ELECTRONIC APPENDIX

VASOPRESSIN, EPINEPHRINE, AND CORTICOSTEROIDS FOR INHOSPITAL CARDIAC ARREST

Spyros D. Mentzelopoulos,[1] Spyros G. Zakynthinos,[1] Maria Tzoufi,[1] Nikos Katsios,[2] Androula Papastylianou, [2] Sotiria Gkizioti,[2] Anastasios Stathopoulos,[2] Androniki Kollintza,[1] Elissavet Stamataki,[2] Charis Roussos[1]

[1] Department of Intensive Care Medicine, University of Athens Medical School.

[2] Department of Anesthesiology, Evaggelismos General Hospital, Athens, Greece.

SUPPLEMENT TO METHODS

Preparation, storage, and chemical stability of experimental drugs

Experimental drugs (i.e., 1 ml containing 20 IU of aqueous arginine-vasopressin and 1ml containing 40 mg of water-reconstituted methylprednisolone sodium succinate) were prepared by the hospital's Pharmacy in 5-ml syringes. Syringes containing the experimental drugs or saline placebo were placed along with ampoules containing 1 mg of epinephrine in boxes bearing patient code-numbers and the time and date of experimental-drug preparation. Epinephrine was not prepared in syringes, because 1) there was no need for blinding to its use, since it was administered to both groups; and 2) of its potential for degradation when exposed to light.[S1] Each box had five separate spaces numbered from 1 to 5. Each space contained drugs for each 1 of the 5 cardiopulmonary resuscitation (CPR)-cycles of the experimental treatment (i.e., 1 or 2 preloaded syringes and 1 ampoule of epinephrine). Boxes were stored at 4 °C (277 °K) at the department of Anesthesiology. Throughout the study period, 2 boxes were available for use at the beginning of each 8-h hospital shift. Experimental drugs had to be used within 24 h of their preparation or discarded and replaced by newly prepared ones after returning the boxes to the hospital's Pharmacy.

During the 10-month study period, the authenticity and chemical stability of vasopressin and methylprednisolone was confirmed in pairs of samples taken from preloaded syringes just after their preparation and after 24 hours of storage. Starting within the first 3 days of study initiation, drug sampling and high-performance chromatography (HPLC) analyses were performed monthly. HPLC techniques included 1) for vasopressin: a 50 x 4.6 mm C18 (3 μm) column, with mobile phase A = 0.15% trifluoracetic acid (TFA) in water, and phase B = 0.13% TFA in 95% acetonitrile/5% water; flow rate = 3.0 mL/min at 216 nm wavelength; temperature =

35° C; and 2) for methylprednisolone: a 150 x 4.6 mm C18 (5 μm) column, with mobile phase = 40% acetonitrile/60% water; flow rate = 1.0 mL/min at 254 nm wavelength; temperature = 35° C. HPLC was performed with System Gold® Beckman Coulter hardware (Beckman Coulter Inc., Fullerton, CA). Determined drug concentration changes in the sample-pairs before and after storage were always <5%.

Resuscitation teams and procedures

Resuscitation teams consisted of 4 members (i.e., 2 emergency physicians and 2 nurses). Team leaders were independent physicians, who ensured adherence to current cardiopulmonary resuscitation (CPR)-standards.[S2] Chest compressions (rate: 90-110/min; depth: 4-5 cm; sought compression-to-decompression ratio: 1:1) were administered by a resuscitation physician and a resuscitation nurse, who rotated every 2-3 min. Endotracheal intubation was performed and/or confirmed within the first CPR-cycle. Patient ventilation comprised 400-600-mL tidal volumes administered at rates of 8-12/min. In hospital-ward or emergency-room patients not intubated before the cardiac arrest, a manual ventilation-bag/reservoir-bag system with O_2 inflow of 10 L/min was used initially (i.e., for 1-2 min), and then, a portable ventilator (Osiris 2, Taema, Antony Cedex, France) was connected to the endotracheal tube; ventilator inspired O_2 fraction (FiO_2) was set at 1.0. During resuscitation, positive end-expiratory pressure (PEEP) was set at $\leq$5 cm H_2O.

For the first 5 CPR-cycles post-randomization, experimental drugs and epinephrine were given by 1 of the investigators, who was not involved in any other resuscitation activity; the same investigator also recorded the patient data. All other CPR-drugs were given by a designated resuscitation nurse. Resuscitation was prolonged in cases of persistent ventricular fibrillation or asystole conversion to ventricular fibrillation.

The decision for termination of the resuscitation efforts was partly dependent on identification and treatment, or on exclusion of reversible causes of cardiac arrest.[S2]

Due to the presence of relevant guidelines,[S2] no specific additional protocol was developed for the treatment of the reversible causes of the cardiac arrest. However, the adherence of resuscitation team leaders to these guidelines and similarity of treatment of the reversible disorders in the study-group and the control-group was to be evaluated during the analysis of the patient data.

Postresuscitation shock

Patients with pre-arrest history and clinical features, and/or electrocardiographic, biochemical, and echocardiographic evidence of acute myocardial infarction[S3-S5] received daily infusions of 300 mg of hydrocortisone[S6] (study-group) or saline-placebo (control-group) for a maximum of 3 days, followed by gradual taper. This time-limit was chosen to prevent any potential retardation of infarct healing by glucocorticoid treatment[S7] in the study-group. Any prescription of corticosteroids by the attending physicians during the first 10 days post-randomization was to cause discontinuation of the study protocol and data rejection during the analysis if patients were assigned to 1) the control-group; and 2) the study-group, but prescribed corticosteroid dose and its subsequent tapering were not in full concordance with our protocol.

Additional description of study endpoints determination

A) Primary endpoints

Return of spontaneous circulation was defined as restoration of a stable cardiac rhythm with a rate of >40 beats/min, in conjunction with a palpable carotid pulse and a systolic arterial pressure of ≥60 mm Hg (8.0 kPa). Such hemodynamic status had to

be maintained for ≥15 min with or without vasopressor/inotropic support, in order to be considered as a positive outcome.

Survival to hospital discharge was defined as presence of attending physician discharge order either to home or to a rehabilitation facility. For patients with a hospital stay of ≥60 days post-arrest, the aforementioned, clearly defined time point was chosen to correspond to the completion of patient follow-up with respect to post-arrest morbidity and complications, and assessment of cerebral performance. Actual and uneventful patient discharge had to be confirmed within the same day on which the aforementioned order was signed. Patients with a hospital stay of <60 days post-arrest were subjected to biweekly outpatient follow-up until day 60. This follow-up comprised clinical examination and obtainment of blood samples, in order to exclude the presence of any new or recurring organ or system dysfunction or failure.

B) Secondary endpoints

Arterial pressure during CPR was determined only in intensive/coronary care unit (ICU/CCU) patients with an arterial line in-place; just prior to the measurements (see also footnote of Table 3 of main text), pressure transducers (Hospira Inc., Donegal, Ireland) were zeroed at the level of the right atrium. Arterial pressure at 15-20 min after CPR, was determined either invasively in ICU/CCU patients and operating-room patients with a new arterial line, or noninvasively (Propaq 102EL monitor, Protocol Systems Inc., Bethlehem, PA) in hospital-ward and emergency-room patients (see also footnote of Table 3 of main text).

To assess the intensity of the post-arrest systemic inflammatory response, we obtained venipuncture-blood samples at pre-specified time points (see subsection "Plasma Cytokine Concentrations" of the main text). The blood samples were allowed to clot for 20-30 minutes in 10-mL sterile vacutainers without anticoagulant and then

centrifuged at 3,000 rotations/min for 10 min to obtain serum. The serum was kept frozen at -80 °C in 0.5-mL aliquots in Eppendorf plastic tubes for later measurement of serum concentrations of cytokines (see subsection "Plasma Cytokine Concentrations" of the main text).

The number of organ failure-free days until follow-up completion was calculated by subtracting the number of days with organ failure from the lesser of 60 days or the number of days to death.

Cerebral performance at hospital discharge was assessed by using the Glasgow-Pittsburgh Cerebral Performance Category (CPC) score.[S8] Briefly, The CPC is a 5-point scale in which 1 = good cerebral performance (i.e., patient is conscious, alert, and able to work and lead a normal life); 2 = moderate cerebral disability (i.e., patient is conscious and has sufficient cerebral function for independent activities of daily life; hemiplegia, seizures, ataxia, dysarthria, dysphasia, or permanent memory or mental changes, and/or noncerebral organ system dysfunction causing moderate disability may be present); 3 = severe cerebral disability (i.e., patient is conscious and ambulatory but dependent on others, because of severe memory disturbance or dementia, or patient is paralyzed and can communicate only with his/her eyes, as in the locked-in syndrome; severe disability from noncerebral organ system dysfunction can coexist); 4 = coma/vegetative state (i.e., patient is unconscious and unable of any verbal and/or psychological interaction with the environment); and 5 = death (i.e. certified brain death).[S9]

Additional definitions used in the *post hoc* analyses of the study results

Circulatory failure was defined as inability to maintain mean arterial pressure >70 mm Hg or systolic arterial pressure >90 mm Hg without using vasopressors[S10] after volume loading;[S11] hemorrhagic shock as circulatory failure associated with clinical,

intraoperative, laboratory, or imaging evidence of internal or external blood loss;[S12] cardiogenic shock as circulatory failure associated with clinical, electrocardiographic, laboratory, or imaging evidence of myocardial ischemia, cardiomyopathy, intra-cardiac mechanical disorders,[S13-S15] or treatment-refractory bradyarrhythmia or tachyarrhythmia on electrocardiogram, and a cardiac index of <2.2 L/min/m^2, in the presence of central venous and/or pulmonary artery wedge pressure of ≥12 mm Hg; obstructive shock as circulatory failure associated with clinical and imaging evidence of mechanical impediment to left or right ventricular filling (e.g., massive pulmonary embolism, tension pneumothorax, or cardiac tamponade);[S15-S17] septic shock as circulatory failure associated with clinical and/or microbiological evidence of sepsis;[S11,S18] anaphylactic shock as circulatory failure associated with clinical features of anaphylaxis[S19] after intravenous drug injection; refractory hypoxemia as PaO_2/FiO_2 <60 mm Hg during mechanical ventilation (with an FiO_2 of 1.0), not responsive to recruitment maneuvers[S20] (employed as hemodynamically tolerated)[S20] and a PEEP of 5-15 cm H_2O; refractory hypotension 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; and cardiac arrest-associated multiple organ failure 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.

