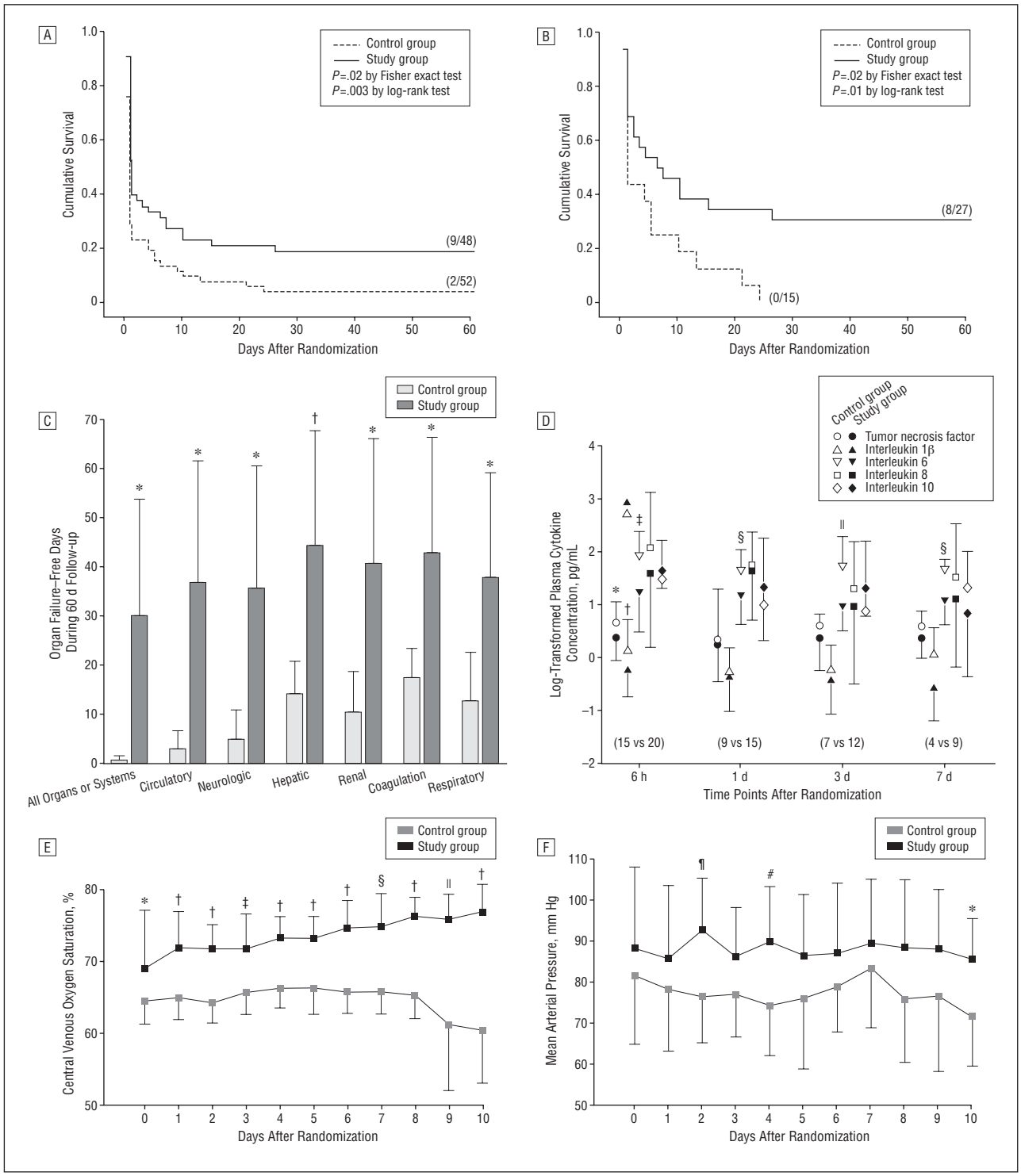

Figure 3. Main results of patient follow-up. A and B, Probability of survival to day 60 after randomization, which was identical to survival to hospital discharge, in all 100 patients (A) and in the 42 patients with postresuscitation shock (B). Numbers in parentheses are number of survivors/total number of patients. C, Organ failure–free days in patients who completed a full course of hydrocortisone sodium succinate (n=12) or isotonic sodium chloride solution placebo (n=6) according to protocol. Bars indicate mean and error bars, standard deviation. *P=.001. †P<.001. D, Plasma cytokines in postresuscitation shock. Numbers in parentheses are number of controls vs study group patients. Symbols indicate mean; error bars, standard deviation. *P=.04. †P=.06. ‡P=.003. §P=.02. ‖P=.01 (independent-samples t test). E and F, Central venous oxygen saturation (E) and mean arterial pressure (F) in postresuscitation shock. Data points indicate mean; error bars, standard deviation. *P=.03. †P<.001. ‡ P=.005. §P=.002. ‖P=.04 ¶P=.006. #P=.01 (independent-samples t test).

nary syndromes received periarrest revascularization therapy[8] (P>.99).

