Resuscitation 85 (2014) 628–636

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical Paper

Hypertonic saline infusion during resuscitation from out-of-hospital cardiac arrest: A matched-pair study from the German Resuscitation Registry☆,☆☆

Christopher Hahn[a], Martin Breil[b], Jens Christian Schewe[b], Martin Messelken[a], Stefan Rauch[a], Jan Thorsten Gräsner[c], Jan Wnent[d], Stephan Seewald[d], Andreas Bohn[e], Matthias Fischer[a,*], the Study Group German Resuscitation Registry

[a] Department of Anaesthesiology and Intensive Care, Klinik am Eichert, ALB FILS Kliniken, Göppingen, Germany
[b] Department of Anaesthesiology and Intensive Care Medicine, Bonn University Hospital, Bonn, Germany
[c] Department of Anaesthesiology and Intensive Care Medicine, Schleswig-Holstein University Hospital, Kiel Campus, Kiel, Germany
[d] Department of Anaesthesiology and Intensive Care Medicine, Schleswig-Holstein University Hospital, Lübeck Campus, Lübeck, Germany
[e] City of Münster Fire Department, Münster, Germany

ARTICLE INFO

Article history:
Received 12 September 2013
Received in revised form 5 December 2013
Accepted 19 December 2013

Keywords:
Out-of-hospital-cardiac-arrest
Small volume resuscitation
Hypertonic saline
RACA-score
Hospital admittance rate
Case control clinical trial

ABSTRACT

Aim: Survival rates after out-of-hospital-cardiac-arrest (OHCA) differ widely between EMS systems. Since hypertonic saline appears to improve long-term outcome after OHCA, some local EMS systems have included it in their treatment protocols for OHCA. Our first aim was to give a quality review of one of these protocols. Our second aim was to assess whether short-term survival improves when hypertonic saline is used in resuscitation after OHCA.
Methods: Matched pairs were identified for the independent "return of spontaneous circulation (ROSC) after cardiac arrest" (RACA) score variables and for use of ACD-CPR, adrenaline, and amiodarone from the German Resuscitation Registry (GRR) for January 2000 to March 2011. Patients received either 2 ml kg^{-1} hypertonic saline with hydroxyethyl starch (7.2% NaCl with 6% hydroxyethyl starch 200,000/0.5, HyperHAES® [HHS]) infused intravenously within 10 min during CPR according to local treatment protocols or standard of care CPR (NON-HHS). The primary endpoint was admission to hospital rate (with spontaneous circulation); secondary endpoint was ROSC rate in relation to RACA score.
Results: 322 matched pairs were defined for 14 variables. Predicted ROSC-rate using RACA-score was similar in HHS (44.63%) and NON-HHS (43.63%; $p = 0.440$). In contrast, 190 (59.0%) HHS patients achieved ROSC compared with only 136 NON-HHS patients (42.2%; χ^2: $p < 0.0001$). Short term survival measured as rate of "admission to hospital with spontaneous circulation" was achieved in 169 HHS patients (52.5%) versus 108 NON-HHS patients (33.5%) (OR 2.19; 95%CI: 1.592–3.009; χ^2: $p < 0.0001$).
Conclusion: Locally implemented treatment protocols using hypertonic saline/HES after OHCA are safe and effective. Also, we verified that short-term survival rates were better in patients receiving HHS.

Abbreviations: ACD-CPR, active-compression–decompression cardiopulmonary resuscitation; BLS-D-teams, basic life support team equipped with semiautomatic defibrillator; CA, cardiac arrest; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; ECG, electrocardiogram; GRR, German Resuscitation Registry; HHS, hypertonic saline with hydroxyethyl starch (7.2% NaCl with 6% hydroxyethyl starch 200,000/0.5, HyperHAES®); HS, hypertonic saline; MBF, myocardial blood flow; OHCA, out-of-hospital cardiac arrest; OR, odds ratio; PCI, percutaneous coronary intervention; pVT, pulseless ventricular tachycardia; ROSC, return of spontaneous circulation; VF, ventricular fibrillation.

☆☆ A Spanish translated version of the abstract of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2013.12.033.