SUPPLEMENT TO RESULTS

Pre-arrest data

Table S1 displays major physiological disturbances recorded on patients charts within 3 hours before the cardiac arrest. Table S2 displays pre-arrest patient

medication. All data reported in Tables S1 and S2 was collected from patients charts retrieved from the hospital's archive. Data collection was performed by two independent reviewers blinded to the objectives of the analysis.

***Post hoc* analyses, additional epinephrine, and reversible disorders**

Return of spontaneous circulation for ≥15 min was achieved in 66 of the 100 patients. In 17 study-group patients and 29 controls, advanced life support was continued with additional epinephrine and treatment of reversible causes, according to the guidelines for resuscitation 2005[S2] (see also Figures 1 and 2 of main text). Thirty study-group patients and 21 controls were successfully resuscitated without receiving additional epinephrine. In 1 study-group patient and 2 controls, the resuscitation attempt was abandoned upon the completion of the 5th post-randomization CPR-cycle; all 3 patients fulfilled the criterion of "ongoing asystole for ≥20 min, in the absence of an identifiable reversible cause and with all advanced life support measures in place",[S22] these patients were excluded from the *post hoc* analysis conducted according to the "use or no-use" of additional epinephrine.

Table S3 displays "potentially reversible" major disorders present during resuscitation and initial cardiac arrest rhythms in the "additional-epinephrine" (n = 46) and "no-additional-epinephrine" (n = 51) subgroups. In the "additional-epinephrine" subgroup, the total number of disorders per patient was similar in study-group patients and controls [2.0 (1.0-2.5) and 2.0 (1.0-2.0), respectively, P = .91]. In contrast, in the "no-additional-epinephrine" subgroup, study-group patients had significantly greater total numbers of disorders per patient compared to controls [1.0 (0.8-2.0) vs. 0.0 (0.0-1.0), P = .01]. Lastly, in the combined population of the 97 patients of the "additional-epinephrine" and "no-additional-epinephrine" subgroups, the total numbers of

disorders per patient did not differ significantly between study-group patients and controls [1.0 (1.0-2.0) and 1.0 (0.0-2.0), respectively, $P = .51$].

Treatment of potentially reversible disorders

By study design, and in concordance with the institutional routine practice, in patients requiring >2 CPR-cycles after randomization, an arterial blood gas sample was taken during the 3rd or 4rth CPR-cycle, either by femoral artery puncture or through a preexisting arterial line. Blood gas analyses (ABL555 or ABL700, Radiometer, Copenhagen, Denmark) were promptly performed. This enabled the identification of disorders such as hypoxemia (i.e., PaO_2/FiO_2 <60 mm Hg), severe acidosis (i.e., arterial pH <7.10), and moderate-to-severe hyper- or hypokalemia (i.e., arterial blood potassium ion concentration of >6.0 or <3.0 mEq/L). In all cases of hypoxemia, the correct placement of the endotracheal tube was reconfirmed by observation of chest expansion, auscultation over the lung fields and epigastrium, and/or repeat direct laryngoscopy.[S2] Severe acidosis was treated with 50-100 mmol of sodium bicarbonate (administered in all cases);[S2] hyperkalemia was treated with calcium chloride or calcium gluconate [i.e., 2.3-6.8 mmol of calcium administered in 9 of 10 study-group cases and all 9 control-group cases),[S2] and hypokalemia (1 study-group case) was treated with 8 mmol of magnesium sulfate, followed by intravenous replacement of potassium (infusion rate, 20 mEq/h).[S2] All patients with clinical evidence of hypovolemia (due to hemorrhage, sepsis, or anaphylaxis) were treated by rapid infusion of colloids, or packed red blood cells, or fresh frozen plasma.[S2] Five of 19 study-group patients (26.3%) and 4 of 13 controls (30.8%) with suspected extensive myocardial necrosis or massive pulmonary embolism received 100 mg (10-mg bolus, followed by infusion of 90 mg) of reverse tissue-type plasminogen activator, according to resuscitation team leader decision;[S2] All 5 cases of tension

pneumothorax, or hemothorax, or hydrothorax were treated by chest tube drainage during CPR.[S2] Lastly, one control-group patient with cardiac tamponade was subjected to pericardiocentesis during resuscitation.[S2]

Shock-refractory ventricular fibrillation

Two of 3 study-group patients and 6 of 7 controls with ventricular fibrillation not responsive to 3 shocks received 300 mg of amiodarone, followed by initiation of a continuous infusion at a rate of 900 mg/24 hours.[S2] One of the aforementioned study-group patients received 8 mmol of magnesium followed by potassium supplementation for concurrent hypokalemia.[S2]

Early post-arrest follow-up data

Tables S4 and S5 display detailed follow-up data for patients who survived for <4 hours (n = 17) and for 4-48 hours (n = 18), respectively. Regarding patients who survived for >48 hours, data for the first day post-arrest are provided in Table S6, whereas the long-term morbidity and complications (i.e., all conditions apart from cardiac arrest-associated multiple organ failure and 1 case of cardiogenic shock) are presented in Table 4 of the main text. In survivors for >48 hours, there was a trend toward a significantly higher frequency of postresuscitation shock at 4 hours post-arrest (i.e., just prior to stress-dose hydrocortisone initiation) in study-group patients compared to controls (P = .08) (Table S6). This was due to an identical trend toward increased frequency of postresuscitation shock in "no-additional-epinephrine" study-group patients versus corresponding controls (14/16, 87.5% vs. 6/11, 54.5%; P = .08). The latter result is consistent with the greater total number of disorders per patient in the "no-additional-epinephrine" study-group patients (Table S3).

Additional follow-up data

Combined 60-day follow-up data on the medication prescribed for patients who survived for 24-48 hours (n = 9) and for those who survived for >48 hours (n = 31) are presented in Figure S1. Data on the use of hydrocortisone in the study-group and vasopressor/inotropic support in both groups during the first 10 days post-randomization, are presented in Figure S2. Lastly, data on arterial blood lactate, fluid balance, hemoglobin concentration, and arterial oxygen saturation during the first 10 days post-randomization are presented in Figure S3.

Historical control data and the Hawthorne effect

Historical control data on the resuscitation and early postresuscitation phase was collected from CPR records of the Department of Anesthesiology, and from patient records and ICU/CCU charts retrieved from the hospital's archive. A reportedly successful resuscitation was considered to correspond to return of spontaneous circulation for ≥15 min. For historical controls, who survived for ≥24 hours, data on post-arrest physiological variables, prescribed medication, complications, and long-term outcome was collected from ICU/CCU charts, patient records, and hospital discharge notes. All historical control data was collected by two independent reviewers blinded to the objectives of the analyses. Analyses were conducted and data is presented as described in the Statistical Analysis subsection of the main text. Pre-arrest historical control characteristics were compared to the pre-randomization characteristics of the total of the 100 prospectively studied patients. CPR and post-arrest historical control data was compared separately to the corresponding actual control-group and study-group data.

The results on the primary outcome measures are reported in the main text. Historical controls and control/study group patients had similar characteristics and cardiac arrest causes (Table S7). CPR and peri-arrest variables did not differ

significantly between historical controls and actual control-group (Tables S8 and S9). Systolic, mean, and diastolic arterial pressure during CPR and early postresuscitation phase was significantly lower in historical controls compared to study-group (P < .001 to = .001 for all comparisons).

On hospital discharge (60.8 ± 5.8 days post-arrest), 3 historical controls reportedly had good cerebral performance,[S8] and 1 had moderate cerebral disability.[S8] Results on medication use were similar to those reported in Figure S1 (data not shown). For 24-hour survivors, all-organ failure-free days were 0.0 (0.0-0.0) and 0.0 (0.0-41.0) in the historical controls and study-group, respectively (P = .09). In the actual control-group, all-organ failure-free days were 0.0 (0.0-2.0) (P = .64 vs. historical controls). Post-arrest morbidity and complications, and death causes were similar in the historical controls and actual control-group and study-group (data not shown).

Results on historical controls with postresuscitation shock

According to data collected from ICU/CCU charts, at 24 hours post-arrest, 22 of 26 surviving historical controls fulfilled the criteria for postresuscitation shock (defined in the subsection "Definitions" of the main text). Survival to hospital discharge was similar versus the corresponding actual controls (1/22, 4.6% vs. 0/10, 0.0%; P = 1.00 by Fisher's exact test) (Figure S4A; P = .99 by log-rank test) and lower versus the corresponding study-group patients (1/22, 4.6% vs. 8/23, 34.8%; P = .02 by Fisher's exact test) (Figure S34B; P = .047 by log-rank test).

Historical controls who survived for ≥24 hours versus corresponding study-group patients had significantly fewer all-organ failure-free days [0.0 (0.0-0.0) vs. 0.0 (0.0-42.0) P = .02], renal failure-free days [1.0 (0.0-9.0) vs. 5.0 (0.0-60.0) P = .004], coagulation failure-free days [1.5 (0.0-11.3) vs. 9.0 (1.0-60.0) P = .02], and respiratory failure-free days [0.0 (0.0-4.3) vs. 6.0 (0.0-49.0) P = .02]. Results on 8

historical controls who survived for ≥10 days versus the corresponding 12 study-group patients were similar, with the addition of fewer circulatory failure-free days (8.1 ± 9.8 vs. 36.8 ± 24.7, *P* = .002). Organ failure-free days were similar in historical controls compared to actual control-group (data not shown).

Significantly differing results on variables determined for the first 10 days post-arrest (see also main text) for historical controls who survived for ≥24 hours versus corresponding study-group patients are presented in Figure S5. There were no significant differences in post-arrest variables between historical controls and actual control-group (data not shown).

The absence of statistically significant differences between historical controls and actual control-group, and the similar differences between 1) historical controls and study-group, and 2) actual control-group and study-group, are evidence that the Hawthorne theory[S23] does not apply to any of the endpoints of this trial (see also main text).

REFERENCES

S1. Brustugun J, Kristensen S, Tonnesen HH. Photostability of sympathomimetic agents in commonly used infusion media in the absence and presence of bisulfite. PDA J Pharm Sci Technol. 2004;58(6):296-308.

S2. Nolan JP, Deakin CD, Soar J, Böttiger BW, Smith G. European Resuscitation Council guidelines for resuscitation 2005. Section 4. Adult advanced life support. Resuscitation 2005;67(Suppl. 1):S39-S86.

S3. No authors listed. Myocardial infarction redefined – a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. Eur Heart J 2000;21(18):1502-1513.

S4. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction – 2002: summary article: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients with Unstable Angina). Circulation 2002;106(14):1893-1900.