Post hoc analyses were conducted according to use or no use of additional epinephrine during resuscitation (Figures 1 and 2). In the additional-epinephrine subgroup, return of spontaneous circulation for 15 minutes or longer was significantly more frequent in study group patients than in controls (9 of 17 [53%] vs 6 of 29 [21%];

Table 4. Post–Cardiac Arrest Morbidity, Complications, and Causes of Death in Those Who Survived for 4 Hours or Longer

	Control Group (n=20)	Study Group (n=29)	*P* Value
Morbidity/complication, No. (%)[a]			
Cardiac arrest–associated MOF[b]	8 (40)	9 (31)	.56
Renal failure	6 (30)	9 (31)	>.99
Ventilator-associated pneumonia	4 (20)	4 (14)	.70
Extubation failure	3 (15)	5 (17)	>.99
ARDS[c]	2 (10)	5 (17)	.69
Heparin-induced thrombocytopenia	0 (0)	3 (10)	.26
Cardiogenic shock	0 (0)	3 (10)	.26
Peritonitis	1 (5)	2 (7)	>.99
Fungemia	0 (0)	2 (7)	.51
Other[d]	1 (5)	9 (31)	.03
Cause of death, No. (%)			
Cardiac arrest–associated MOF[b]	8 (40)	9 (31)	.56
ARDS-induced hypoxemia	1 (5)	3 (10)	.64
Recurrent myocardial ischemia	2 (10)	2 (7)	>.99
Cardiogenic shock	2 (10)	1 (3)	.56
ARDS-induced MOF	1 (5)	2 (7)	>.99
Intra-abdominal sepsis and shock	1 (5)	2 (7)	>.99
Recurrent pulmonary embolism	1 (5)	1 (3)	>.99
Lethal arrhythmia	2 (10)	0 (0)	.16

Abbreviations: ARDS, acute respiratory distress syndrome; MOF, multiple organ failure.

[a] Recorded until day 60 after randomization. Some patients experienced more than 1 complication.

[b] Defined as postresuscitation shock culminating in refractory hypotension and at least 1 new postarrest organ failure (see also the "Definitions" subsection of the "Methods" section) sustained for more than 24 hours or until death after the initial return of spontaneous circulation; refractory hypotension was defined as systolic arterial pressure less than 90 mm Hg, not responsive to norepinephrine infusion rates of 0.5 µg/kg/min or more, in the presence of central venous and/or pulmonary artery wedge pressure greater than 12 mm Hg; all patients with this complication died within 4 to 48 hours after the initial return of spontaneous circulation.

[c] Attributed to bilateral, intensive care unit–acquired pneumonia in 2 study group patients and 1 control.

[d] Includes 2 cases of urinary tract infection, 2 cases of pneumothorax, and 1 case each of tracheal laceration, hemorrhagic cystitis, endocarditis, treatment-refractory atrial fibrillation, pulmonary aspiration, and hypercapnic respiratory arrest.

P=.048). Two (12%) of the study group patients survived to hospital discharge, 1 with moderate and 1 with severe cerebral disability; all 29 controls died before hospital discharge. After exclusion of 1 study group patient and 2 controls, the subgroup without additional epinephrine included 51 successfully resuscitated patients. During resuscitation, the 30 study group patients had a significantly greater total number of "potentially reversible" major disorders (eg, hypoxemia, hyperkalemia, hypovolemia)[8] per patient than the 21 controls (median [IQR], 1.0 [0.8-2.0] vs 0.0 [0.0-1.0]; *P*=.01) (Table S3 of the online material). Seven (23%) of the 30 study group patients (6 with good cerebral performance and 1 with moderate cerebral disability) and 2 (10%) of the 21 controls (both with good cerebral performance) survived to hospital discharge.

