VASOPRESSIN, EPINEPHRINE, AND CORTICOSTEROIDS FOR INHOSPITAL CARDIAC ARREST

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ABSTRACT

Background: Cardiac arrest animal-data 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 **s**ingle-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/cardiopulmonary resuscitation-cycle) plus epinephrine (1-mg/resuscitation-cycle) (study-group, n = 48) or saline-placebo plus epinephrine (1-mg/resuscitation-cycle) (control-group, n = 52) for the first 5 resuscitation-cycles post-randomization, followed by additional epinephrine if needed. On the first resuscitation-cycle post-randomization, study-group patients received methylprednisolone (40-mg) and controls received saline-placebo. Postresuscitation shock was treated with stress-dose hydrocortisone (300-mg daily for 7 days maximum, and gradual taper) (study-group, n = 27) or saline-placebo (control-group, n = 15). Primary endpoints were return of spontaneous circulation for ≥15 min and survival to hospital discharge.

Results: Study-group patients versus controls had more frequent return of spontaneous circulation (81.3% vs. 51.9%; *P* = .003) and improved survival to hospital discharge (18.8% vs. 3.8%; *P* = .02). Study-group patients with postresuscitation shock versus corresponding controls had improved survival to hospital discharge (29.6% vs. 0.0%; *P* = .02), improved hemodynamics and central-

venous oxygen saturation, and more organ failure-free days. Adverse events were similar in the 2 groups.

Conclusions. 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.

INTRODUCTION

The incidence of in-hospital cardiac arrest is 1-5/1,000 patient admissions.[1] Survival to hospital discharge is approximately 20%.[1] Survival after refractory cardiac arrest, i.e., refractory ventricular fibrillation/pulseless ventricular tachycardia (VF/VT) or asystole/pulseless electrical activity (PEA), ranges within 5-15%.[2]

In non-survivors of cardiopulmonary resuscitation (CPR), plasma vasopressin is lower compared to 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 with vasopressin-epinephrine compared to 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, combined vasopressin-epinephrine during CPR and corticosteroid supplementation during and after CPR versus epinephrine alone during CPR and no corticosteroid 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 did 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. Patient eligibility comprised refractory cardiac arrest, defined as epinephrine requirement for VF/VT or asystole/PEA according to guidelines for resuscitation 2005.[8] Exclusion criteria were age <18 years, terminal illness[2] or do-not-resuscitate status, cardiac arrest due to exsanguination, cardiac arrest before hospital admission, pre-arrest treatment with intravenous corticosteroids, and previous enrolment in or exclusion from the current study. Consent was not obtained for the CPR-drug combination.[2] The patients' families and patients were informed about the trial.[9] Informed, written next-of-kin consent, and non-written patient consent (whenever feasible) were obtained for stress-dose hydrocortisone in postresuscitation shock and for blood sampling to determine plasma cytokines. The Scientific Council of Evaggelismos hospital approved the study.

Study Design and Protocol

We conducted a single-center, prospective, randomized, double-blind, placebo-controlled, parallel-group clinical trial.

Randomization. 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 corresponded each time to 1 of the 100 consecutively enrolled patients as his/hers code. Vasopressin and methylprednisolone were prepared by the hospital's Pharmacy in identical, preloaded 5-mL syringes and placed along with epinephrine ampoules in boxes bearing patient codes (electronic appendix). On

patient randomization, a box was opened and study-drugs were injected intravenously according to protocol. Drug injection was followed by 10 mL of normal-saline.

CPR interventions. Adult in-patients with VF/VT-induced cardiac arrest not responsive to two defibrillations separated by 2-3 min of CPR[8] or asystole/PEA were randomized to receive either combined arginine-vasopressin (20 IU/CPR-cycle; Monarch Pharmaceuticals, Bristol, TN) and epinephrine (1 mg/CPR-cycle; Demo, Athens, Greece) (study-group), or normal saline-placebo and epinephrine (1 mg/ CPR-cycle) (control-group) for the first 5 CPR-cycles post-randomization. Forty milligrams of methylprednisolone sodium succinate (Pfizer, Athens, Greece) and saline-placebo were administered during the first CPR-cycle post-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 (electronic appendix). Advanced life support was conducted according to current standards[8] (electronic appendix).

Postresuscitation shock. At 4 hours postresuscitation, surviving study-group patients with postresuscitation shock received stress-dose hydrocortisone (300 mg daily for 7 days maximum, and gradual taper; Pfizer, Athens, Greece)[10]. Hydrocortisone was available in vials containing 100 mg of hydrocortisone sodium succinate powder. Each daily dose was diluted in 100 mL of normal-saline at the hospital's Pharmacy and administered to study-group patients as a continuous infusion. On vasopressor cessation or on day 8 post-arrest, daily hydrocortisone was consecutively reduced to 200 mg, 100 mg, and discontinued (electronic appendix).

Control-group patients with postresuscitation shock received daily infusions of 100 ml saline-placebo. Normal-saline infusion-bags were bearing the patient codes.

Definitions

Circulatory failure was defined as inability to maintain mean arterial pressure >70 mm Hg (9.3 kPa) without using vasopressors after volume loading,[10] respiratory failure as ratio of arterial oxygen partial pressure-to-inspired oxygen fraction of ≤200 mm Hg, coagulation failure as platelet count of $\leq 50 \times 10^3/\mu L$ ($50 \times 10^9/L$), hepatic failure as serum bilirubin concentration of ≥6 mg/dL (102.6 μmol/L), renal failure as serum creatinine of ≥3.5 mg/dL (309.4 μmol/L) and/or requirement of renal-replacement therapy, and neurologic failure as Glasgow Coma Score of ≤9.

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

Documentation and patient follow-up

CPR-attempts were documented according to the Utstein style. Additional data comprised peri-arrest arterial pressure, gas-exchange, electrolytes, lactate, vasopressor/inotropic support, and intravenous fluids. Daily follow-up was conducted by 4 blinded investigators. Follow-up to day 60 post-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 was entered into a database by 2 investigators and independently cross-checked by another 2 investigators. Data was independently scrutinized by the Steering Committee.

Plasma Cytokine Concentrations

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

Study Endpoints

Primary endpoints were return of spontaneous circulation for ≥15 min, and survival to hospital discharge, defined as presence of attending physician discharge order either to home or to a rehabilitation facility. Secondary endpoints were arterial pressure during and 15-20 min after CPR, intensity of post-arrest systemic inflammatory response, number of organ failure-free days until follow-up completion, and cerebral performance according to the Glasgow-Pittsburgh scale at hospital discharge (see electronic appendix for details on endpoints determination).

Statistical Analysis

Initial rhythm is asystole in 75-80% 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 versus 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 alpha-value of 0.05 and a power of 0.80, estimated sample size was 68 (i.e., 34 patients/group). The inclusion of 100 patients resulted in a safety margin of 32/68 (47%).

An intention-to-treat analysis was conducted with the Statistical Package for Social Sciences (SPSS) version 12.0 (SPSS, Chicago, IL). Data are reported as mean ± standard deviation, or median (interquartile range), 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's exact test. Continuous variables were compared by a two-tailed, independent samples *t* test or the Mann-Whitney exact *U* test.

In postresuscitation shock, we used linear mixed-model analysis to determine the overall effects of group, time, and of their interaction (group∗time) on log-transformed plasma cytokine concentrations throughout the first 7 days post-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 post-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's 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's exact test to determine any non-random 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 study-group and control-group 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 two-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 37/139 (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 the first author 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 cardiac arrest causes. Study-group patients versus control-group patients had significantly higher rates of return of spontaneous circulation for ≥15 min (39/48, 81.3% vs. 27/52, 51.9%, $P = .003$) (Table 2). In the study-group, average mean arterial pressure during CPR (determined only in ICU/CCU patients with an arterial line in-place) and 15-20 min 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 postresuscitation, 27 of 29 surviving study-group patients and 15 of 20 surviving controls had postresuscitation shock and were assigned to stress-dose hydrocortisone and saline-placebo, respectively (Figure 2). Within 12 hours post-arrest, all surviving patients were in the ICU or CCU. Survival to hospital discharge was significantly higher in the study-group compared to control-group (9/48, 18.8% vs. 2/52, 3.8%; P = .02 by Fisher's exact test) (Figure 3A; P = .003 by log-rank test). Multivariate Cox regression analysis revealed that independent risk factors for death were assignment to study-group and completion of a full post-arrest course of hydrocortisone according to protocol (relative risk: 0.15, 95% confidence interval: 0.06-0.38; P < .001), peri-arrest lactate (see also Table 3, footnote) (relative risk: 1.07, 95% confidence interval: 1.02-1.11; P = .003), and successful resuscitation after ≤3 CPR-cycles (relative risk: 0.49, 95% confidence interval: 0.29-0.83; P = .008). *Post hoc* analysis revealed that "fast" (i.e., lasting for ≤3 CPR-cycles) successful resuscitation was more frequent in the study-group compared to control-group (22/48, 45.8% vs. 11/52, 21.2%, P = .01).