S5. Antman EM, Anbe DT, Wayne Armstrong P, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction. Circulation 2004;110(9):82-292.

S6. Giugliano GR, Giugliano RP, Gibson CM, Kuntz RE. Meta-analysis of corticosteroid treatment in acute myocardial infarction. Am J Cardiol 2003;91(9):1055-1059.

S7. Shizukuda Y, Miura T, Ishimoto R, Itova M, Iimura O. Effect of prednisolone on myocardial infarct healing: characteristics and comparison with indomethacin. Can J Cardiol 1991;7(10):447-454.

S8. The Brain resuscitation clinical trial II study group. A randomized clinical trial of calcium entry blocker administration to comatose survivors of cardiac arrest: design, methods, and patient characteristics. Controlled Clin Trials 1991;12(4):525-545.

S9. Oh TE. Brain death. In: Bersten AD, Soni N, eds. Oh's Intensive Care Manual 5th ed. Philadelphia, PA: Butterworth-Heinemann; 2003:515-520.

S10. Vincent JL, de Mendonca A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: Results of a multicenter prospective study. Crit Care Med 1998;26(11):1793-1800.

S11. Dellinger RD, Carlet JM, Masur H, et al, for the Surviving Sepsis Campaign Management Guidelines Committee. Surviving sepsis campaign guidelines for the management of severe sepsis and septic shock. Crit Care Med 2004;32(3):858-873.

S12. McLuckie A. Shock: an overview. In: Bersten AD, Soni N, eds. Oh's Intensive Care Manual 5th ed. Philadelphia, PA: Butterworth-Heinemann; 2003:71-78.

S13. Power B. Acute myocardial infarction. In: Bersten AD, Soni N, eds. Oh's Intensive Care Manual 5th ed. Philadelphia, PA: Butterworth-Heinemann; 2003:129-148.

S14. Wilansky S, Moreno CA, Lester SJ. Complications of myocardial infarction. Crit Care Med 2007 35(8, Suppl.):S348-S354.

S15. Donovan KD, Clreavy FB. Echocardiography in intensive care. In: Bersten AD, Soni N, eds. Oh's Intensive Care Manual 5th ed. Philadelphia, PA: Butterworth-Heinemann; 2003:71-79.

S16. Davies AR. Pulmonary embolism. In: Bersten AD, Soni N, eds. Oh's Intensive Care Manual 5th ed. Philadelphia, PA: Butterworth-Heinemann; 2003:351-360.

S17. Padley SPG. Imaging the chest. In: Bersten AD, Soni N, eds. Oh's Intensive Care Manual 5th ed. Philadelphia, PA: Butterworth-Heinemann; 2003:387-404.

S18. Horan TC, Gaynes RP. Surveillance of nosocomial infections. In: Mayhall CG, ed. Hospital Epidemiology and Infection Control. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2004:1659-1702.

S19. Fisher MM. Anaphylaxis. In: Bersten AD, Soni N, eds. Oh's Intensive Care Manual 5th ed. Philadelphia, PA: Butterworth-Heinemann; 2003:617-620.

S20. [No authors listed] Effect of recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome ventilated with high positive end-expiratory pressure. The ARDS Clinical Trials Network; National Heart, Lung, and Blood Institute; National Institutes of Health. Crit Care Med 2003;31(11):2592-2597.

S21. Arntz HR, Bossaert L, Fillipatos GS. European Resuscitation Council guidelines for resuscitation 2005. Section 5. Initial management of acute coronary syndromes. Resuscitation 2005;67(Suppl. 1):S87-S96.

S22. Baskett PJF, Steen PA, Bossaert L. European Resuscitation Council guidelines for resuscitation 2005. Section 8. The ethics of resuscitation and end-of-life decisions. Resuscitation 2005;67(Suppl. 1):S171-S180.

S23. Adair G. The Hawthorne effect: A reconsideration of the methodological artefact. J Appl Psych 1984;69(2):334-345.

Table S1. Physiological disturbances recorded within 3 hours before the cardiac arrest.

Physiologic Disturbance – no. (%)	Control group (n = 52)	Study group (n = 48)
Hypotension (systolic blood pressure < 90 mm Hg)	22 (42.3)	27 (56.3)
Oxygenation disturbances (SpO_2 <90% and/or PaO_2/FiO_2 <200 mm Hg)	34 (65.4)	27 (56.3)
Moderate-to-severe acidosis (arterial pH <7.20)	6 (11.5)	7 (14.6)
Hypercapnia ($PaCO_2$ >60 mm Hg)	3 (5.8)	4 (8.3)
Arterial blood lactate concentration >3 mmol/L	5 (9.6)	9 (18.8)
Significant hypo- or hyperkalemia *	0 (0.0)	2 (4.2)
Tachypnea >30 breaths/min	22 (42.3)	20 (41.7)
Sinus tachycardia (100-150 beats/min)	16 (30.8)	19 (39.6)
Paroxysmal supraventricular tachycardia (>150 beats/min)	5 (9.6)	5 (10.4)
Acute-onset atrial fibrillation	2 (3.8)	4 (8.3)
Conduction disturbances† and/or sinus bradycardia (<40 beats/min)	8 (15.4)	7 (14.6)
New electrocardiographic ST segment elevation or depression	18 (34.6)	22 (45.8)

SpO_2, peripheral oxygen saturation; PaO_2 and $PaCO_2$, arterial partial pressure of oxygen and carbon dioxide, respectively; FiO_2, inspired O_2 fraction. Some patients had more than 1 concurrent disturbances. Episodes of hypotension were treated with vasopressors/intropes and/or intravenous fluids. Episodes of hypoxemia were treated by 1) increasing FiO_2 and/or positive end-expiratory pressure (in mechanically ventilated

patients), and 2) underlying cause-specific pharmacological regimens (e.g., nitroglycerin with/without a bolus dose of a loop diuretic for cardiogenic pulmonary edema). Other disturbances were treated in concordance with standard recommendations.[S2,S21]

*, Defined as arterial blood potassium ion concentration <3.0 or >6.0 mEq/L, respectively.

†, Möbitz II antrioventricular block or complete heart block.

Table S2. Medication prescribed before the occurrence of the cardiac arrest.

Drug class – no. (%)	Control group (n = 52)	Study group (n = 48)
Antiplatelet drugs	14 (26.9)	13 (27.1)
Anticoagulants	26 (50.0)	22 (23.0)
ACEIs or angiotensin receptor blockers	24 (46.2)	20 (41.7)
Nitroglycerin	9 (17.3)	4 (8.3)
Diuretics	14 (26.9)	10 (20.8)
Calcium channel blockers	9 (17.3)	9 (18.8)
Digoxin	1 (1.9)	1 (2.1)
Amiodarone	2 (3.8)	4 (8.3)
Sedatives and/or analgesics	24 (46.2)	25 (52.1)
Insulin or oral hypoglycemics	10 (19.2)	16 (33.3)
At least 2 broad-spectrum antibiotics	13 (25.0)	15 (31.3)
Bronchodilators	13 (25.0)	16 (33.3)
Inhaled steroids	5 (9.6)	3 (6.3)
Vasopressors and/or Inotropes	10 (19.2)	13 (27.1)
Other *	20 (38.5)	25 (52.1)

ACEIs, Angiotensin converting enzyme inhibitors.

*, Includes proton pump inhibitors, H_2 receptor antagonists, nonsteroidal anti-inflammatory drugs (besides acetylsalicylic acid), and antiepileptic drugs.

Table S3. "Potentially reversible" major disorders present during cardiopulmonary resuscitation and initial cardiac arrest rhythms.

	No Additional Epinephrine *			Additional Epinephrine *		
	Control group (n = 21)	**Study group (n = 30)**	***P* value**	**Control group (n = 29)**	**Study group (n = 17)**	***P* value**
Hypoxemia (PaO_2/FiO_2 <60 mm Hg) – no (%)	1 (4.8)	3 (10.0)	.63	10 (34.5)	4 (23.5)	.52
Metabolic Disorder – no (%) †	3 (14.3)	8 (26.7)	.49	20 (69.0)	10 (58.8)	.53
Arterial pH <7.10 – no (%)	2 (9.5)	7 (23.3)	.28	19 (65.5)	9 (52.9)	.53
Significant hypo- or hyperkalemia – no (%) **§**	2 (9.5)	4 (13.3)	1.00	7 (24.1)	7 (41.2)	.32
Hypovolemia – no (%) #	4 (19.0)	8 (26.7)	.74	5 (17.2)	3 (17.6)	1.00
Sepsis-related – no (%)	2 (9.5)	3 (10.0)	1.00	4 (13.8)	2 (11.8)	1.00
Blood loss-related – no (%)	2 (9.5)	5 (16.7)	.69	1 (3.4)	1 (5.9)	1.00
Thrombosis – no (%)	2 (9.5)	9 (30.0)	.10	11 (37.9)	10 (58.8)	.23
Extensive myocardial ischemia/necrosis – no (%)‡	0 (0.0)	4 (13.3)	.13	9 (31.0)	7 (41.2)	.53
Massive pulmonary embolism – no (%) **	2 (9.5)	5 (16.7)	.69	2 (6.9)	3 (17.6)	.34
Tension pneumothorax or hemothorax or hydrothorax – no (%)	1 (4.8)	4 (13.3)	.39	0 (0.0)	1 (5.9)	.37
Drug toxicity – no (%) ††	0 (0.0)	1 (3.3)	1.00	0 (0.0)	1 (5.9)	1.00
Cardiac tamponade – no (%)	0 (0.0)	0 (0.0)	1.00	1 (3.4)	0 (0.0)	.72

436 **Table S3 (cont). "Potentially reversible" major disorders present during cardiopulmonary resuscitation and initial cardiac arrest**

437 **rhythms.**

	No Additional Epinephrine *			Additional Epinephrine *		
	Control group (n = 21)	**Study group (n = 30)**	***P* value**	**Control group (n = 29)**	**Study group (n = 17)**	***P* value**
Total number of disorders per patient §§	0.0 (0.0-1.0)	1.0 (0.8-2.0)	.01	2.0 (1.0-2.0)	2.0 (1.0-2.5)	.91
Initial Rhythm						
Asystole – no (%)	14 (66.7)	17 (56.7)	.57	16 (55.2)	12 (70.6)	.36
Pulseless electrical activity – no (%)	5 (23.8)	8 (26.7)	1.00	9 (31.0)	3 (17.6)	.49
Ventricular fibrillation/tachycardia – no (%)	2 (9.5)	5 (16.7)	.69	4 (13.8)	2 (11.8)	1.00

438

439 FiO_2, inspired O_2 fraction.

440 *, One study-group patient and 2 controls were excluded from this analysis; in these patients, the resuscitation attempt was abandoned[S22] at the

441 end of the 5th cardiopulmonary resuscitation-cycle after randomization (see also Figure 1 of main text).