Within the first 10 days after randomization, blood glucose level was 201 mg/dL or more (to convert to millimoles per liter, multiply by 0.0555) in 325 of 1098 (29.6%) and 181 of 678 (26.7%) ICU/CCU chart recordings in the study and control groups, respectively (*P*=.19). Relative to controls, study group patients had more hyperglycemic episodes on days 2 and 3 (*P*<.001 and *P*=.01, respectively). Those who survived for more than 48 hours in the study group (n=19) and control group (n=12) developed a median (IQR) of 0.0 (0.0-2.0) and 0.0 (0.0-1.0) ICU-associated infectious complications, respectively (*P*=.64); ventilator-free days were 0.0 (0.0-42.0) and 0.0 (0.0-0.0), respectively (*P*=.21). Six study group patients (32%) and 3 controls (25%) underwent tracheostomy after weaning and/or extubation failure (*P*>.99). Among those who survived for 10 days or longer, paresis[11] was noted in 4 of 13 study group patients (31%) and 2 of 6 controls (33%) (*P*>.99).

THE HAWTHORNE EFFECT

The conduct of this study could constitute a change in the working conditions of resuscitation teams and ICU/CCU physicians and staff. This might result in enhanced productivity and improved patient outcomes (Hawthorne effect).[12] To investigate this possibility, after study completion, we retrospectively analyzed CPR and postarrest data from 93 consecutively identified patients who (1) received advanced life support[8] for refractory in-hospital cardiac arrest within the period from December 1, 2005, to May 31, 2006; (2) fulfilled the present study's enrollment criteria; and (3) were not assigned to the experimental arm of any ongoing trial. Data were collected from CPR records of the Department of Anesthesiology and from patient records and ICU/CCU charts retrieved from the hospital's archive. Data collection was conducted by 2 independent reviewers blinded to the objectives of the analysis.

Historical controls and actual control and study group patients had similar characteristics and causes of cardiac arrest (data not shown). Within 12 hours after arrest, all successfully resuscitated and surviving historical controls were admitted to the ICU or CCU. Regarding the primary end points, historical controls vs the study group had a significantly lower rate of return of spontaneous circulation for 15 minutes or longer (47 of 93 patients [51%] vs 39 of 48 [81%]; *P*<.001); this rate was similar to the rate of the actual control group (*P*>.99). Survival to hospital discharge was also similar in historical controls and the actual control group (**Figure 4**A) and significantly lower in historical controls than in the study group (Figure 4B). Thus, there was no Hawthorne effect on the primary outcomes of this trial.

COMMENT

The findings of this single-center study constitute the first evidence, to our knowledge, of increased efficacy of adding vasopressin and methylprednisolone to epinephrine during CPR and treating postresuscitation shock with stress-dose hydrocortisone.

Methylprednisolone was chosen for initial treatment because it enhances the contractile function of both the heart during and after myocardial ischemia[13] and the peripheral arteries during endotoxemia.[14] Myocardial dysfunction[15] and sepsislike vasoplegia[6] are key components of early postresuscitation shock.[6,15] The early cardiovascular effects of the methylprednisolone dose used may be partly