Full follow-up data were obtained for all CPR survivors. In survivors for ≥4 hours, prescribed medication was similar, except vasopressor use throughout follow-up, which was significantly lower in the study-group (P = .002) (electronic appendix). All-organ failure-free days were 0.0 (0.0-36.0) and 0.0 (0.0-0.0) in the study-group and control-group, respectively (P = .27). Post-arrest morbidity, complications, and death causes were similar in both groups (Table 4). For the 11 long-term survivors, ICU/CCU and hospital discharge occurred at 37.6 ± 27.4 and 58.8 ± 31.2 days post-arrest, respectively.

Follow-up in postresuscitation shock

Study-group patients with postresuscitation shock versus corresponding controls had significantly improved survival to hospital discharge (8/27, 29.6% vs. 0/15, 0.0%; *P* = .02 by Fisher's exact test) (Figure 3B; *P* =.01 by log-rank test), a trend toward significantly more all-organ failure-free days [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) versus corresponding controls (n = 6) had significantly more all-organ, circulatory, neurologic, hepatic, renal, coagulation, and respiratory failure-free days (*P* = .001-.04) (Figure 3C).

Linear mixed-model analysis revealed significant effects of group on log-transformed plasma IL-6 (*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 (*P* <.001), daily norepinephrine infusion-rate (*P* = .004), and positivity of daily fluid balance (*P* = .001) (electronic appendix)..

Plasma IL-6 was significantly lower in the study-group compared to control-group throughout the first week post-randomization (*P* = .002-.02). Six hours post-randomization, plasma TNF-a was significantly lower (*P* = .04) and plasma IL-1-β 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 compared to control-group throughout the first 10 days (*P* < .001 to = .04) and at days 3, 5, and 10 (*P* = .006-.03) post-randomization, respectively (Figure 3E and 3F). Arterial oxygen saturation,

hemoglobin concentration, and dobutamine and epinephrine daily infusion-rates were similar in the two groups (data not shown).

Additional analyses (see also electronic appendix)

Pre-arrest physiological disturbances and medication had similar distributions in the 2 groups. Four study-group patients (8.3%) and 4 controls (7.7%) with acute coronary syndromes received peri-arrest revascularization therapy[8] ($P = 1.00$).

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 min was significantly more frequent in study-group patients versus controls (9/17, 52.9% vs. 6/29, 20.7%; $P = .048$). Two (11.8%) 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. Following exclusion of 1 study-group patient and 2 controls (electronic appendix), the "no-additional-epinephrine" subgroup included 51 successfully resuscitated patients. During resuscitation, the 30 study-group patients had a significantly greater total number of "potentially reversible" major disorders (e.g. hypoxemia, hyperkalemia, hypovolemia, etc.)[8] per patient versus the 21 controls [1.0 (0.8-2.0) vs. 0.0 (0.0-1.0), $P = .01$] (see Table S3 of electronic appendix). Seven (23.3%) of the study-group patients (6 with good cerebral performance and 1 with moderate cerebral disability) and 2 (9.5%) of the controls (both with good cerebral performance) survived to hospital discharge.

Within the first 10 days postrandomization, blood glucose was ≥201 mg/dL (11.1 mmol/L) in 325 of 1,098 (29.6%) and 181 of 678 (26.7%) ICU/CCU chart recordings of the study-group and control-group, respectively ($P = .19$). Relative to controls, study-group patients had more hyperglycemic episodes on days 2 and 3 ($P < .001$ and

= .01, respectively). Survivors for >48 hours of the study-group (n = 19) and control-group (n = 12) developed 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 (31.6%) and 3 controls (25.0%) were tracheostomized after weaning and/or extubation failure (*P* = 1.00). Regarding survivors for ≥10 days, paresis[11] was noted in 4 of 13 study-group patients (23.1%) and 2 of 6 controls (33.3%) (*P* = 1.00).

The Hawthorne effect.

The present study's conduct 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 post-arrest data from 93 consecutively identified patients, who 1) received advanced life support[8] for refractory in-hospital cardiac arrest within the period extending 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 was 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 two independent reviewers blinded to the objectives of the analysis.

Historical controls and actual control/study group patients had similar characteristics and cardiac arrest causes (data not shown). Within 12 hours post-arrest, all successfully resuscitated and surviving historical controls were admitted to the ICU or CCU. Regarding the primary endpoints, historical controls versus study-group had a significantly lower rate of return of spontaneous circulation for ≥15 min (47/93, 50.5% vs. 39/48, 81.3%, *P* < .001); this rate was similar to the rate of the actual

control-group (P = 1.00). Survival to hospital discharge was also similar in historical controls and actual control-group (Figure 4A), and significantly lower in historical controls compared to 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 for 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 both the contractile function of the heart during and after myocardial ischemia[13] and of the peripheral arteries during endotoxemia.[14] Myocardial dysfunction[15] and sepsis-like vasoplegia[6] are key components of early postresuscitation shock.[6,15] The early cardiovascular effects of the employed methylprednisolone dose may be partly nongenomic,[16,17] and are expected within 30-60 min following 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 cytokines 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 >72

hours postresuscitation (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 sepsis-like 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 "fast" successful resuscitation. This was associated with halving of 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 post-arrest therapeutic hypothermia was limited mainly to VF cardiac arrest,[8] and was similar in the control-group compared to study-group (14.8% vs. 17.9% of successfully resuscitated patients, $P = 1.00$). Lastly, our results are most likely transportable, because 1) our experimental treatment comprises the addition of widely available and used drugs during and after CPR; 2) the studied population had a broad case-mix with primarily cardiovascular pathology (Table 1);[2] and 3) major peri-arrest factors (i.e., 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 three-center trial of in-hospital cardiac arrest.[2]

Limitations

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 "no-additional-epinephrine" study-group patients had more "potentially reversible" major disorders[8] compared to controls. These disorders (e.g. hypoxemia, hyperkalemia, hypovolemia, etc.) are actually considered as causes for failed or prolonged resuscitation.[8] Consequently, the aforementioned imbalance was probably due to a more rapid and favorable response of more severe study-group patients to a superior treatment.

The contribution of the "additional-epinephrine" subgroup to the positive study-results was relatively minor: only 2 of 17 study-group patients survived with, moderate-to-severe neurological deficits. For this subgroup (n = 46), the determination of an experimental treatment-related rise in survival from 2% to 8% (with alpha = 0.05 and power = 0.80) would require ≥86 patients, corresponding to a total study-population of >180.

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

CONCLUSIONS

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 post-arrest mean arterial pressure and central-venous oxygen saturation, and attenuated post-arrest systemic inflammatory response and organ dysfunction in the study-group.

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Study Organization. *Study Chairpersons:* Spyros D. Mentzelopoulos (principal investigator); Spyros G. Zakynthinos (study director); Charis Roussos (study chair).

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FIGURE LEGENDS

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

Figure 2. Study Flowchart.

VF/VT, ventricular fibrillation/ventricular tachycardia; DC, direct current; ROSC, return of spontaneous circulation; CPR, cardiopulmonary resuscitation; Parentheses, number of patients with postresuscitation shock receiving saline-placebo or hydrocortisone/total number of surviving patients at that particular time point.

Figure 3. Main results of patient follow-up.

A, B: Probability of survival to day 60 post-randomization, which was identical to survival to hospital discharge, in all 100 patients (A) and in the 42 patients with postresuscitation shock (B). Parentheses, survivors/total number of patients.

C: Organ failure-free days in patients who completed a full course of hydrocortisone (n = 12) or saline-placebo (n = 6) according to protocol. Bars, mean; Error-bars, standard deviation; *, $P = .001$; †, $P < .001$.

D: Plasma-cytokines in postresuscitation shock. Parentheses, numbers of controls vs. study-group patients; Symbols, mean; Error-bars, standard deviation; *, $P = .04$; †, $P = .003$; §, $P = .02$; #, $P = .01$; ‡, $P = .06$ (independent-samples *t* test).

E, F: Central-venous oxygen saturation (E) and mean arterial pressure (F) in postresuscitation shock. Dots, mean; Error-bars, standard deviation. *, $P = .03$; †, $P < .001$; §, $P = .006$; #, $P = .005$; ‡, $P = .01$; **, $P = .002$; ††, $P = .04$ (independent-samples *t* test).

1 mm Hg = 0.133 kPa

Figure 4. Probabilty of survival to day 60 post-randomization, which was identical to survival to hospital discharge, in historical controls versus actual controls (A) and study-group (B). Parentheses, survivors/total number of patients.