442 †, Defined as severe acidosis with or without severe hypo- or hyperkalemia.

443 §, Defined as arterial blood potassium ion concentration <3.0 or >6.0 mEq/L, respectively.

#, Considered as present in patients with pre-arrest systolic blood pressure of <90 mm Hg and evidence of sepsis/septic shock,[S11,S18] or hemorrhage.

‡, Considered as present in patients with at least 1 of the following "pre-arrest" criteria: 1) electrocardiographic evidence of anterolateral (i.e., ST segment elevation in leads I, aVL, and V2-V6) or inferolateral (i.e., ST segment elevation in leads II, III, aVF, I, aVL, V5, and V6) myocardial infarction; 2) diagnosis of acute coronary syndrome, and echocardiographic evidence of mechanical complications of acute myocardial infarction[S14]; 3) diagnosis of acute coronary syndrome, and systolic arterial pressure of <90 mm Hg and cardiac index of <2.2 L/min/m^2, in the presence of central venous and/or pulmonary artery wedge pressure of >12 mm Hg.

**, Considered as present in patients with at least 1 of the following "peri-arrest" criteria: 1) detection of intracardiac thrombi with transthoracic echocardiography;[S16] 2) identification of emboli in the proximal pulmonary arteries with transesophageal echocardiography;[S16] and 3) identification of emboli in the proximal pulmonary arteries with contrast-enhanced, spiral computerized tomography.[S16]

††, Refers to anaphylactic shock leading to cardiac arrest after an intravenous injection of ampicillin (1 case) and an intravenous injection of lidocaine (1 case).

§§, Defined as the total number of disorders present concurrently in each patient; for example, a patient with acidosis and/or significant hyperkalemia (i.e., a metabolic disorder), and hypovolemia secondary to blood loss was considered to have 2 concurrent disorders; data are median (interquartile range).

459

460

461

462 **Table S4. Follow-up data of survivors for less than 4 hours.**

	Control group (n = 7)	**Study group (n = 10)**	***P* value**
"No Additional Epinephrine"- no (%)	6 (85.7) *	7 (70.0) †	.60
"Additional epinephrine" – no (%)	1 (14.3) §	3 (30.0) #	.60
Unwitnessed arrest – no (%)	0 (0.0)	1 (10.0)	.59
ECG rhythm on ROSC			
Sinus tachycardia (100-150 beats/min) – no (%)	4 (57.1)	4 (40.0)	.42
Supraventricular tachycardia (>150 beats/min) – no (%)	2 (28.6)	0 (0.0)	.15
Accelerated idioventricular rhythm (60-100 beats/min) – no (%)	1 (14.3)	6 (60.0)	.13
Mean arterial pressure at 15 min following ROSC – mm Hg	64.0 ± 19.8	74.0 ± 27.8	.42
Peri-arrest lactate (mmol/L)	10.7 ± 2.9	9.5 ± 6.6	.65
Hemodynamic support ‡			
Norepinephrine – μg/kg/min	0.6 ± 0.4	0.4 ± 0.4	.23
Intravenous fluids - mL (%) **	757 ± 754	605 ± 719	.68
Survival following ROSC – hours	2.1 ± 1.3	1.4 ± 1.2	.29
Additional medication			
Sedatives / analgesics – no (%)	7 (100.0)	8 (80.0)	.49
Neuromuscular blocking agents – no (%)	3 (42.9)	5 (50.0)	1.00
Low molecular weight or unfractionated heparin – no (%) ††	3 (42.9)	5 (50.0)	1.00
Antiplatelet drugs – no (%)	1 (14.3)	1 (10.0)	1.00
At least 2 broad-spectrum antiobiotics – no (%)	2 (28.6)	4 (40.0)	1.00
Insulin – no (%)	2 (28.6)	4 (40.0)	1.00
Amiodarone – no (%) §§	2 (28.6)	0 (0.0)	.15
Atropine – no (%) ##	1 (14.3)	6 (60.0)	.13
Transvenous pacing – (no%)	0 (0.0)	1 (10.0)	1.00
Peri-arrest thrombolysis and/or PTCA for ACS – (no%)	1 (14.3)	1 (10.0)	1.00
Peri-arrest thrombolysis for massive pulmonary embolism – (no%)	1 (14.3)	0 (0.0)	.41

463

464 ECG, electrocardiogram; ROSC, return of spontaneous circulation; PTCA,

465 percutaneous transluminal coronary angioplasty; ACS, acute coronary syndrome.

*, 2 patients (1 with bilateral pneumonia and 1 with alveolar hemorrhage) died in the intensive care unit (ICU) of refractory hypoxemia; 1 patient originally admitted for severe and multiple trauma, had ongoing blood loss and severe acidosis (i.e., arterial pH <7.10), and died in the operating room of hemorrhagic shock; 1 patient with ACS scheduled for emergency surgical treatment of a DeBakey type A acute aortic dissection died in the coronary care unit (CCU) of cardiogenic shock; 1 patient died in a ward of the department Orthopedic Surgery of septic shock; 1 patient died in the emergency room of massive pulmonary embolism-induced obstructive shock.

†, 2 patients originally admitted for severe and multiple trauma, had ongoing blood loss and severe acidosis (i.e., arterial pH <7.10), and died in the operating room of hemorrhagic shock; 1 patient died in the emergency room and 1 patient died in a ward of the department of Orthopedic Surgery of massive pulmonary embolism-induced obstructive shock; 1 patient died in the CCU of cardiogenic shock (the patient had already received peri-arrest thrombolysis and was scheduled for emergency PTCA); 1 patient with bilateral pneumonia died in the ICU of refractory hypoxemia; 1 patient with septic shock died in the ICU after developing refractory hypotension.

§, The patient died in the CCU of cardiogenic shock after peri-arrest thrombolysis and emergency PTCA.

#, 1 patient died in a ward of the department of Thoracic Surgery of a lethal arrhythmia (i.e., complete heart block followed by bradycardia and asystole not responsive to advanced life support and transvenous pacing), after developing new post-arrest ST segment elevation in leads II, III, and aVF; 1 patient with ACS died in the CCU of cardiogenic shock after developing refractory hypotension; 1 patient with bilateral pneumonia died in the ICU of refractory hypoxemia.

‡, Additional support comprised dobutamine infusions of 15, 15, and 20 μg/kg/min in 1 control with massive pulmonary embolism, 1 control with cardiogenic shock, and 1 study-group patient with massive pulmonary embolism, respectively; and epinephrine infusions of 0.1 μg/kg/min in 1 study-group patient with septic shock and 1 study-group patient with cardiogenic shock.

**, Refers to cumulative administered volume of crystalloids, colloids, packed red blood cells, and fresh frozen plasma from 15 min after the initial ROSC until the time of death.

††, Administered alone as prophylactic anticoagulation (to 4 study-group patients and 1 control) or therapeutic anticoagulation (to 1 control with pulmonary embolism), as well as in combination with antiplatelet drugs (to 1 study-group patient and 1 control with ACS).

§§, Both controls received amiodarone as a continuous infusion initiated after the administration of a 300-mg bolus for shock refractory ventricular fibrillation during resuscitation.

##, Corresponds to patients with idioventricular rhythm.

516 **Table S5. Follow-up data of survivors for 4-48 hours.**

	Control group (n = 8)	**Study group (n = 10)**	***P* value**
"No Additional Epinephrine"- no (%)	4 (50.0)	7 (70.0)	.63
"Additional epinephrine" – no (%)	4 (50.0)	3 (30.0)	.63
Unwitnessed arrest – no (%)	2 (25.0)	2 (20.0)	1.00
New Organ failure following ROSC			
Respiratory failure – no (%)	2 (25.0)	4 (40.0)	1.00
Renal failure / anuria – no (%)	7 (87.5)	4 (40.0)	.07
Hepatic failure – no (%)	3 (37.5)	3 (30.0)	1.00
Coagulation failure - no (%)	0 (0.0)	2 (20.0)	.48
Mean arterial pressure at 15 min following ROSC – mm Hg	87.3 ± 37.1	96.4 ± 47.0	.65
Peri-arrest lactate (mmol/L)	12.4 ± 4.7	10.1 ± 3.8	.37
Systolic arterial pressure – mm Hg *	73.4 ± 6.7	77.0 ± 9.3	.61
Hemodynamic support †			
Norepinephrine – μg/kg/min *	0.7 ± 0.2	1.0 ± 0.6	.08
Dobutamine – μg/kg/min *	3.7 ± 7.4	11.7 ± 14.3	.17
Intravenous fluids - mL (%) §	3435 ± 1870	4227 ± 5991	.73
Survival following ROSC – hours	19.1 ± 7.3	21.9 ± 14.9	.26
Additional medication			
Sedatives / analgesics – no (%)	8 (100.0)	8 (80.0)	.48
Neuromuscular blocking agents – no (%)	0 (0.0)	2 (20.0)	.48
Low molecular weight or unfractionated heparin – no (%) #	6 (75.0)	6 (60.0)	.64
Antiplatelet drugs – no (%)	2 (25.0)	4 (40.0)	.59
At least 2 broad-spectrum antiobiotics – no (%) ‡	0 (0.0)	4 (40.0)	.09
Insulin – no (%)	2 (25.0)	4 (40.0)	.64
Amiodarone – no (%) **	3 (37.5)	5 (50.0)	.66
IABPC – (no%) ††	1 (12.5)	0 (0.0)	.44
Transvanous pacing – (no%) §§	1 (12.5)	0 (0.0)	.44
Peri-arrest thrombolysis and/or PTCA for ACS – no (%)	2 (25.0)	2 (20.0)	1.00

517

ROSC, return of spontaneous circulation. IABPC, intraaortic balloon counterpulsation; PTCA, percutaneous transluminal coronary angioplasty; ACS, acute coronary syndrome. All patients died in the intensive care unit or the coronary care unit. The 8 controls and 9 of the 10 study-group patients fulfilled the criterion of cardiac arrest-associated multiple organ failure, and died after developing refractory hypotension (see also subsection "Additional Definitions"). One study-group patient did not develop any new post-arrest organ failure, but died of cardiogenic shock. Neurologic status could not be evaluated in most patients, because of the use of sedation. Infusions of hydrocortisone or saline-placebo were started at 4 hours post-arrest in all patients, as part of the study protocol. Stress ulcer prophylaxis was prescribed in all cases.