* Corresponding author at: Department of Anaesthesia and Intensive Care, Klinik am Eichert, ALB FILS KLINIKEN GmbH, Postfach 660, D-73006 Göppingen, Germany.
E-mail address: Matthias.Fischer@af-k.de (M. Fischer).
URL: http://www.alb-fils-kliniken.de/ (M. Fischer).

0300-9572/$ – see front matter © 2014 The Authors. Published by Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.resuscitation.2013.12.033

1. Introduction

Out-of-hospital-cardiac-arrest (OHCA) is a major problem in all industrialized countries with an incidence of more than 100 victims per 100,000 inhabitants per year.[1] The incidence of treated OHCA is about 50 per 100,000 inhabitants per year[2] but differs between emergency medical services (EMS) systems. The number of live patients admitted to hospital ranges from 5 to 30 per 100,000 inhabitants each year.[1,3,4] These widely varying survival rates after OHCA between EMS systems[1,3,4] could be improved by implementing high quality basic life support,[5,6] adrenaline,[7,8] or amiodarone[9,10] during resuscitation and use of therapeutic hypothermia,[11,12] percutaneous coronary intervention (PCI),[13,14] and standard operating procedures in the post-resuscitation phase.[15]

High quality basic life support to reperfuse the heart is the first step for cardiopulmonary resuscitation (CPR) success. It has to be emphasized, however, that myocardial blood flow (MBF) is limited even when thoracic compressions are optimized. Therefore pharmacological measures, which potentially will further increase MBF during CPR, are needed. One of these measures is the use of adrenaline. Two randomized clinical trials (RCTs) demonstrated that adrenaline alone[8] or combined with other intravenous drugs[7] significantly increases short-term survival after OHCA. Experimental studies have shown that adrenaline increases MBF during CPR by vasoconstriction.[16] But other pathophysiological changes limiting reperfusion like endothelial cell swelling, perivascular oedema, rolling and sticking of leukocytes, and haemoconcentration[17–21] are not addressed by adrenaline. Experimental studies demonstrated that pharmacological therapy using 2 ml kg^{-1} body weight hypertonic saline (7.2%) (HS) reduces these changes in several animal shock models.[22–24] Such studies have also shown that treatment with HS after CA improves microcirculatory reperfusion of the brain and heart[22,25–28] and short-term survival,[26–28] reduces protein-S100 and troponin release after CPR,[29] and improves neurological recovery after forebrain ischaemia.[30]

Based on these findings we undertook a randomized clinical trial (RCT) using 2 ml kg^{-1} body weight HS/hydroxyethyl starch (HES) or HES alone during CPR after OHCA.[31,32] In 200 patients, we failed to demonstrate that administration of HS improves admission to hospital or hospital discharge rate. But in contrast, more OHCA patients were discharged with good neurological recovery after pharmacological treatment with hypertonic saline/HES.[32] Unfortunately, the relatively small number of 100 patients receiving hypertonic saline/HES limits the impact of this RCT.

EMS systems in Germany employ specially trained emergency physicians for Advanced Life Support (ALS). Based on experimental studies and our RCT,[32] local treatment protocols for the use of hypertonic saline in OHCA treatment were developed first in the EMS systems of Bonn and Göppingen. According to these protocols, hypertonic saline with HES is given during CPR if the emergency physician prescribes this solution for an individual.

The first aim of the present study was to provide a quality review of the implemented local treatment protocol in Göppingen, which includes hypertonic saline/HES during CPR. Our second important aim was to assess whether short-term survival after OHCA is improved when hypertonic saline/HES is given. For this main objective we used a matched-pairs-analysis using data in the German Resuscitation Registry (GRR).[33,34]

2. Methods

This is a retrospective case–control study performed in accordance with the Helsinki Declaration and was approved by the ethics committee of the regional medical board of registration (Landesärztekammer Baden-Württemberg 29.01.13).

Data for this study were taken from the GRR, which was developed by the "Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin". This registry covers 17 million inhabitants with more than 27,000 patients after OHCA and more than 550 patients receiving hypertonic saline/HES as a result of local treatment protocols. This registry is constructed in accordance with the Utstein style.[33,35] Time of cardiac arrest (CA) – defined as the cessation of cardiac mechanical activity[35] – is recorded in the database. If the beginning of CA is not witnessed, presumed time of CA is documented. If rescuers on the scene do not consider trauma, submersion, drug overdose, asphyxia or exsanguination as cause of CA, a cardiac aetiology is adopted.