632 **Table 1. Patient characteristics before cardiac arrest and causes of cardiac**
633 **arrest.**

Characteristic	Control group (n = 52)	Study group (n = 48)
Age – yr	69.2 ± 17.7	65.4 ± 17.6
Male sex – no. (%)	29 (55.8)	30 (62.5)
Body-mass index - kg/m^2	25.3 ± 4.7	27.3 ± 8.6
Pre-arrest hospital stay – days	3.4 ± 4.2	3.9 ± 3.5
Cardiovascular history – no. (%)		
Hypertension	33 (63.5)	31 (64.6)
Coronary artery disease	18 (34.6)	21 (43.8)
Diabetes	15 (28.8)	14 (29.2)
Cardiac conduction disturbances	5 (9.6)	4 (8.3)
Cardiac arrhythmia	4 (7.7)	4 (8.3)
Valvular heart disease	4 (7.7)	4 (8.3)
Peripheral vascular disease	8 (15.4)	11 (22.9)
Other chronic comorbidity-no. (%) *	33 (63.5)	32 (66.7)
Hospital Admission Cause – no. (%) †		
Acute cardiovascular disease	26 (56.5)	20 (41.7)
Acute respiratory disease	7 (13.5)	8 (16.7)
Acute renal disease	4 (7.7)	1 (2.1)
Acute digestive disease	3 (5.8)	4 (8.3)
Acute neurologic disease	1 (1.9)	6 (12.5)
Malignancy	6 (11.5)	7 (14.6)
Trauma	5 (9.6)	9 (18.8)
Other	2 (3.8)	4 (8.3)
Cause of cardiac arrest-no.(%) §		
Acute coronary syndrome	12 (23.1)	12 (25.0)
Cardiogenic shock	4 (7.7)	5 (10.4)
Lethal arrhythmia	3 (5.8)	2 (4.2)

Hypoxemia-pulmonary edema	7 (13.5)	2 (4.2)
Cardiac tamponade	1 (1.9)	0 (0.0)
Hypoxemia-pneumonia	10 (19.2)	8 (16.7)
Hypoxemia-COPD exacerbation	2 (3.8)	1 (2.1)
Pulmonary embolism	6 (11.5)	10 (20.8)
Septic shock	4 (7.7) #	3 (6.3) ‡
Electrolyte disturbances	6 (11.5)	2 (4.2)
Tension pneumothorax-hemothorax	1 (1.9)	3 (6.3)
Hypovolemia	3 (6.3)	3 (6.3)
Other	1 (1.9)	4 (8.3)

COPD denotes chronic obstructive pulmonary disease.

* Includes chronic respiratory, neurologic, digestive, renal, and musculoskeletal disease, malignancy, and immunosuppression.

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

§ In some patients, there were more than 1 major disturbances precipitating the cardiac arrest; "other" causes included 2 cases of drug toxicity, and 1 case of vagotonic arrest, intracerebral hemorrhage, and tension hydrothorax.

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

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

652 **Table 2. Documentation of cardiopulmonary resuscitation procedures.**

	Control group (n = 52)	Study group (n = 48)	*P* value
Location of Cardiac Arrest - no. (%)			
Ward	25 (48.1)	21 (43.8)	.69
Intensive care unit or coronary care unit	14 (26.9)	17 (35.4)	.39
Emergency department	10 (19.2)	8 (16.7)	.80
Operating room	3 (5.8)	2 (4.2)	1.00
Initial Rhythm - no. (%)			
Ventricular fibrillation/tachycardia	7 (13.5)	7 (14.6)	1.00
Asystole	31 (59.6)	30 (62.5)	.84
Pulseless electrical activity	14 (26.9)	11 (22.9)	.82
Witnessed arrest – no. (%)	43 (82.7)	38 (79.2)	.80
Time to ALS initiation in witnessed arrest – min	1.1 ± 1.0	1.0 ± 0.9	.56
ALS duration - min	31.2 ± 29.9	25.1 ± 23.6	.27
Not intubated at arrest – no. (%) *	36 (69.2)	34 (70.8)	1.00
Number of cardiopulmoanry resuscitation cycles †	8.0 ± 7.5	6.4 ± 5.6	.26
Number of defibrillations	0.7 ± 1.9	0.5 ± 1.2	.47
Rate of ROSC ≥ 15 min – no. (%)	27 (51.9)	39 (81.3)	.003
Medication §			
Vasopressin - IU	0.0 ± 0.0	73.3 ± 30.1	
Epinephrine - mg	7.8 ± 7.0	6.3 ± 5.8	.26
Methylprednisolone – mg	0.0 ± 0.0	40.0 ± 0.0	
Atropine – mg	2.9 ± 0.6	2.7 ± 0.9	.26
Amiodarone – mg #	0.0 (0.0-300.0)	0.0 (0.0-300.0)	.27
Bicarbonate – mmol	27.7 ± 32.3	25.3 ± 32.0	.71
Calcium – mmol	1.3 ± 2.6	1.1 ± 2.8	.68
Magnesium - mmol	0.3 ± 1.6	0.2 ± 1.2	.61
Reverse tissue-type plasminogen activator – mg #	0.0 (0.0-100.0)	0.0 (0.0-100.0)	.73
Crystalloids – mL	120 (80-200)	100 (60-190)	.14
Colloids - mL #	0 (0-1000)	0 (0-2000)	.59
Packed red blood cells – units #	0.0 (0.0-5.0)	0.0 (0.0-5.0)	.81
Fresh frozen plasma – units #	0.0 (0.0-2.0)	0.0 (0.0-0.0)	.50
Temporary pacing – no. (%)	2 (3.8)	3 (6.3)	.67

653

654 ALS, advanced life support; ROSC, return of spontaneous circulation.

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

† The average duration of cardiopulmonary resuscitation cycles was 3.9 ± 0.4 min and was determined from the recorded time intervals between the intermittent administrations of the study drugs during the first 5 cycles following randomization or epinephrine after the first 5 cycles following randomization (see also Figure 1).

§ All drugs were injected exclusively intravenously either via a central venous catheter (intensive or coronary care unit patients), or via a 14, 16, or 18 gauge peripheral venous catheter. A functional intravenous line was present prior to the cardiac arrest in all but 2 controls and 3 study-group patients. In all these 5 cases, an intravenous line was started within 1 min after the confirmation of asystole.

Data presented as median (range).

680 **Table 3. Physiological variables during and 15-20 min after cardiopulmonary**
681 **resuscitation (CPR).**

682

Variable	Control group (n = 52)	Study group (n = 48)	*P* value
During resuscitation			
Systolic arterial pressure - mm Hg *	74.6 ± 21.2	105.9 ± 28.5	.002
Mean arterial pressure - mm Hg *	54.5 ± 16.5	72.0 ± 17.9	.009
Diastolic arterial pressure - mm Hg *	44.5 ± 14.5	55.0 ± 14.4	.05
PaO_2 - mm Hg †	91.9 ± 57.6	109.1 ± 111.3	.47
$PaCO_2$ - mm Hg †	56.2 ± 16.8	55.6 ± 32.6	.94
Arterial pH †	7.07 ± 0.17	7.06 ± 0.20	.80
Potassium ion - mEq/L †	5.6 ± 1.2	5.4 ± 1.8	.65
Sodium ion - mEq/L †	144.6 ± 10.2	140.0 ± 10.8	.08
Calcium ion - mEq/L †	2.2 ± 1.2	2.0 ± 0.6	.18
Glucose - mg/dL †	262.9 ± 75.0	286.6 ± 183.1	.55
After return of spontaneous circulation			
Systolic arterial pressure - mm Hg §	106.1 ± 34.6	131.2 ± 50.4	.03
Mean arterial pressure - mm Hg §	73.8 ± 23.6	92.9 ± 35.4	.02
Diastolic arterial pressure - mm Hg §	57.7 ± 20.0	73.8 ± 29.3	.02
Heart rate - beats/min §	117.9 ± 26.3	112.4 ± 29.8	.45
PaO_2 - mm Hg §	142.4 ± 89.6	193.7 ± 137.2	.07
$PaCO_2$ - mm Hg §	46.2 ± 17.6	42.8 ± 22.3	.52
Arterial pH §	7.25 ± 0.15	7.22 ± 0.18	.49
Potassium ion - mEq/L §	4.7 ± 1.0	4.7 ± 1.4	.96
Sodium ion - mEq/L §	141.9 ± 10.2	142.8 ± 11.4	.73
Calcium ion - mEq/L §	2.2 ± 1.6	2.2 ± 1.2	.67
Glucose - mg/dL §	278.3 ± 83.3	281.9 ± 144.1	.91
Peri-arrest Lactate - mmol/L #	10.2 ± 5.2	9.9 ± 5.8	.78
Norepinephrine - µg/kg/min §, ‡	0.5 ± 0.4	0.5 ± 0.4	.92
Dobutamine - µg/kg/min §, ‡	0.0 (0.0-10.0)	0.0 (0.0-4.0)	.44
Epinephrine - µg/kg/min §, ‡	0.0 (0.0-0.0)	0.0 (0.0-0.1)	.47
Intravenous fluids - mL **	130 (110-230)	130 (90-330)	.39

683

684 PaO_2 and $PaCO_2$, arterial partial pressure of oxygen and carbon dioxide, respectively.

* 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 5-15 minutes of CPR and resulting mean values were analyzed.

† Data are from 40 control-group and 26 study-group patients, who received more than 3 cardiopulmonary resuscitation cycles.

§ Data are from 27 control-group and 39 study-group patients, who were successfully resuscitated. Invasive blood pressure measurements were averaged over the 5-min period mentioned in the Table's legend. Noninvasive blood pressure measurements were taken every 60 sec during the aforementioned 5-min period and averaged. Only mean values of blood pressure measurements were analyzed.

Arterial blood gas analysis-derived lactate concentrations during cardiopulmonary resuscitation or 15-20 min after 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 two lactate concentration values was used in the presented analysis.