*, Last values recorded on patients charts before the occurrence of death.

†, Additional support comprised epinephrine infusions ranging within 0.1-1.2 μg/kg/min in 1 control and 3 study-group patients.

§, Refers to cumulative administered volume of crystalloids, colloids, packed red blood cells, and fresh frozen plasma from 15 min after the initial ROSC until the time of death.

#, Administered alone as prophylactic anticoagulation (to 3 study-group patients and 4 controls) or in combination with antiplatelet drugs (to 3 study-group patients and 2 controls with ACS).

‡, Administered to 4 study-group patients with pneumonia or sepsis.

**, Administered to 1 control and 4 study-group patients for recurrent, postresuscitation supraventricular arhhythmias, and to 1 study-group patient for recurrent, postresuscitation ventricular tachycardia; also, 2 controls received

amiodarone as a continuous infusion initiated after the administration of a 300-mg bolus for shock refractory ventricular fibrillation during resuscitation.

††, Employed in 1 control patient with complete heart block and

§§, Employed in 1 control patient with cardiogenic shock.

Table S6. First post-arrest day follow-up data of survivors for more than 48 hours.

	Control group (n = 12)	Study group (n = 19)	*P* value
"No Additional Epinephrine"- no (%)	11 (91.7)	16 (84.2)	1.00
"Additional epinephrine" – no (%)	1 (8.3)	3 (15.8)	1.00
Unwitnessed arrest – no (%)	0 (0.0)	3 (15.8)	.27
New Organ failure following ROSC			
Respiratory failure – no (%)	5 (41.7)	5 (26.3)	.45
Renal failure / anuria – no (%)	1 (8.3)	1 (5.3)	1.00
Mean arterial pressure at 15 min following ROSC – mm Hg	74.6 ± 18.5	101.1 ± 29.7	.01
Peri-arrest lactate (mmol/L)	9.2 ± 6.5	9.6 ± 6.4	.88
Postresuscitation shock at 4 hours following ROSC – (no%)	7 (58.3)	17 (89.5)	.08
Hemodynamic support *			
Norepinephrine – μg/kg/min †	0.3 ± 0.4	0.5 ± 0.3	.37
Dobutamine – μg/kg/min †	4.1 ± 6.1	4.2 ± 7.3	.96
Intravenous fluids - mL (%) §	2516 ± 658	2447 ± 1485	.88
Additional medication			
Sedatives / analgesics – no (%) #	8 (66.7)	18 (94.7)	.06
Low molecular weight or unfractionated heparin – no (%)‡	7 (58.3)	12 (63.2)	1.00
Antiplatelet drugs – no (%)	4 (33.3)	3 (15.8)	.38
At least 2 broad-spectrum antiobiotics – no (%)	3 (25.0)	9 (47.4)	.27
Insulin – no (%)	5 (41.7)	3 (15.8)	.21
Amiodarone – no (%) **	2 (16.7)	3 (15.8)	1.00
Diuretics – no (%) ††	3 (25.0)	3 (15.8)	.65
Transvanous pacing – (no%)	1 (8.3)	0 (0.0)	.44
Peri-arrest thrombolysis and/or PTCA for ACS – (no%)	1 (8.3)	1 (5.3)	1.00
Peri-arrest thrombolysis for massive pulmonary embolism – (no%)	0 (0.0)	2 (10.5)	.51

ROSC, return of spontaneous circulation. IABPC, intraaortic balloon counterpulsation; PTCA, percutaneous transluminal angioplasty; ACS, acute coronary syndrome. All patients were admitted to the intensive care unit or the coronary care unit within 12 hours post-arrest. Neurologic status could not be evaluated in most patients, because of the use of sedation. Infusions of hydrocortisone or saline-placebo were started at 4 hours post-arrest in all patients, as part of the study protocol. Stress ulcer prophylaxis was prescribed in all cases.

*, Additional support comprised epinephrine infusions ranging within 0.08-0.3 μg/kg/min in 2 controls and 2 study-group patients.

†, Average infusion rates during the first 24 hours post-arrest.

§, Refers to cumulative administered volume of crystalloids, colloids, packed red blood cells, and fresh frozen plasma within the first 24 hours post-arrest.

#, Result was due to the lower frequency of postresuscitation shock in the control-group, which enabled more frequent discontinuation of sedation for neurologic status evaluation.

‡, Administered alone as prophylactic anticoagulation (to 4 study-group patients and 4 controls) or therapeutic anticoagulation (to 3 study-group patients and 1 control with pulmonary embolism), as well as in combination with antiplatelet drugs (to 3 study-group patients and 2 controls with ACS).

**, Administered to 2 controls and 2 study-group patients as a continuous infusion initiated after the administration of a 300-mg bolus for shock refractory ventricular fibrillation during resuscitation, and to 1 study-group patient for recurrent, postresuscitation ventricular tachycardia.

††, Prescribed for 2 study-group patients and 2 controls with the acute respiratory distress syndrome, and for 1 study-group patient and 1 control with acute heart failure.

595 **Table S7.** Patient characteristics before cardiac arrest and causes of cardiac arrest.

Characteristic	**Historical Controls (n = 93)**	**Control and Study group (n = 100)**	***P* value**
Age – years	65.9 ± 13.9	67.4 ± 17.1	.51
Male sex – no. (%)	62 (66.7)	59 (59.0)	.30
Body-mass index - kg/m^2 *	26.0 ± 5.7	25.3 ± 5.5	.64
Pre-arrest hospital stay – days	3.5 ± 4.6	3.6 ± 3.9	.82
Cardiovascular history – no. (%)			
Hypertension	69 (74.2)	64 (64.0)	.16
Coronary artery disease	29 (31.2)	39 (39.0)	.29
Diabetes	33 (35.5)	29 (29.0)	.36
Cardiac conduction disturbances	12 (12.9)	9 (9.0)	.49
Cardiac arrhythmia	12 (12.9)	8 (8.0)	.35
Valvular heart disease	6 (6.5)	8 (8.0)	.79
Peripheral vascular disease	10 (10.8)	19 (19.0)	.10
Other chronic comorbidity-no. (%) †	64 (68.8)	65 (65.0)	.65
Hospital Admission Cause – no. (%) §			
Acute cardiovascular disease	45 (48.4)	46 (46.0)	.77
Acute respiratory disease	21 (22.8)	15 (15.0)	.20
Acute renal disease	9 (9.7)	5 (5.0)	.27
Acute digestive disease	7 (7.6)	7 (7.0)	1.00
Acute neurologic disease	8 (8.6)	7 (7.0)	.79
Malignancy	10 (10.8)	13 (13.0)	.66
Trauma	8 (8.6)	14 (14.0)	.27
Other	5 (6.7)	6 (6.0)	1.00
Cause of cardiac arrest-no.(%) #			
Acute coronary syndrome	22 (24.4)	24 (24.0)	1.00
Cardiogenic shock	6 (6.5)	9 (9.0)	.60
Lethal arrhythmia	8 (8.6)	5 (5.0)	.39
Hypoxemia-pulmonary edema	11 (11.8)	9 (9.0)	.64
Cardiac tamponade	1 (1.1)	1 (1.0)	1.00

Hypoxemia-pneumonia	17 (18.3)	18 (18.0)	1.00
Hypoxemia-COPD exacerbation	1 (1.11)	3 (3.0)	.62
Pulmonary embolism	8 (8.6)	16 (16.0)	.13
Septic shock	6 (6.5)	7 (7.0)	1.00
Electrolyte disturbances	3 (3.2)	8 (8.0)	.22
Tension pneumothorax-hemothorax	4 (4.3)	4 (4.0)	1.00
Hypovolemia	5 (5.4)	6 (6.0)	1.00
Other	3 (3.2)	5 (5.0)	.72
Unknown	5 (5.4) **	0 (0.0)	.03

596

597 COPD, chronic obstructive pulmonary disease.

598 * Data compared between intensive/coronary care unit (ICU/CCU) patients (historical

599 controls, n = 32; control-group and study-group, n = 31).

600 † Includes chronic respiratory, neurologic, digestive, renal, and musculoskeletal

601 disease, malignancy, and immunosuppression.

602 § Some patients had more than 1 cause of hospital admission; in historical controls,

603 "other" causes included 2 cases of drug toxicity, and 1 case of kidney abscess, and

604 rupture of the left ventricular anterior papillary muscle.

605 # In some patients, there were more than 1 major disturbances recorded as causes of

606 the cardiac arrest. In historical controls, "other" causes included 2 cases of drug

607 toxicity and 1 case of rupture of the left ventricular anterior papillary muscle.

608 ** No cause of cardiac arrest recorded.

609

610

611

612

Table S8. Data on cardiopulmonary resuscitation procedures. Brackets contain *P*-values versus historical controls.

	Historical controls (n = 93)	Control group (n = 52)	Study group (n = 48)
Location of Cardiac Arrest - no. (%)			
Ward	46 (49.5)	25 (48.1); [1.00]	21 (43.8); [.60]
Intensive care unit or coronary care unit	32 (34.4)	14 (26.9); [.46]	17 (35.4); [1.00]
Emergency department	13 (14.0)	10 (19.2); [.48]	8 (16.7); [.80]
Operating room	2 (2.2)	3 (5.8); [.35]	2 (4.2); [.61]
Initial Rhythm - no. (%)			
Ventricular fibrillation/tachycardia	9 (9.7)	7 (13.5); [.58]	7 (14.6); [.41]
Asystole	68 (73.1)	31 (59.6); [.10]	30 (62.5); [.25]
Pulseless electrical activity	16 (17.2)	14 (26.9); [.20]	11 (22.9); [.50]
Witnessed arrest – no. (%) *	77 (82.8)	43 (82.7); [.82]	38 (79.2); [.65]
Time to ALS initiation 3 min or less †	74 (79.5)	43 (82.7); [1.00]	38 (79.2); [.64]
ALS duration – min †,§	28.5 ± 24.1	31.2 ± 29.9; [.56]	25.1 ± 23.6; [.43]
Not intubated at arrest – no. (%) *, #	61 (65.6)	36 (69.2); [.72]	34 (70.8); [.57]
Number of cardiopulmonary resuscitation cycles †,‡	7.6 ± 6.5	8.0 ± 7.5; [.72]	6.4 ± 5.8; [.31]
Number of defibrillations *	0.7 ± 2.4	0.7 ± 1.9; [.93]	0.5 ± 1.2; [.59]
Rate of ROSC ≥ 15 min – no. (%)	47 (50.5)	27 (51.9); [1.00]	39 (81.3); [< .001]
Medication **			
Vasopressin – IU	0.0 ± 0.0	0.0 ± 0.0	73.3 ± 30.1
Epinephrine – mg †	7.5 ± 6.3	7.8 ± 7.0; [.79]	6.3 ± 5.9; [.29]
Methylprednisolone - mg	0.0 ± 0.0	0.0 ± 0.0	40.0 ± 0.0
Atropine – mg †	2.7 ± 1.0	2.9 ± 0.6; [.19]	2.7 ± 0.9; [.94]
Amiodarone – mg ††	0.0 (0.0-300.0)	0.0 (0.0-300.0); [.67]	0.0 (0.0-300.0); [.65]
Bicarbonate – mmol ††	0.0 (0.0-90.0)	0.0 (0.0-90.0); [1.00]	0.0 (0.0-90.0); [.23]
Calcium – mmol ††	0.0 (0.0-6.8)	0.0 (0.0-6.8); [.07]	0.0 (0.0-6.8); [.62]
Reverse tissue-type plasminogen activator – mg ††	0.0 (0.0-100.0)	0.0 (0.0-100.0); [.30]	0.0 (0.0-100.0); [.33]
Temporary pacing-no./total no. (%) ††	2/32 (6.3)	2/14 (14.3); [.57]	2/17 (11.8); [.60]

ALS, advanced life support; ROSC, return of spontaneous circulation. For variables with missing values, data availability is reported below.