The matched-pair analysis was approved by the scientific advisory board of the GRR (Ref no: GRR 01/2013). Subjects in the HHS group received 2 ml kg^{-1} estimated bodyweight of hypertonic saline with hydroxyethyl starch (HHS) (7.2% NaCl with 6% hydroxyethyl starch 200,000/0.5, HyperHAES®, Fresenius KABI, 61346 Bad Homburg, Germany). This solution was infused intravenously in a 10-min interval during CPR before ROSC occurred. In patients found in VF/VT the solution was given after the first shocks failed and in patients with asystole/EMD hypertonic saline/HES was given after the first dose of i.v. epinephrine. Cases were excluded from the analysis if they met one or more of the following criteria:

- Age < 18 years
- Traumatic CA/exsanguination
- Incomplete dataset for matching criteria or outcome

Subjects in the NON-HHS group did not receive HHS. All patients were treated according to the European Resuscitation Guidelines 2000 or 2005 because the sample period spanned implementation times for both (January 2000 through March 2011). According to the above defined inclusion and exclusion criteria, 11,125 subjects were identified in the GRR (Fig. 1).

3. Emergency medical services (EMS) system of Göppingen and the locally implemented treatment protocol

A detailed description of the EMS system of Göppingen was given by Neukamm et al.[36] The EMS system covers both urban and rural areas, serves 192,000 inhabitants, and has a service area of 354 km^2. The first vehicle reached 77.9% of the patients within 8 min after alert. The BLS-D crew members are trained to perform thorax compressions using an "active compression decompression device" combined with an "impedance threshold device".[37,38] Adrenaline, atropine and amiodarone were given according to the guidelines. HHS is infused intravenously in 10 min during CPR before ROSC if the emergency physician prescribes this solution for the individual. In patients found in VF/VT the solution was given after the first shocks failed and in patients with asystole/EMD hypertonic saline/HES was given after the first dose of i.v. epinephrine. The EMS system of Göppingen implemented this protocol in 2005 and has delivered CPR Data to the GRR since June 2006.

3.1. ROSC after CA (RACA) score

The RACA-score was developed to predict short-term survival after OHCA.[34] It was defined using a multivariate logistic regression model, with "ever ROSC" as the short-term outcome variable. The probability of "ever ROSC" was calculated using the formula $1/(1+e^{-x})$, where x is the sum of the following independent factors that have a significant positive or negative impact on the probability of "ever ROSC":

- Age ≥80 years (−0.2);