‡ Data are from individual average infusion rates recorded during the 5-min period mentioned in the Table's legend.

** Refers to cumulative administered volume of crystalloids, colloids, packed red blood cells and fresh frozen plasma from the onset of CPR to 15 min following return of spontaneous circulation.

1 mm Hg = 0.133 kPa. For Potassium and Sodium: 1 mEq/L = 1 mmol/L. For Calcium: 2 mEq/L = 1 mmol/L. For Glucose: 1 mg/dL = 0.0555 mmol/L.

Table 4. Post-arrest morbidity and complications, and causes of death in survivors for 4 hours or more.

	Control group (n = 20)	Study group (n = 29)	*P* value
Morbidity/Complications*- no. (%)			
Cardiac arrest-associated MOF †	8 (40.0)	9 (31.0)	.56
Renal failure	6 (30.0)	9 (31.0)	1.00
Ventilator-associated pneumonia	4 (20.0)	4 (13.8)	.70
Extubation failure	3 (15.0)	5 (17.2)	1.00
ARDS §	2 (10.0)	5 (17.2)	.69
Heparin-induced thrombocytopenia	0 (0.0)	3 (10.3)	.26
Cardiogenic shock	0 (0.0)	3 (10.3)	.26
Peritonitis	1 (5.0)	2 (6.9)	1.00
Fungemia	0 (0.0)	2 (6.9)	.51
Other #	1 (5.0)	9 (31.0)	.03
Causes of Death - no. (%)			
Cardiac arrest-associated MOF †	8 (40.0)	9 (31.0)	.56
ARDS-induced hypoxemia	1 (5.0)	3 (10.3)	.64
Recurrent myocardial ischemia	2 (10.0)	2 (6.9)	1.00
Cardiogenic shock	2 (10.0)	1 (3.4)	.56
ARDS-induced MOF	1 (5.0)	2 (6.9)	1.00
Intraabdominal sepsis and shock	1 (5.0)	2 (6.9)	1.00
Recurrent pulmonary embolism	1 (5.0)	1 (3.4)	1.00
Lethal arrhythmia	2 (10.0)	0 (0.0)	.16

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

* Recorded until day 60 following randomization. Some patients experienced more than one complications.

†, Defined as postresuscitation shock culminating into refractory hypotension and at least 1 new post-arrest organ failure (see also subsection "Definitions" of main text)

sustained for >24 hours or until death after the initial return of spontaneous circulation; refractory hypotension was defined as systolic arterial pressure <90 mm Hg, not responsive to norepinephrine infusion rates of ≥0.5/μg/kg/min, in the presence of central venous and/or pulmonary artery wedge pressure of >12 mm Hg; all patients with this complication died within 4-48 hours after the initial return of spontaneous circulation.

§, Attributed to bilateral, intensive care unit-acquired pneumonia in 2 study-group patients and 1 control.

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

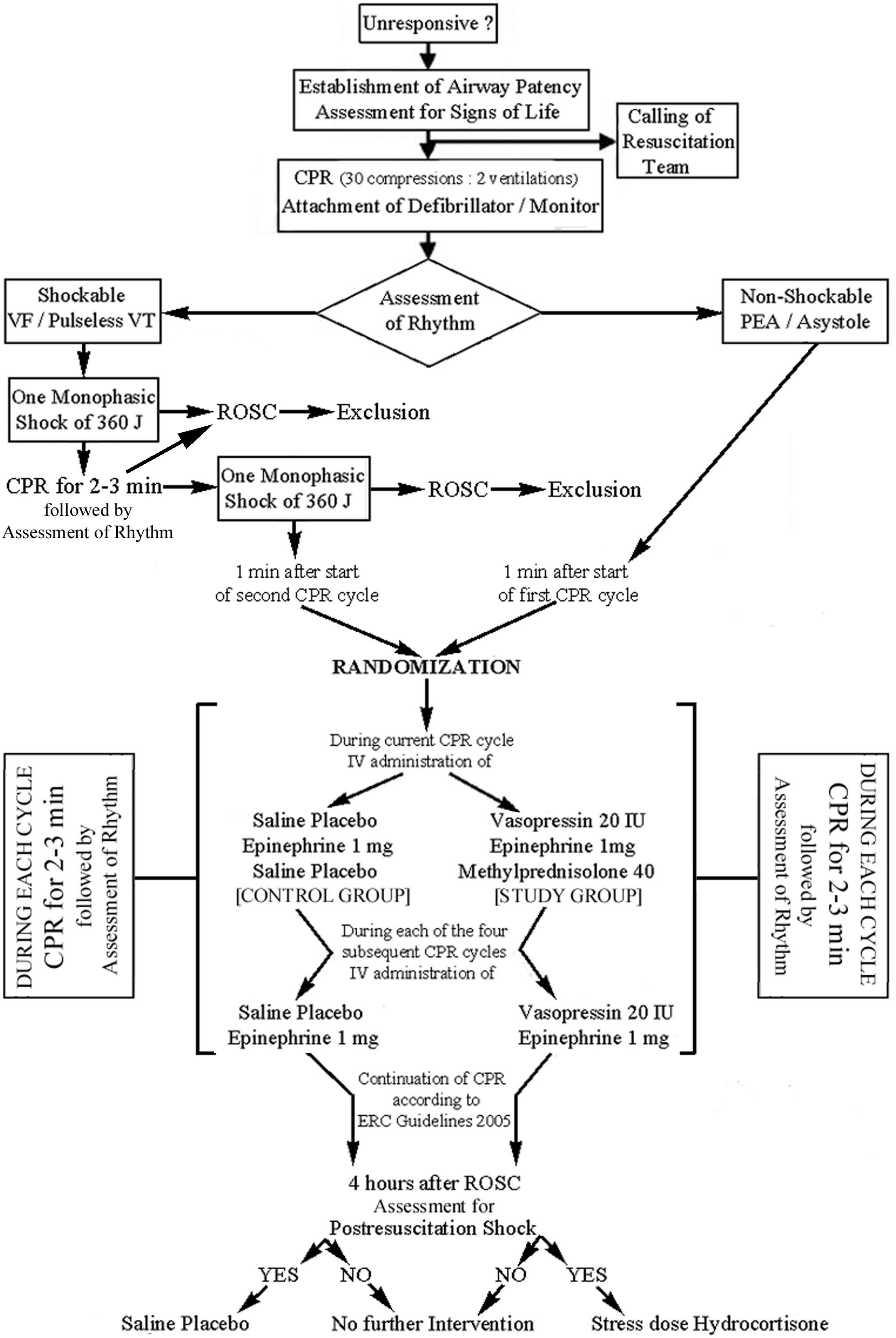

Unresponsive ?
Establishment of Airway Patency
Assessment for Signs of Life
Calling of Resuscitation Team
CPR (30 compressions : 2 ventilations)
Attachment of Defibrillator / Monitor
Assessment of Rhythm
Shockable VF / Pulseless VT
Non-Shockable PEA / Asystole
One Monophasic Shock of 360 J
ROSC
Exclusion
CPR for 2-3 min
followed by
Assessment of Rhythm
One Monophasic Shock of 360 J
ROSC
Exclusion
1 min after start of second CPR cycle
1 min after start of first CPR cycle
RANDOMIZATION
DURING EACH CYCLE
CPR for 2-3 min
followed by
Assessment of Rhythm
During current CPR cycle
IV administration of
Saline Placebo
Epinephrine 1 mg
Saline Placebo
[CONTROL GROUP]
Vasopressin 20 IU
Epinephrine 1mg
Methylprednisolone 40
[STUDY GROUP]
During each of the four subsequent CPR cycles
IV administration of
Saline Placebo
Epinephrine 1 mg
Vasopressin 20 IU
Epinephrine 1 mg
Continuation of CPR according to ERC Guidelines 2005
DURING EACH CYCLE
CPR for 2-3 min
followed by
Assessment of Rhythm
4 hours after ROSC
Assessment for
Postresuscitation Shock
YES
NO
NO
YES
Saline Placebo
No further Intervention
Stress dose Hydrocortisone