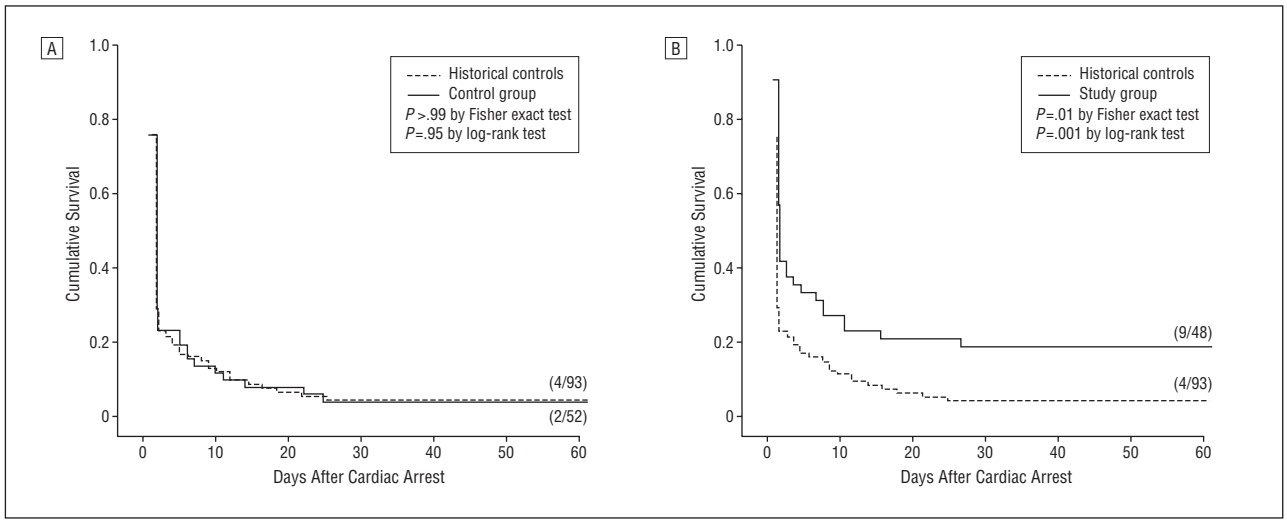

Figure 4. Probability of survival to day 60 after randomization, which was identical to survival to hospital discharge, in historical controls vs actual controls (A) and study group patients (B). Numbers in parentheses are number of survivors/total number of patients.

nongenomic[16,17] and are expected within 30 to 60 minutes after administration.[16,17] Thus, the results on arterial pressure during CPR (Table 3) are explained mainly by the combined and simultaneous vasopressin-epinephrine action. Increased mean arterial pressure suggests improved coronary perfusion,[18] facilitating restoration of spontaneous cardiac rhythm. This explains the more frequent return of spontaneous circulation.[5,19]

Hydrocortisone was chosen for postresuscitation shock for its vascular[17,20] and immune[21,22] modulatory effects. In postresuscitation shock, study group results on cytokine levels indicate attenuation of the systemic inflammatory response. Furthermore, mean arterial pressure was higher during the early and late postresuscitation periods (Table 3 and Figure 3F). Central venous oxygen saturation was also higher for more than 72 hours after resuscitation (Figure 3E). These results indicate improved hemodynamics and peripheral oxygen supply-demand balance[23] and can thus explain the observed increase in organ failure–free days and improved survival in this severe sepsislike syndrome.[6,23-25]

According to post hoc analysis, our new CPR-drug combination resulted in a 2.2-fold increase in the frequency of rapid successful resuscitation. This was associated with halving of the death risk, thus implying an additional potential mechanism for survival improvement. Also, the treatment of postresuscitation shock with a full course of hydrocortisone resulted in a 6.7-fold reduction of death risk, suggesting combined benefit of vasopressin-epinephrine and corticosteroids in refractory cardiac arrest followed by postresuscitation shock.

The use of postarrest therapeutic hypothermia was limited mainly to ventricular fibrillation cardiac arrest[8] and was similar in the control group and the study group (15% vs 18% of successfully resuscitated patients; $P > .99$). Finally, our results are most likely generalizable because (1) our experimental treatment comprises the addition of widely available and widely used drugs during and after CPR; (2) the studied population had a broad case mix with primarily cardiovascular disease (Table 1)[2]; and (3) major periarrest factors (ie, frequency of primary cardiac causes of cardiac arrest and of witnessed arrest, resuscitation team response times, and leading initial cardiac rhythm) were similar in this trial and a preceding 3-center trial of in-hospital cardiac arrest.[2]

Thirty study group patients (as opposed to just 21 controls) were successfully resuscitated without additional epinephrine. This could be regarded as a between-group imbalance biasing the study results. However, our post hoc analyses showed that, during advanced life support, the study group patients who received no additional epinephrine had more potentially reversible major disorders[8] than did controls. These disorders (eg, hypoxemia, hyperkalemia, and hypovolemia) are considered causes of failed or prolonged resuscitation.[8] Consequently, the aforementioned imbalance was probably due to a more rapid and favorable response of more severely ill study group patients to a superior treatment.

The contribution of the subgroup who received additional epinephrine to the positive study results was relatively minor: only 2 of 17 study group patients (12%) survived, with moderate to severe neurologic deficits. For this subgroup (n=46), the determination of an experimental treatment–related rise in survival from 2% to 8% (with $\alpha = .05$ and power=0.80) would require 86 patients or more, corresponding to a total study population of more than 180.

Results could have been similar if hydrocortisone had been used instead of methylprednisolone during CPR. We chose methylprednisolone on the basis of contemporary literature.[13] Finally, for reasons of protocol feasibility, we did not determine baseline stress hormone concentrations.

In conclusion, the results of this trial suggest that the combined use of vasopressin, epinephrine, and corticosteroids may improve by a factor of 4.5 the long-term survival after refractory in-hospital cardiac arrest. This result is supported and explained by the more frequent successful resuscitation, increased postarrest mean arterial pressure and central venous oxygen saturation, and attenuated postarrest systemic inflammatory response and organ dysfunction in the study group.

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