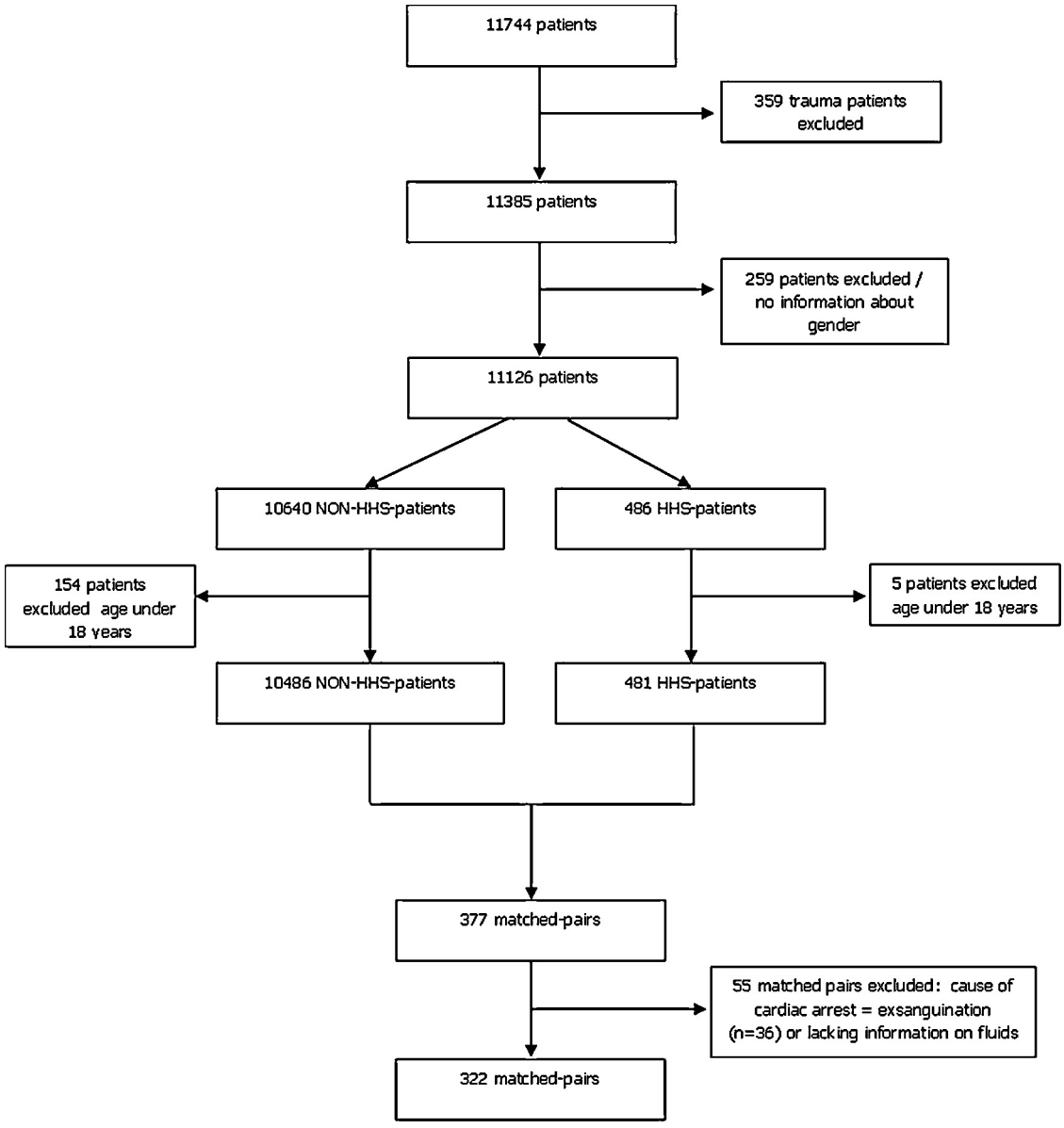

Fig. 1. Flowchart for extracting the 322 matched pairs out of 11,744 patients in the German Resuscitation Registry (within the study period from January 2000 to March 2011). The 322 patients of the HHS-group received CPR according to the ERC-guidelines and an infusion of 2 ml kg^{-1} body weight of hypertonic saline with hydroxyethyl starch in a 10-min interval during CPR; the NON-HHS-group received standard treatment.

- asystole (−1.1) or pulseless electric activity (PEA; −0.8) as first rhythm;
- bystander CPR (+0.2);
- location of arrest at a medical institution (+0.5), doctor's office (+1.2), public place (+0.3), or nursing home (−0.3);
- male gender (−0.2);
- presumed aetiology of hypoxia (+0.7), intoxication (+0.5), or trauma (−0.6);
- time to the arrival of professionals (−0.04 per min); and
- witnessed by laypeople (+0.6) or by professionals (+0.5).

3.2. Statistical analysis

Matched pairs were built first on the basis of the RACA-score variables (variables 1–11) and, second, on therapeutic measures having shown their impact on short term survival in RCTs (variables 12–14):

(1)	Gender female	(YES/NO)
(2)	Age > 80 years	(YES/NO)
(3)	Cardiac origin	(YES/NO)
(4)	Collapse witnessed	(YES/NO)
(5)	Bystander CPR performed	(YES/NO)
(6)	First ECG rhythm shockable	(YES/NO)
(7)	Location of arrest "nursing home"	(YES/NO)
(8)	Location of arrest "public/doctor's office"	(YES/NO)
(9)	Time until arrival ≤5 min[a]	(YES/NO)
(10)	Time until arrival = 6–10 min[a]	(YES/NO)
(11)	Time until arrival ≥10 min[a]	(YES/NO)
(12)	Active Compression Decompression-CPR performed[37,38]	(YES/NO)
(13)	Administration of adrenaline[7,8]	(YES/NO)
(14)	Administration of amiodarone[10]	(YES/NO)

[a] Time until arrival = time interval from collapse/dispatch alert until first EMS vehicle stopped at scene.