Figure 1

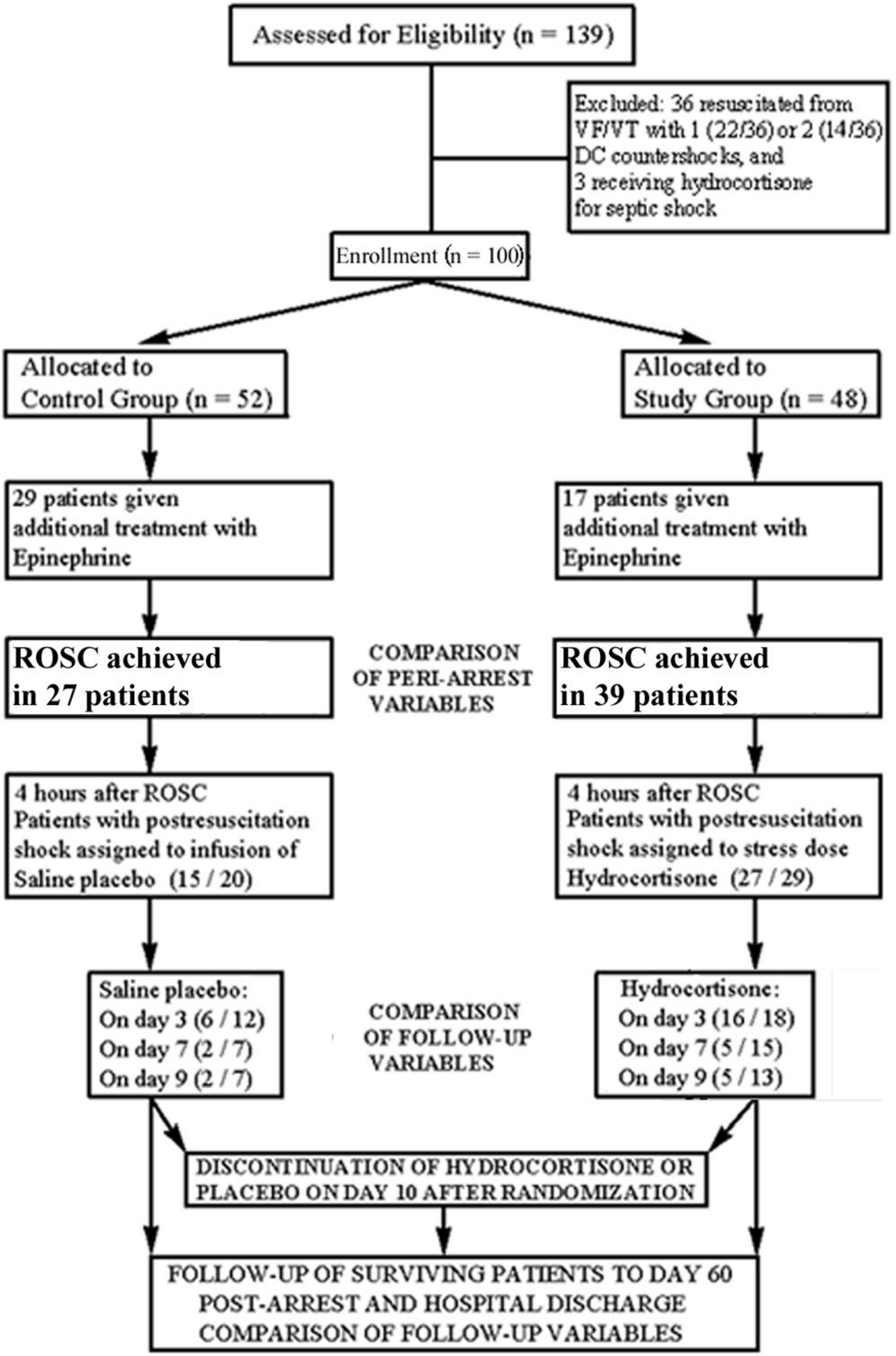
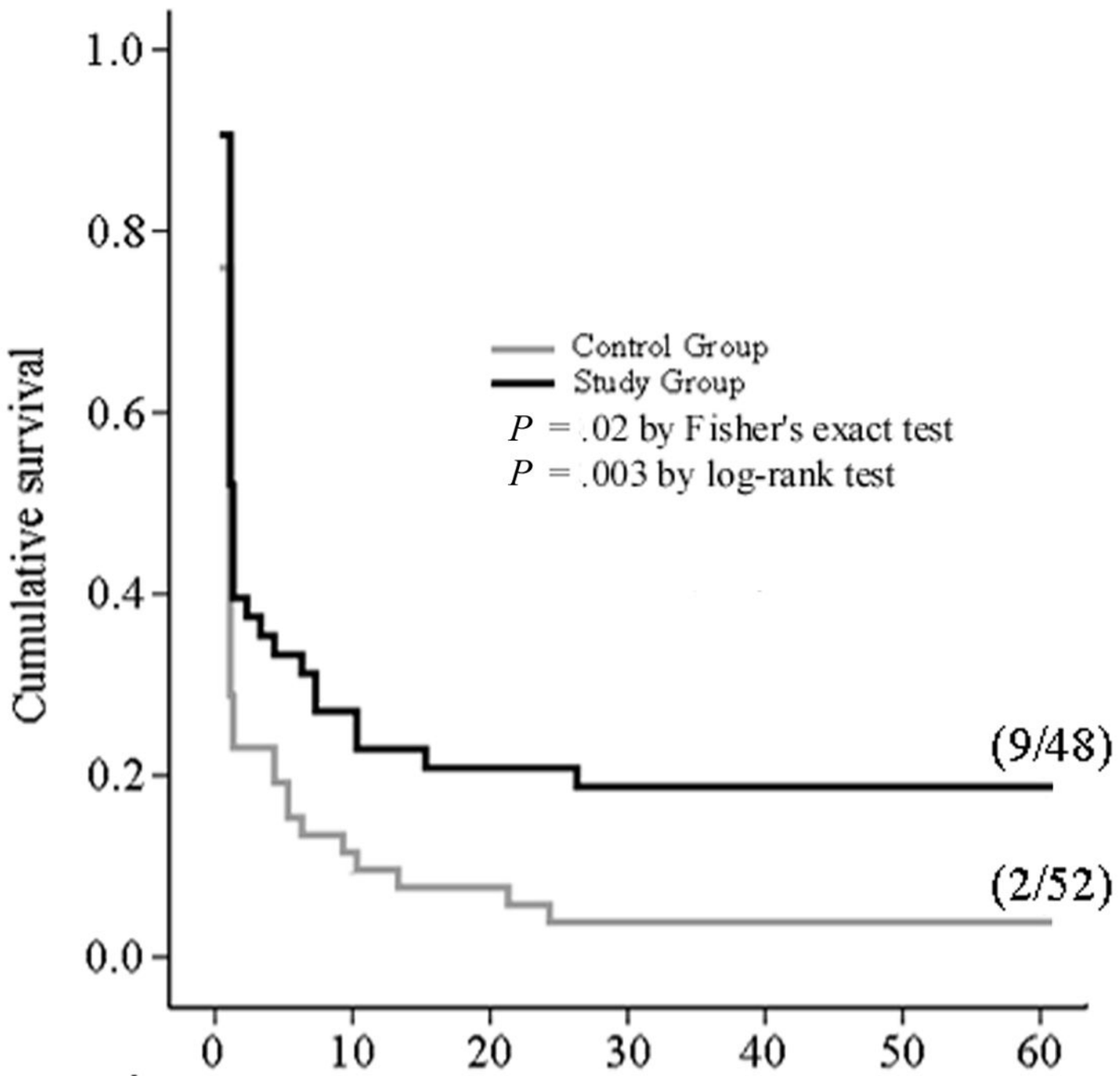
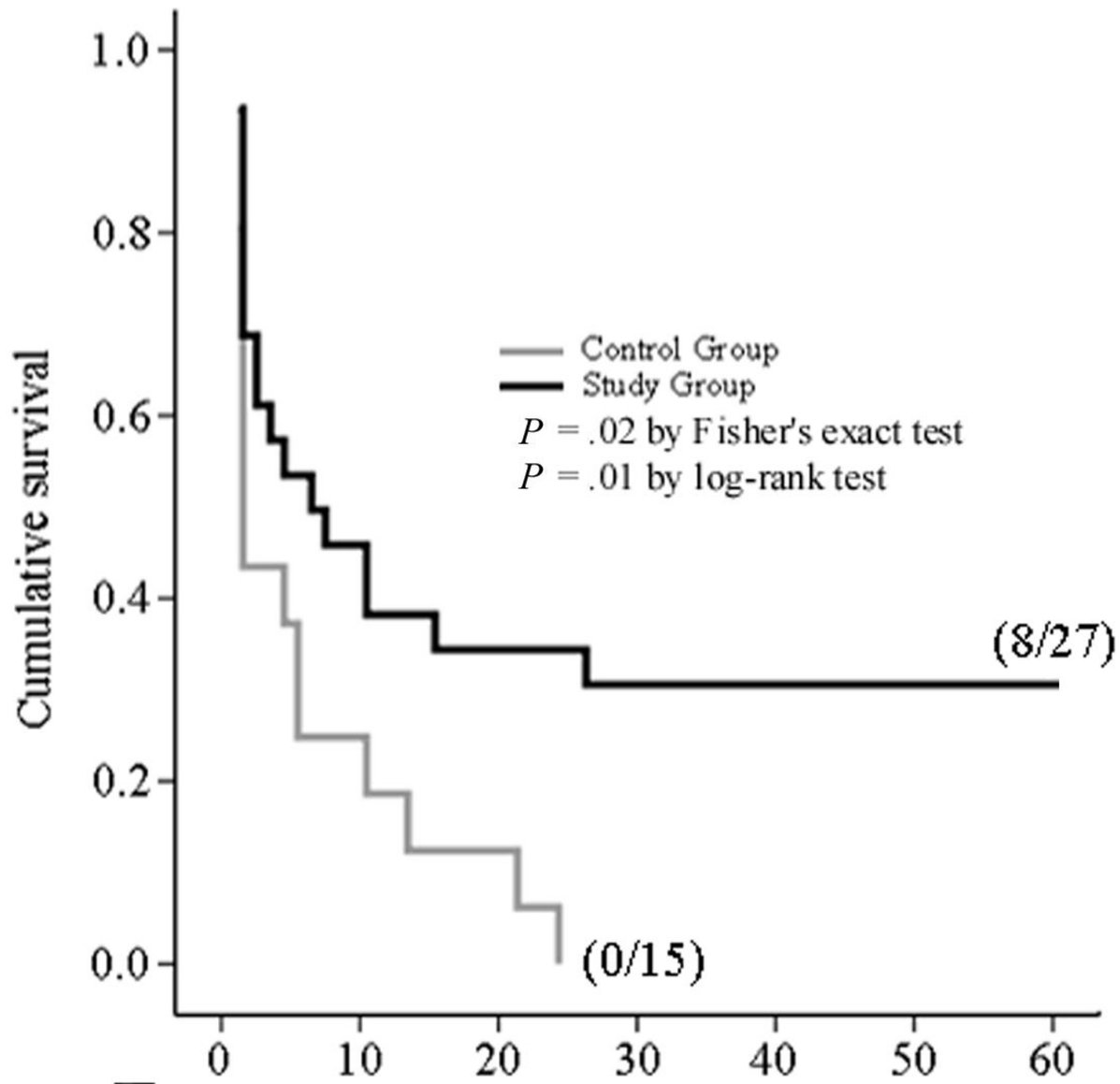
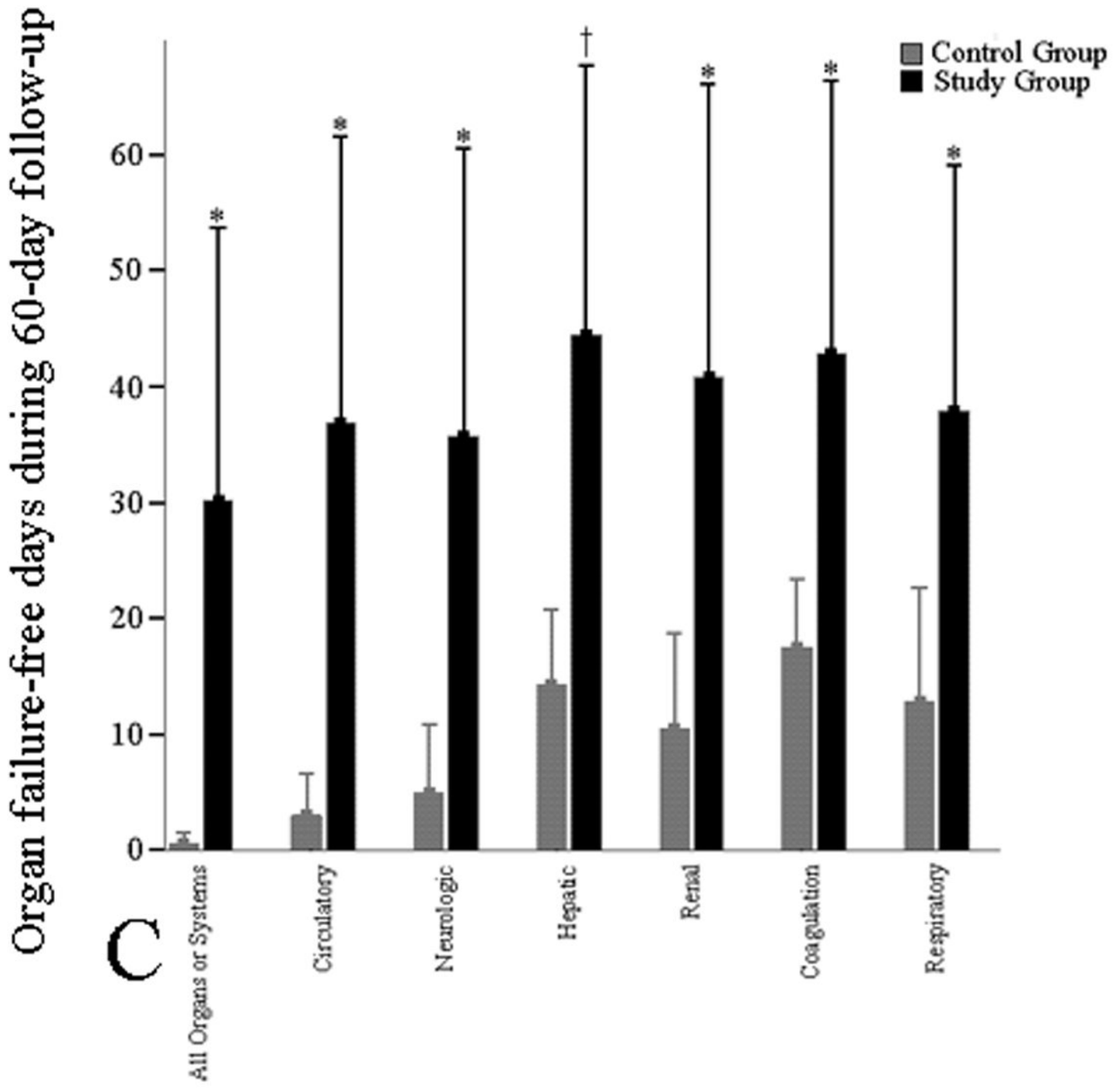
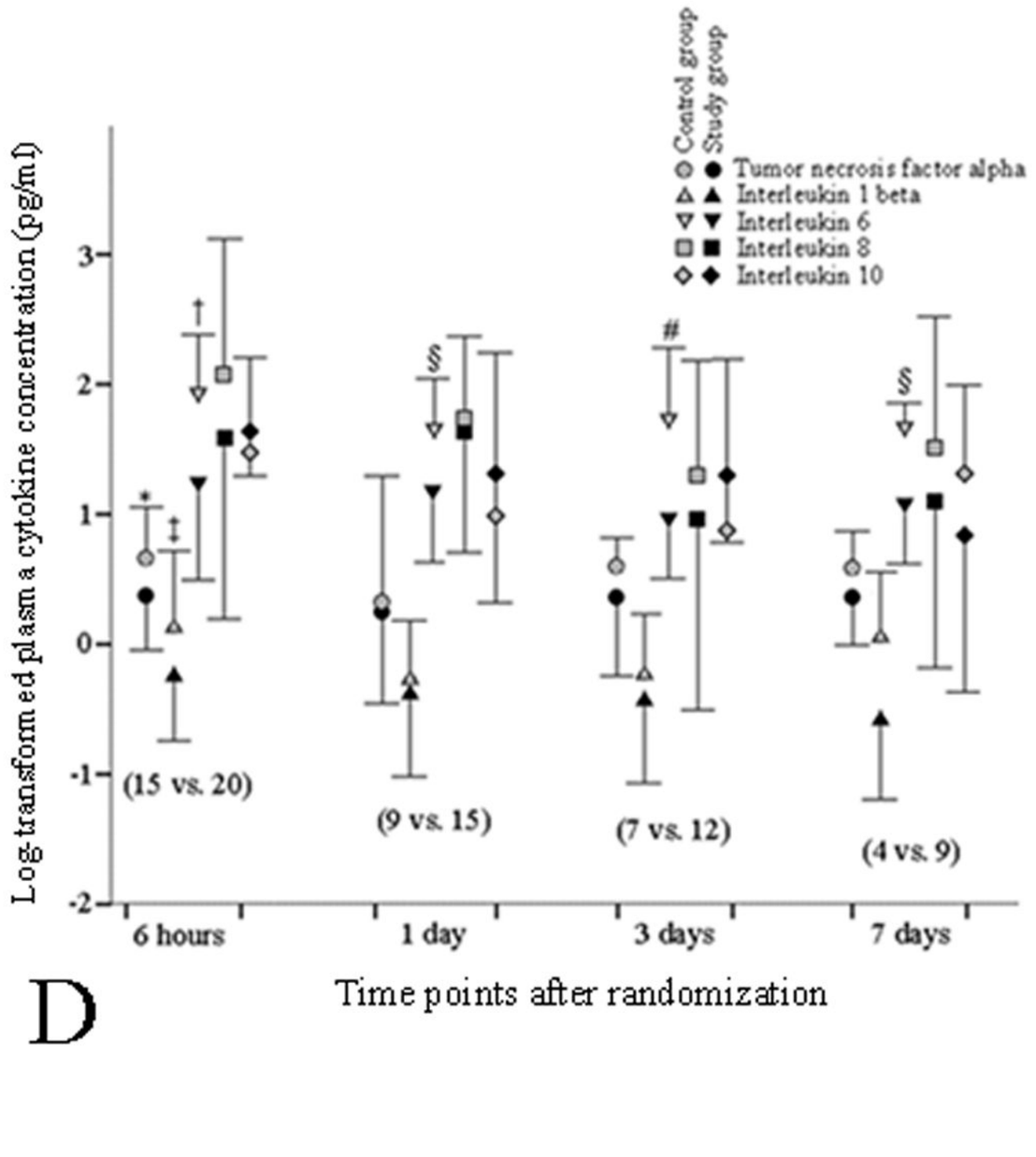