* Recordings of data were available for ≥88 historical controls.

† In 7 historical controls, at least 1 value of these variables was not recorded.

§ For historical controls, ALS duration was recorded in ranges of 1 to 5 min (e.g. 4 to 5 min, or 25 to 30 min); the mean values of the recorded ranges were calculated and analyzed.

There was no recorded case of difficult endotracheal intubation.

‡ Missing historical control data were retrieved from individual patient records (4 cases), or derived according to the recorded epinephrine dose (2 cases).

** In historical controls, there was no recorded case of difficult intravenous cannulation or drug administration via an alternative route; thus, we presumed that all drugs were given intravenously.

*,†,§,#,‡,** Source: records of cardiopulmonary resuscitation procedures of the Department of Anesthesiology.

†† Data presented as median (range). Recorded data were available only from the 32 intensive care or coronary care unit patients of the historical control-group; these data were compared with the data from the 14 and 17 intensive care or coronary care unit patients of the control-group and study-group, respectively.

Table S9. Physiological variables during and within 30-min after cardiopulmonary resuscitation. Brackets contain *P*-values versus historical control.

	Historical controls (n = 93)	Control group (n = 52)	Study group (n = 48)
During resuscitation			
Systolic arterial pressure - mm Hg *	76.0 ± 17.9	76.0 ± 21.2; [.82]	105.9 ± 28.5; [< .001]
Mean arterial pressure - mm Hg *	52.4 ± 11.7	54.5 ± 16.5; [.67]	72.0 ± 17.9; [< .001]
Diastolic arterial pressure - mm Hg *	40.6 ± 9.1	44.5 ± 14.5; [.37]	55.0 ± 14.4; [< .001]
PaO_2 - mm Hg †	98.0 ± 50.6	91.9 ± 57.6; [.60]	109.1 ± 111.3; [.63]
$PaCO_2$ - mm Hg †	54.1 ± 15.4	56.2 ± 16.8; [.54]	55.6 ± 32.6; [.82]
Arterial pH †	7.10 ± 0.13	7.07 ± 0.17; [.36]	7.06 ± 0.20; [.33]
Potassium ion - mEq/L †	5.6 ± 1.3	5.6 ± 1.2; [.87]	5.4 ± 1.8; [.72]
Sodium ion - mEq/L †	143.1 ± 9.8	144.6 ± 10.2; [.45]	140.0 ± 10.8; [.20]
Calcium ion - mEq/L †	2.1 ± 0.9	2.1 ± 1.2; [.58]	2.0 ± 0.6; [.20]
Glucose - mg/dL †	254.7 ± 86.9	262.9 ± 75.0; [.64]	286.6 ± 183.1; [.42]
After return of spontaneous circulation			
Systolic arterial pressure - mm Hg §	103.8 ± 22.8	106.1 ± 34.6; [.68]	131.2 ± 50.4; [.001]
Mean arterial pressure - mm Hg §	70.6 ± 15.3	73.8 ± 23.6; [.54]	92.9 ± 35.4; [< .001]
Diastolic arterial pressure - mm Hg §	54.2 ± 12.5	57.7 ± 20.0; [.41]	73.8 ± 29.3; [.001]
Heart rate - beats/min #	118.4 ± 20.7	117.9 ± 26.3; [.92]	112.4 ± 29.8; [.30]
PaO_2 - mm Hg #	144.5 ± 106.5	142.4 ± 89.6; [.94]	193.7 ± 137.2; [.07]
$PaCO_2$ - mm Hg #	48.8 ± 13.5	46.2 ± 17.6; [.49]	42.8 ± 22.3; [.14]
Arterial pH #	7.22 ± 0.12	7.25 ± 0.15; [.39]	7.22 ± 0.18; [.96]
Potassium ion - mEq/L #	4.8 ± 1.0	4.7 ± 1.0; [.89]	4.7 ± 1.4; [.82]
Sodium ion - mEq/L #	140.6 ± 9.6	141.9 ± 10.2; [.60]	142.8 ± 11.4; [.33]
Calcium ion - mEq/L #	1.7 ± 0.6	2.2 ± 1.6; [.10]	2.2 ± 1.2; [.07]
Glucose - mg/dL #	281.8 ± 102.3	278.3 ± 83.3; [.88]	281.9 ± 144.1; [1.00]
Peri-arrest Lactate - mmol/liter ‡	10.4 ± 4.6	10.2 ± 5.2; [.86]	9.9 ± 5.8; [.64]
Norepinepheine - μg/kg/min **	0.4 ± 0.4	0.4 ± 0.4; [.59]	0.5 ± 0.4; [.60]
Dobutamine - μg/kg/min **	0.0 (0.0-13.8)	0.0 (0.0-15.0); [1.00]	0.0 (0.0-0.0); [.17]
Epinephrine - μg/kg/min **	0.0 (0.0-0.1)	0.0 (0.0-0.0); [.58]	0.0 (0.0-0.1); [.46]
Intravenous fluids - ml **††	140 (70-185)	104 (64-520); [.58]	90 (75-215); [.46]

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

For variables with missing values, data availability is reported below.

* Data are from reviewed charts of 25 of 32 historical controls, and from 14 control-group, and 17 study-group patients; all these patients were in the intensive or coronary care unit.

† Data are from 50 of 72 historical controls, and from 40 control-group and 26 study-group patients; all these patients received more than 3 cardiopulmonary resuscitation cycles.

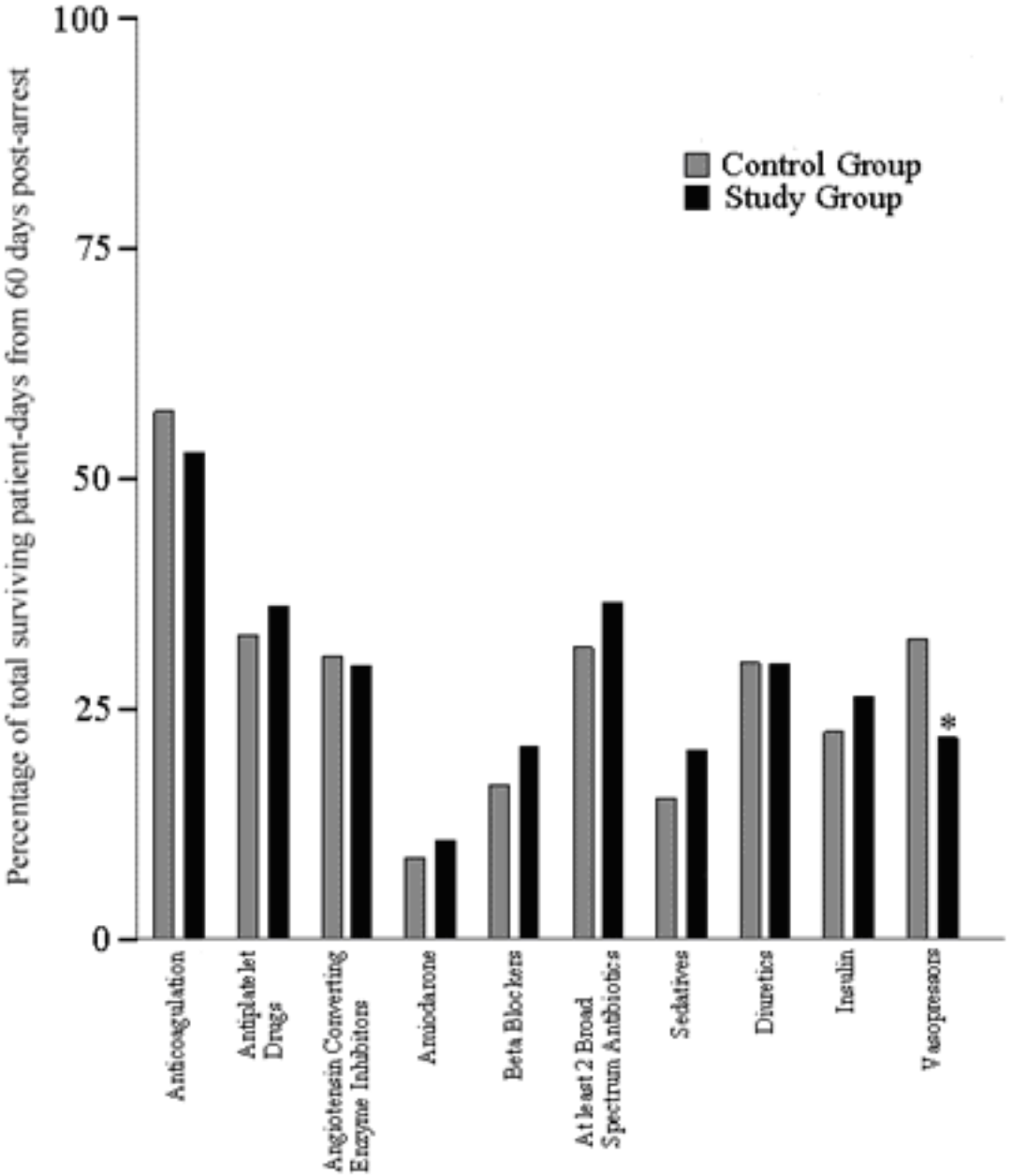
§ Systolic, diastolic, and mean arterial pressure data are from 46 of 47, 43 of 47, and 43 of 47 historical controls, respectively, and from 27 control-group and 39 study-group patients; all these patients were successfully resuscitated.