Matched pairs were created and all data were computed using Excel XP (Microsoft Corp., Redmond, WA, USA) and SPSS version 18 (SPSS Inc., Chicago, IL, USA). If more than one matching partner was found for an HHS patient, the control patient was randomly chosen. After the matching procedure was finished, 322 matched pairs were identified. The primary endpoint of the matched pairs analysis was "admission to hospital with spontaneous circulation", secondary endpoints were "ROSC rate" and "ROSC rate in relation to RACA-score".[34]

All numerical data are expressed as means ± standard deviation. Differences between groups were analysed for significance by the χ^2-test and Student's *t*-test. Statistical significance was assumed for $p < 0.05$ and the confidence interval was set to 95%.

4. Results

Our first aim was to provide a quality review of the implemented local treatment protocol in Göppingen EMS system. This OHCA protocol combines the concepts of high quality CPR, adrenaline, and HHS during CPR. Using this approach it has achieved remarkably high survival rates in 704 patients between June 2006 and March 2013. The CPR incidence reached 55.3 per 100,000 inhabitants per year. Adrenaline and HHS were given to 80.5% and 36.1% of the patients, respectively. ACD-ITV CPR was performed in only 37.5% due to delivery difficulties of the ITV devices during that period. For all 704 patients, the predicted ROSC rate was 39.4% using RACA-score,[34] but we achieved a significantly higher ROSC rate of 48.8% (CI 44.3–53.3%); the hospital admittance rate with spontaneous circulation reached 47.3%. Of the 704 patients, 15.8% were discharged from hospital. The hospital discharge rate for OHCA patients with CPC 1 and CPC 2 was a remarkable 13.1%. In the subgroup of patients with VF/VT and cardiac aetiology we counted 153 patients. Of these patients 72.1% were admitted to hospital with spontaneous circulation, 35.1% could be discharged from hospital and 31.8% could be discharged with CPC 1 or 2.

For our second aim of assessing whether short-term survival after OHCA is improved when hypertonic saline/HES is given, our analysis included 644 patients, 322 matching pairs. There were not any statistical differences between the HHS-group and the NON-HHS-group within the 14 matching variables listed above (Table 1).

The median age of the patients was 67.81 ± 13.72 years in the HHS-group and 66.63 ± 15.54 years in the NON-HHS-group ($p = 0.304$). In both groups 72% of patients were male and 28% were female. Cardiac origin of arrest was presumed in 78.6% of both groups. Time until arrival on scene of the first team was similar with 4.78 ± 5.08 min in the HHS-group and 5.03 ± 5.19 min in the NON-HHS-group ($p = 0.258$). Collapse was witnessed in 60.6% of both groups. Location of arrest was "nursing home" in 3.4% and "public" or "doctor's office" in 10.2% in both groups. First rhythm was shockable in 32.3% and bystander-CPR was performed in 30.1% of both groups.

No statistical differences were found between the HHS- and NON-HHS-groups in drug administration for drugs with known impact on short-term survival. Adrenaline was given to 95.3% of the patients in both groups with a mean dosage of 8.74 ± 5.75 mg in the HHS-group and 9.01 ± 6.50 mg in the NON-HHS-group ($p = 0.587$). Amiodarone was given to 35.4% of the patients of each group. When it was administered, the dosage in the groups was the comparable (HHS-group = 294.30 ± 91.39 mg; NON-HHS-group = 298.25 ± 95.92; $p = 0.751$).

For drugs without impact on short term survival the following results were found. Vasopressin was given to 15.2% of the patients in the HHS-group and 3.4% in the NON-HHS-group ($p < 0.001$), but the mean dosage was comparable when given (HHS-group = 40.41 ± 9.57 I.E.; NON-HHS-group = 34.64 ± 12.67 I.E.; $p = 0.094$). Atropine was given to 32.3% of the patients in both groups with similar dosages (HHS-group = 2.62 ± 0.81 mg; NON-HHS-group = 2.70 ± 1.53 mg; $p = 0.612$) (Table 2).