Assessed for Eligibility (n = 139)
Excluded: 36 resuscitated from VF/VT with 1 (22/36) or 2 (14/36) DC countershocks, and 3 receiving hydrocortisone for septic shock
Enrollment (n = 100)
Allocated to Control Group (n = 52)
Allocated to Study Group (n = 48)
29 patients given additional treatment with Epinephrine
17 patients given additional treatment with Epinephrine
ROSC achieved in 27 patients
COMPARISON OF PERI-ARREST VARIABLES
ROSC achieved in 39 patients
4 hours after ROSC Patients with postresuscitation shock assigned to infusion of Saline placebo (15 / 20)
4 hours after ROSC Patients with postresuscitation shock assigned to stress dose Hydrocortisone (27 / 29)
Saline placebo: On day 3 (6 / 12) On day 7 (2 / 7) On day 9 (2 / 7)
COMPARISON OF FOLLOW-UP VARIABLES
Hydrocortisone: On day 3 (16 / 18) On day 7 (5 / 15) On day 9 (5 / 13)
DISCONTINUATION OF HYDROCORTISONE OR PLACEBO ON DAY 10 AFTER RANDOMIZATION
FOLLOW-UP OF SURVIVING PATIENTS TO DAY 60 POST-ARREST AND HOSPITAL DISCHARGE COMPARISON OF FOLLOW-UP VARIABLES