Data are from 43 of 47 historical controls, and from 27 control-group and 39 study-group patients; all these patients were successfully resuscitated. .

‡ Arterial blood gas analysis-derived lactate concentrations during cardiopulmonary resuscitation or within 30 min after return of spontaneous circulation. In 67 of the 93 historical controls, there was at least 1 recorded value of peri-arrest lactate. In 16 successfully resuscitated historical controls, there were recordings of lactate concentrations for both the resuscitation and immediate (i.e., first 30 min) post-resuscitation phase. Such "double" peri-arrest lactate values, were also available from 33 control-group and study-group patients. All "double" peri-arrest lactate values were first averaged and then analyzed.

** Recordings of data within 15-30 min following successful resuscitation were available for 28 intensive or coronary care unit patients of the historical control-group. These data were compared with the data from 10 and 17 intensive or coronary care unit patients of the control-group and study-group, respectively.

675 †† Refers to cumulative administered volume of crystalloids, colloids, packed red
676 blood cells and fresh frozen plasma from the onset of cardiopulmonary resuscitation
677 to 15-30 min following return of spontaneous circulation.
678 1 mm Hg = 0.133 kPa. For Potassium and Sodium: 1 mEq/L = 1 mmol/L. For
679 Calcium: 2 mEq/L = 1 mmol/L. For Glucose: 1 mg/dL = 0.0555 mmol/L.
680
681
682
683
684
685
686
687
688
689
690



691

692 **Figure S1.** Use of various classes of drugs (i.e., drug-days) expressed as percentage of
693 the sum of the numbers of days each patient survived within a 60-day period
694 following randomization.

695 * *P* =.002 vs. control.

696

697

698

699

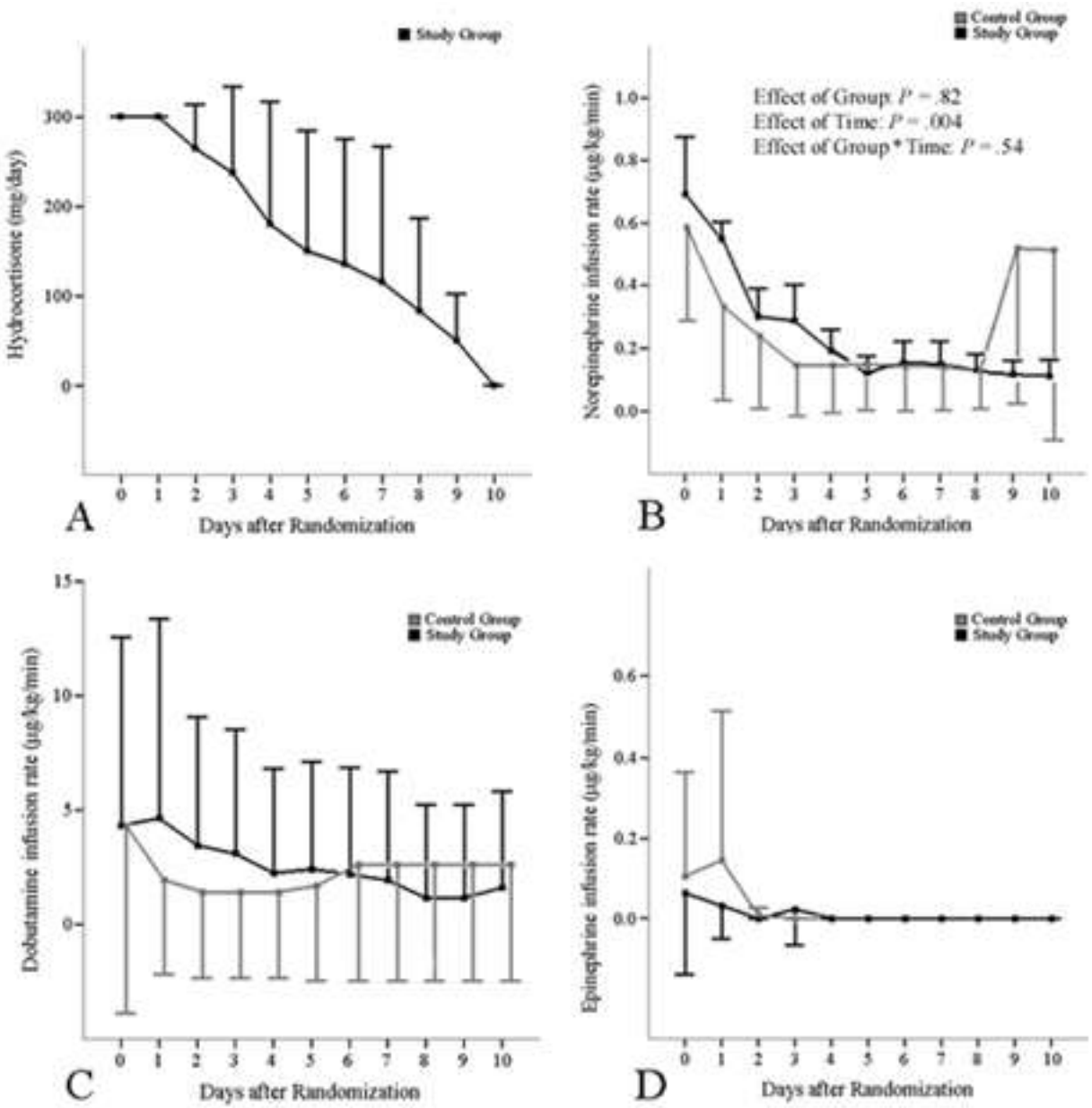
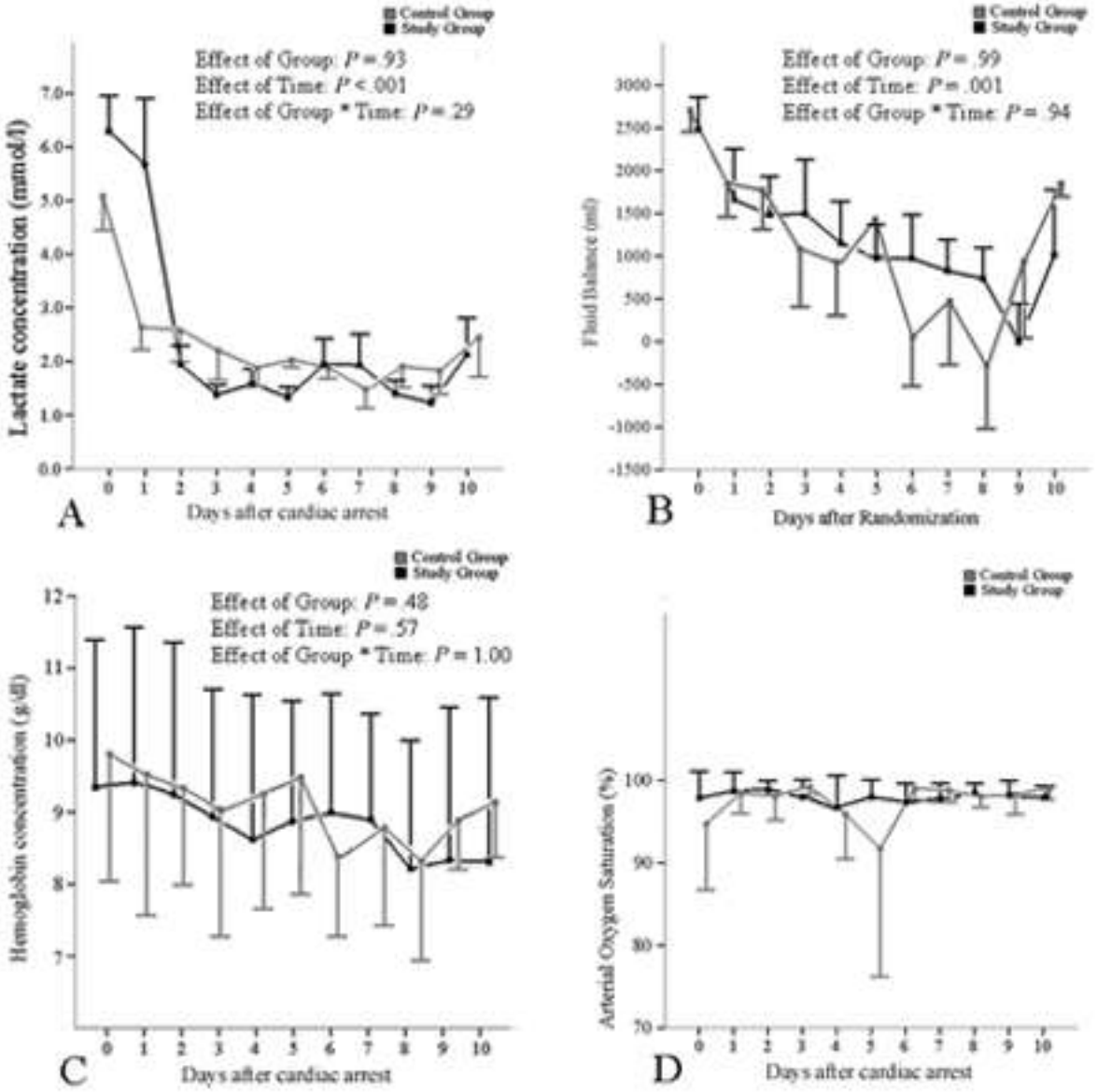


Figure S2. A: Daily dose of hydrocortisone in the study group during the first 10 days post-randomization in patients with postresuscitation shock who survived for 4 hours or more following return of spontaneous circulation B: Data on average daily norepinephrine infusion rate; results of mixed-model analysis are presented within the diagram. C and D: Data on daily dosages of dobutamine and epinephrine (respectively); the distributions of these two variables were skewed; however, respective data are reported as mean ± standard deviation, in order to simplify the