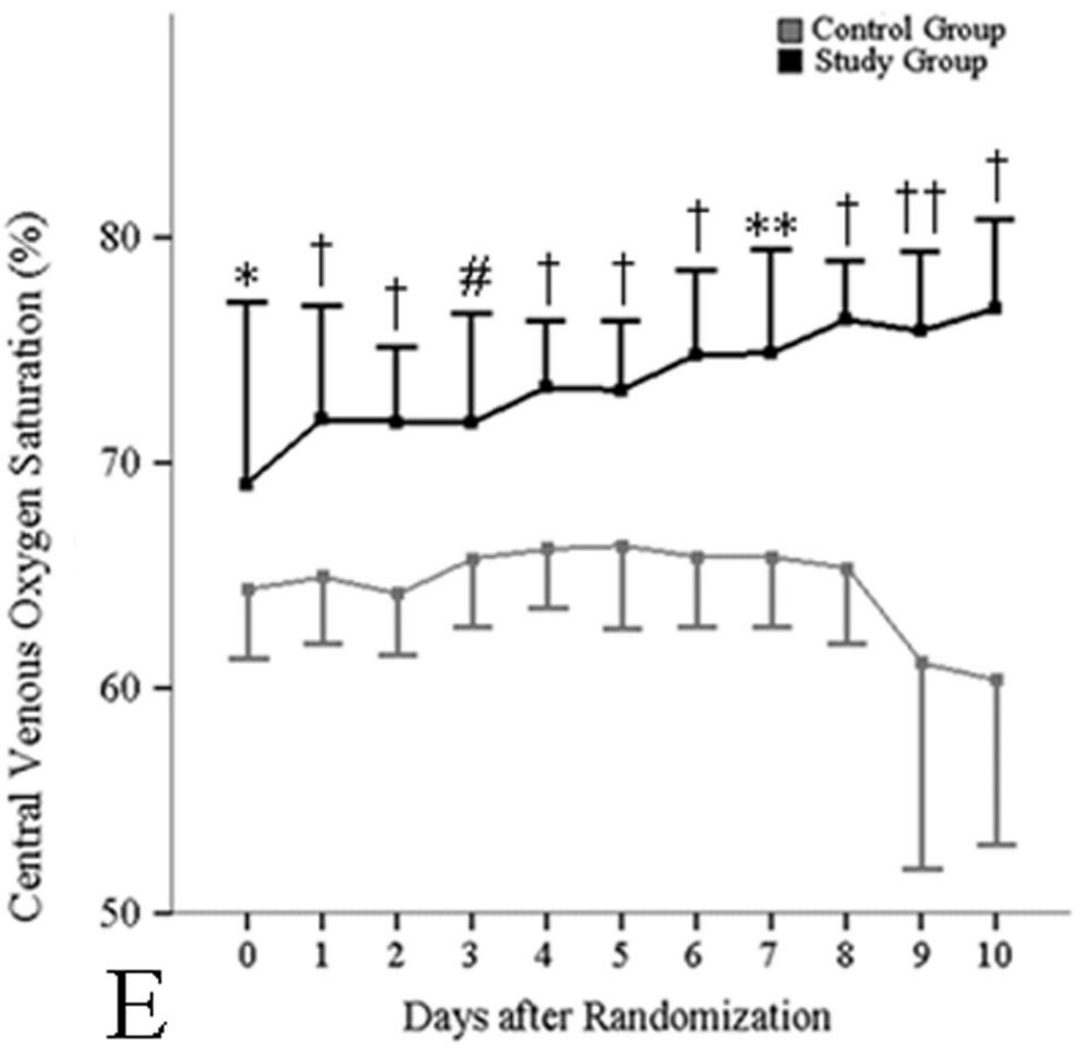
Figure 2


Cumulative survival
1.0
0.8
0.6
0.4
0.2
0.0
Control Group
Study Group
P = .02 by Fisher's exact test
P = .003 by log-rank test
(9/48)
(2/52)
0
10
20
30
40
50
60
Days after randomization
A


Cumulative survival
1.0
0.8
0.6
0.4
0.2
0.0
Control Group
Study Group
P = .02 by Fisher's exact test
P = .01 by log-rank test
(8/27)
(0/15)
0
10
20
30
40
50
60
Days after randomization
B


Organ failure-free days during 60-day follow-up
60
50
40
30
20
10
0
Control Group
Study Group
All Organs or Systems
Circulatory
Neurologic
Hepatic
Renal
Coagulation
Respiratory
C


Log-transformed plasma cytokine concentration (pg/ml)
3
2
1
0
-1
-2
Control group
Study group
Tumor necrosis factor alpha
Interleukin 1 beta
Interleukin 6
Interleukin 8
Interleukin 10
(15 vs. 20)
(9 vs. 15)
(7 vs. 12)
(4 vs. 9)
6 hours
1 day
3 days
7 days
Time points after randomization
D


Central Venous Oxygen Saturation (%)
80
70
60
50
Control Group
Study Group
0
1
2
3
4
5
6
7
8
9
10
Days after Randomization
E

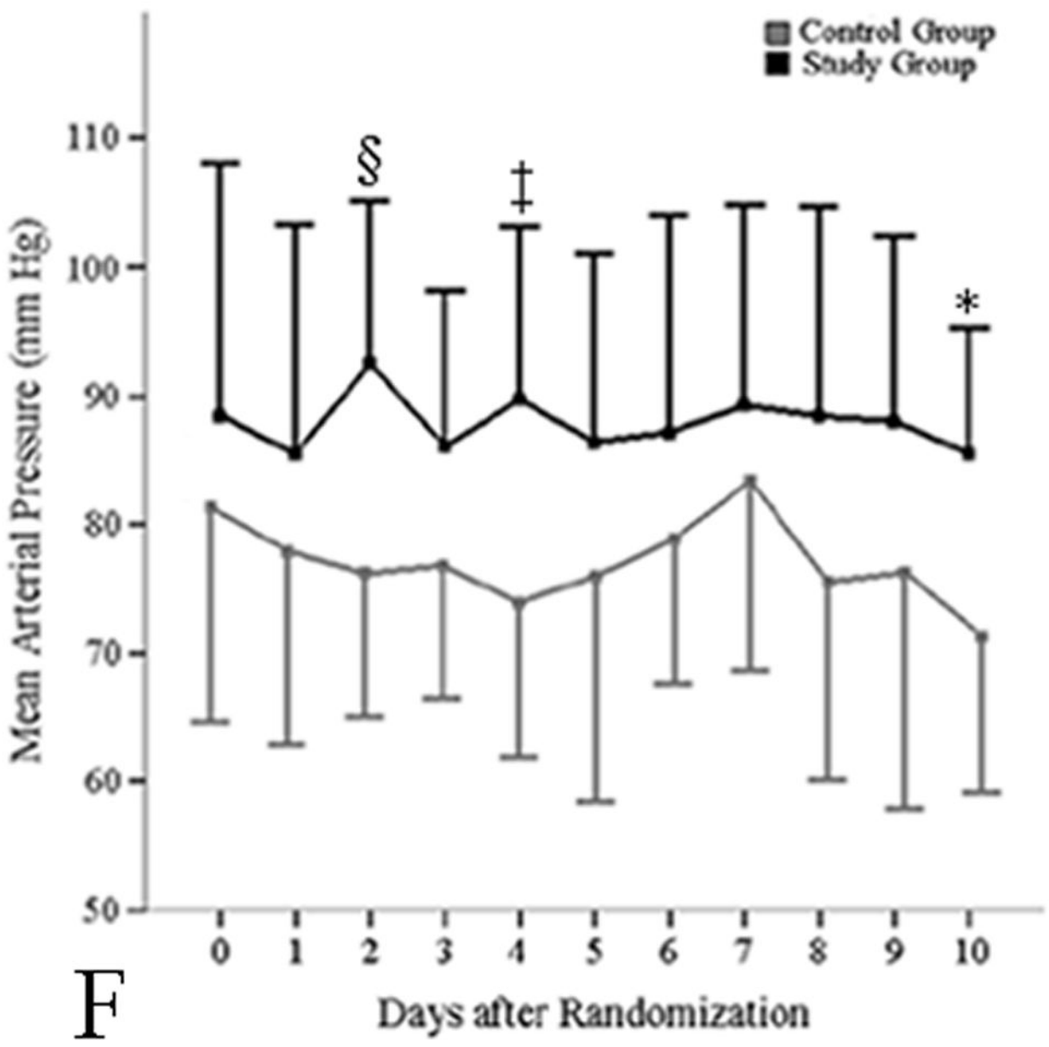
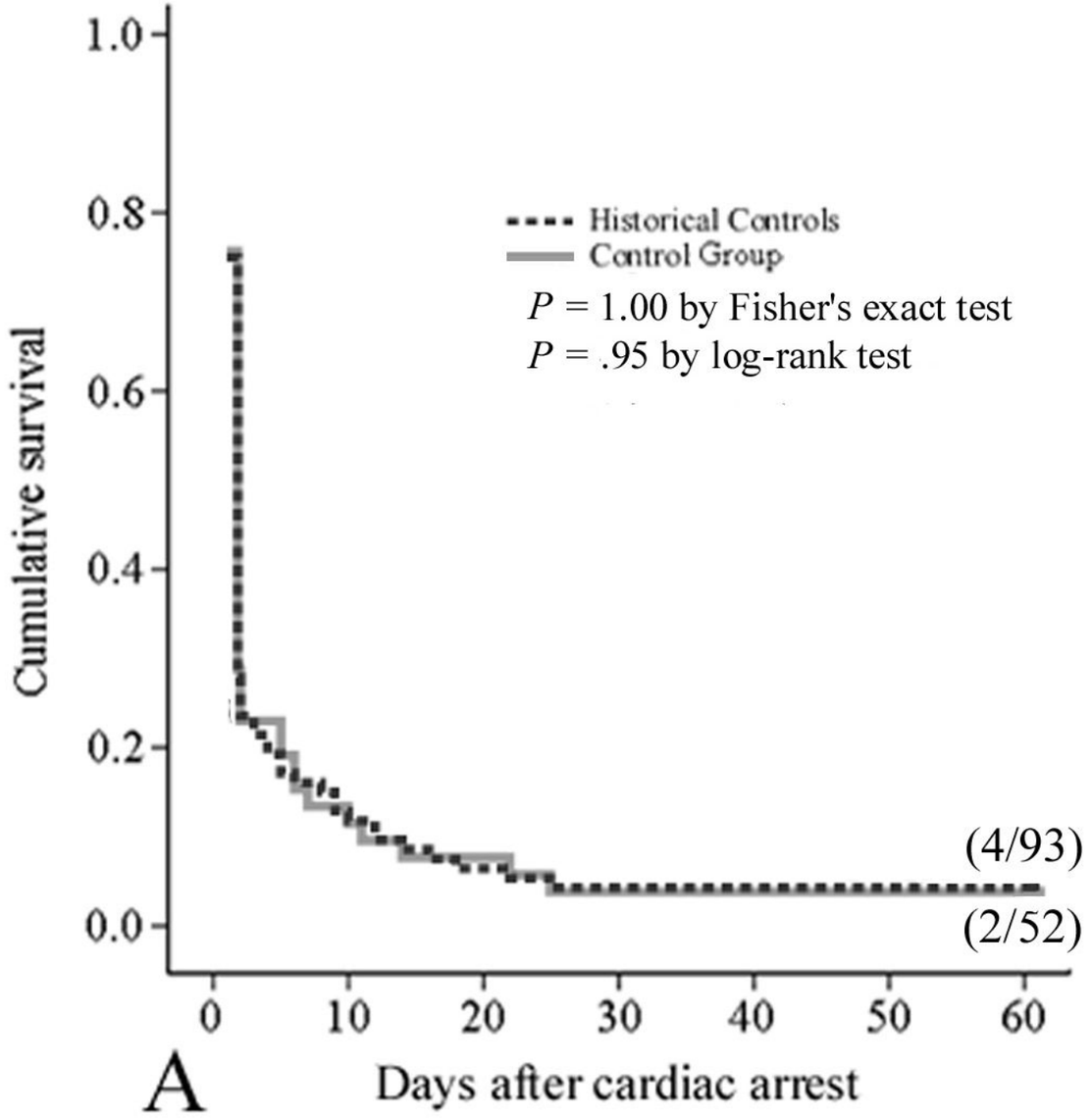

Mean Arterial Pressure (mm Hg)
110
100
90
80
70
60
50
Control Group
Study Group
0
1
2
3
4
5
6
7
8
9
10
Days after Randomization
F

Figure 3


1.0
0.8
0.6
0.4
0.2
0.0
Cumulative survival
Historical Controls
Control Group
P = 1.00 by Fisher's exact test
P = .95 by log-rank test
(4/93)
(2/52)
0
10
20
30
40
50
60
A
Days after cardiac arrest

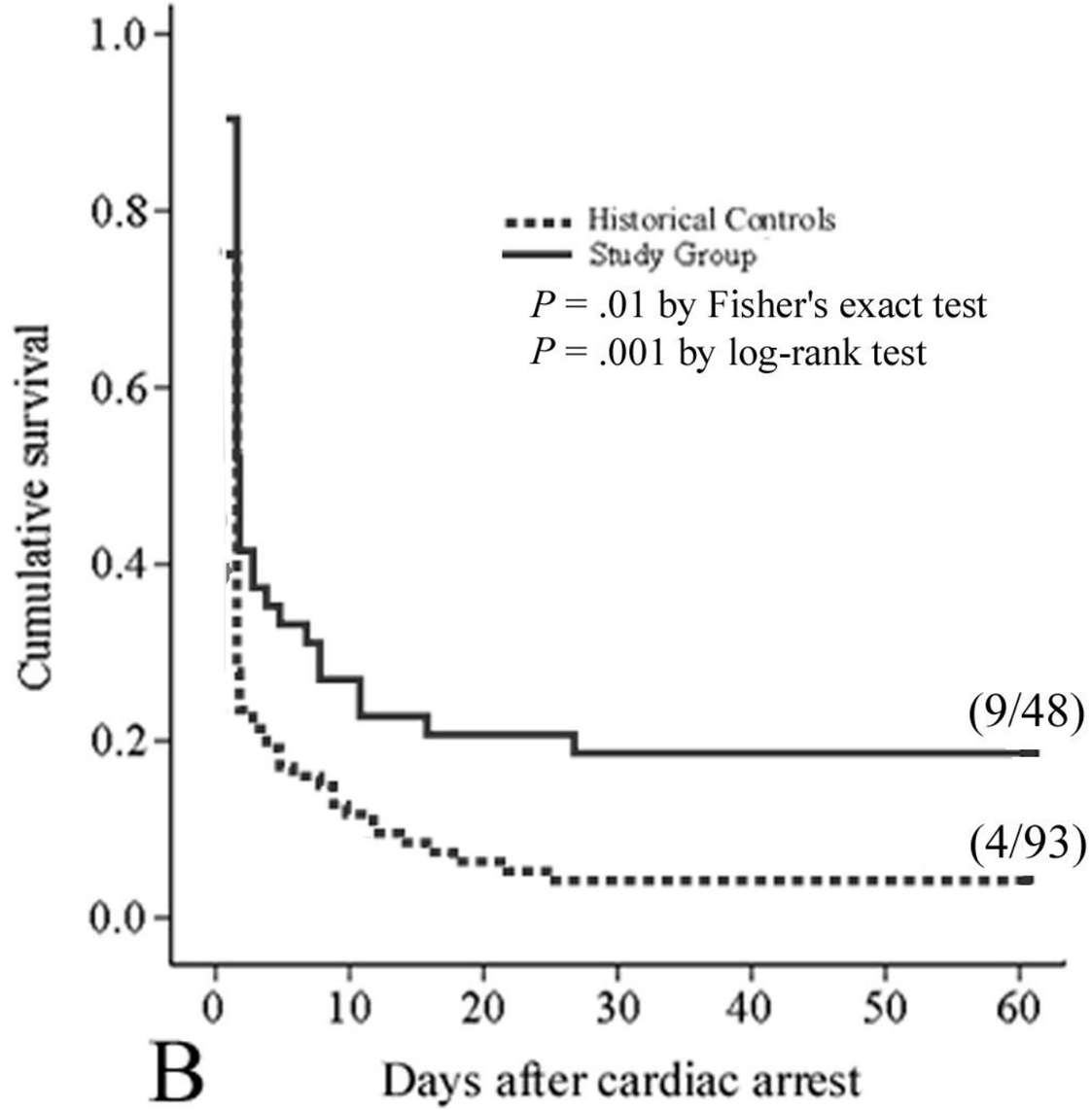

1.0
0.8
0.6
0.4
0.2
0.0
Cumulative survival
Historical Controls
Study Group
P = .01 by Fisher's exact test
P = .001 by log-rank test
(9/48)
(4/93)
0
10
20
30
40
50
60
B
Days after cardiac arrest

Figure 4