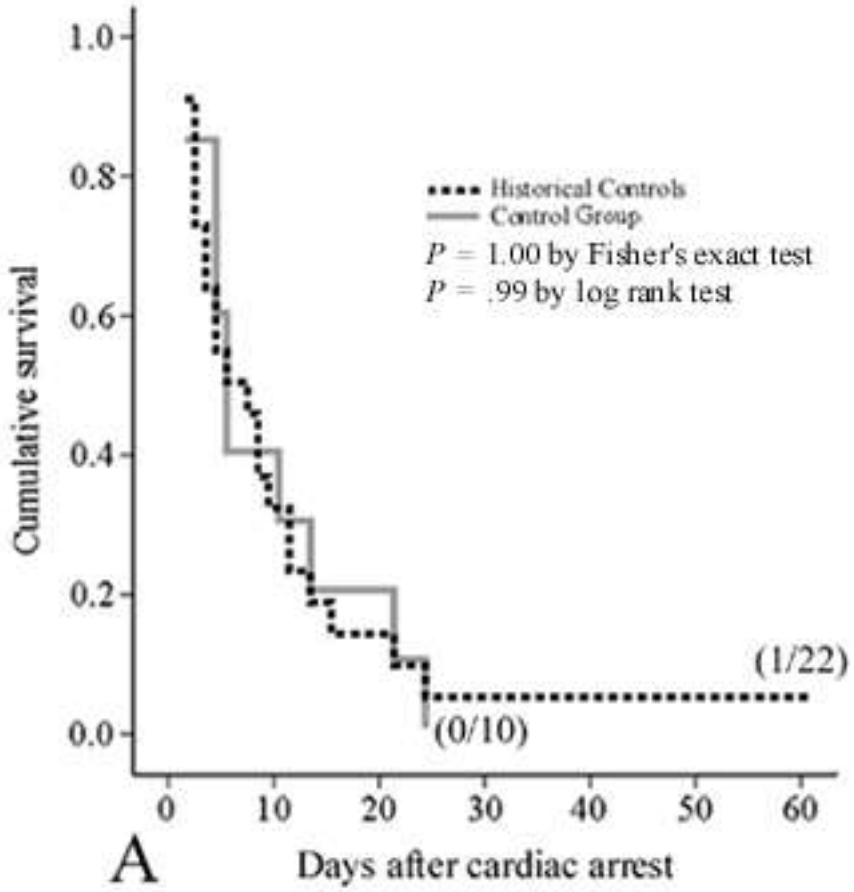
presentation. In A,C,D: Dots, mean value; Error-bars, standard deviation. In B: Dots, mean value; Error-bars, standard error (to facilitate the presentation).

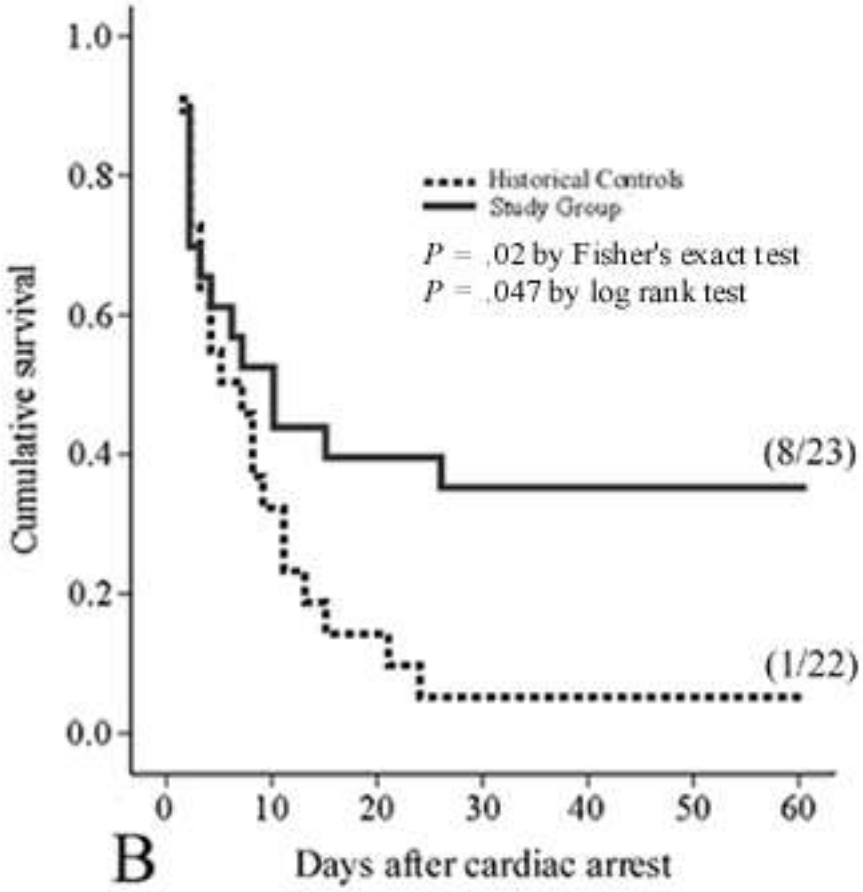


734
735

736 **Figure S3.** Data on arterial blood lactate (A), fluid balance (B), hemoglobin
737 concentration (C), and arterial oxygen saturation (D) recorded during the first 10 days
738 post-arrest in patients with postresuscitation shock who survived for 4 hours or more
739 following return of spontaneous circulation. A-C: results of mixed-model analyses are
740 presented within each diagram. In A,B: Dots, mean value; Error-bars, standard error
741 (to facilitate the presentation). In C,D: Dots, mean value; Error-bars, standard
742 deviation. In D, Data on arterial oxygen saturation are reported as mean ± standard

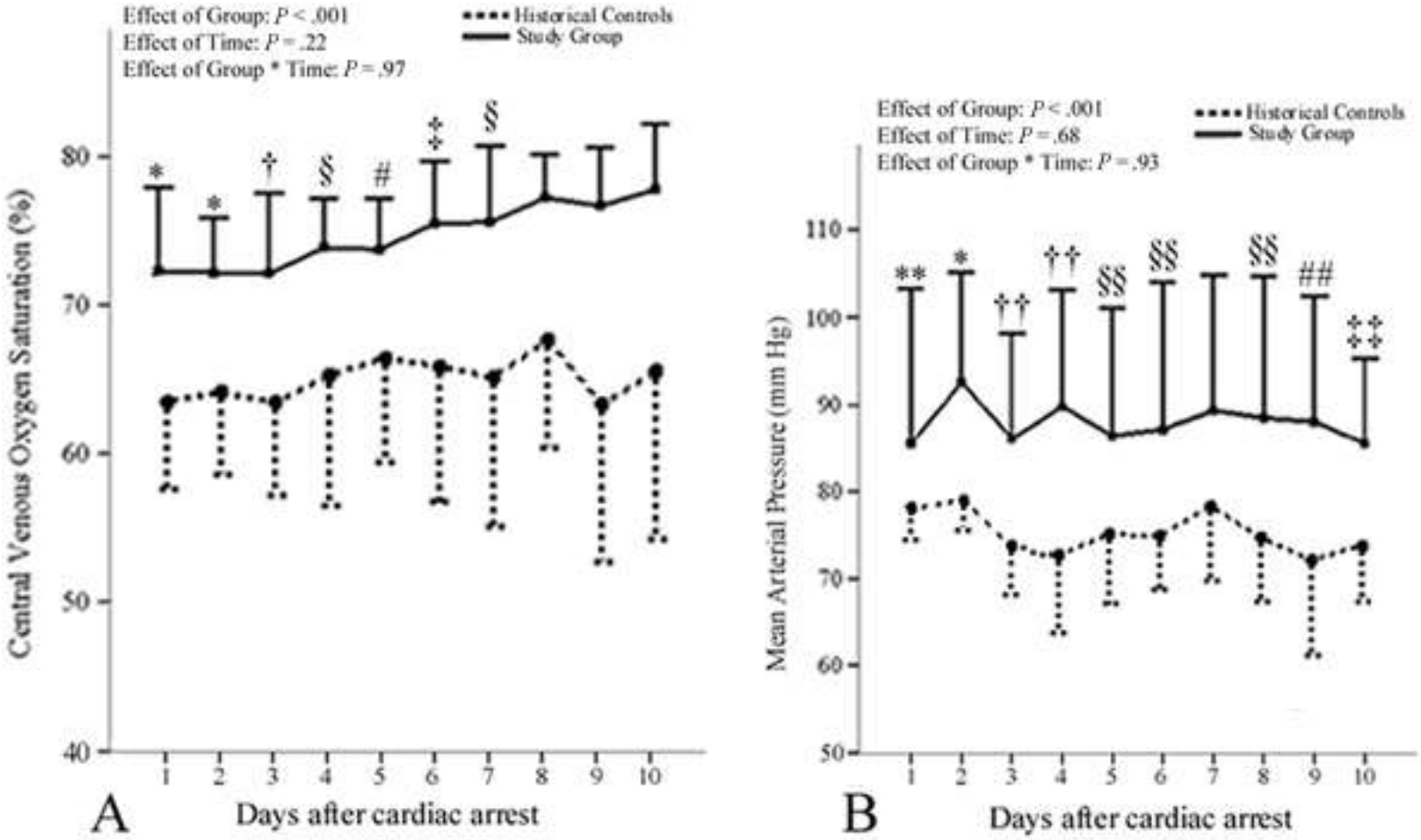
deviation for simpler presentation, despite the fact that distributions of daily values were not always normal.


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 = .99 by log rank test
(1/22)
(0/10)
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 = .02 by Fisher's exact test
P = .047 by log rank test
(8/23)
(1/22)
0
10
20
30
40
50
60
B
Days after cardiac arrest

768

769 **Figure S4.** Probabilty of survival to day 60 after cardiac arrest in 22 historical controls versus 10 actual control group-patients (A) and 23 study-
770 group patients (B); all patients survived for 24 hours or more after the cardiac arrest. Parentheses, survivors/total number of patients. Survival
771 rates to day 60 after cardiac arrest were identical to survival rates to hospital discharge.



772

773 **Figure S5.** Historical controls vs. study-group: Time course of central-venous oxygen saturation (A) and mean arterial pressure (B) in historical

774 controls and study-group patients with postresuscitation shock. In historical controls, 37 of 126 (29.4%) of daily oxygen saturation values were

775 missing. Results of linear mixed-model analysis are presented at the top left corner of each diagram. Dots, mean; Error-bars, standard deviation.
776 * $P < .001$; †, $P = .003$; §, $P = .04$; #, $P = .008$; ‡, $P = .007$; **, $P = .004$; ††, $P = .001$; §§, $P = .03$; ##, $P = .02$; ‡‡, $P = .01$ (independent
777 samples *t* test).
778
779
780