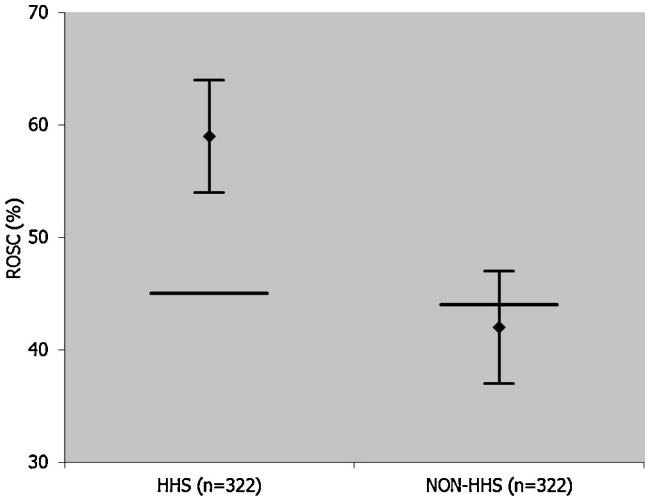

Fig. 2. The predicted RACA-ROSC rate (%) is represented by the horizontal lines; achieved ROSC rate is shown by the diamonds (±confidence interval). Patients of the HHS-group received an infusion of 2 ml kg^{-1} body weight of hypertonic saline with hydroxyethyl starch in a 10-min interval during CPR.

Only the HHS-group received hypertonic saline/HES. The mean volume administered in the HHS-group was 215.11 ± 48.17 ml. Colloids were administered in 5.3% and 7.1% of the patients in the HHS- and NON-HHS-groups, respectively ($p = 0.327$). The HHS-group received slightly higher volumes of colloids than the NON-HHS-group although the difference did not reach statistical significance (HHS-group = 500.35 ± 337.29 ml; NON-HHS-group = 331.30 ± 216.68 ml; $p = 0.061$).

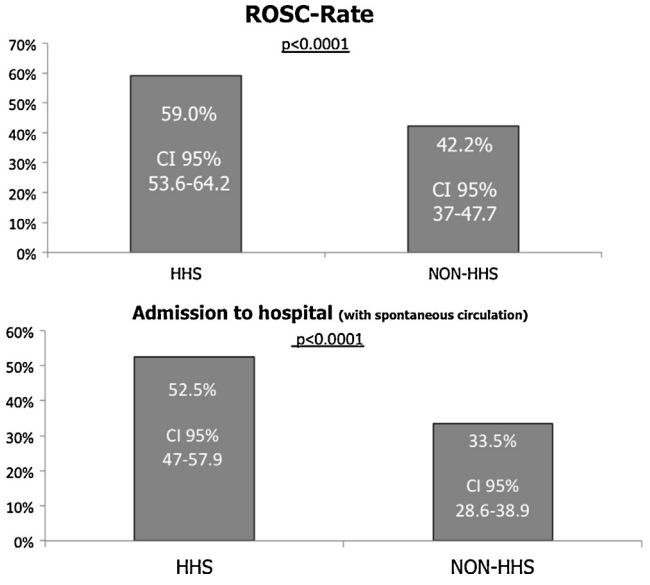

Fig. 3. (Top panel) ROSC rate (%) of HHS- and NON-HHS-group; $n = 322$ in each group; patients of the HHS-group received an infusion of 2 ml kg^{-1} body weight of hypertonic saline with hydroxyethyl starch in a 10-min interval during CPR. (ROSC-rate: HHS-group: 59.0%; NON-HHS-group: 42.2%; OR 1.97; CI 95%: 1.439–2.693; χ^2: $p < 0.0001$). (Bottom panel) Admission to hospital with spontaneous circulation rate (%) of HHS- and NON-HHS-group; $n = 322$ in each group. Patients of the HHS-group received an infusion of 2 ml kg^{-1} body weight of hypertonic saline with hydroxyethyl starch in a 10-min interval during CPR (admission-rate: HHS-group: 52.5%; NON-HHS-group: 33.5%; OR 2.19; CI 95% 1.592–3.009; χ^2: $p < 0.0001$).

Table 1
Matching criteria.

	Overall	HHS-group	NON-HHS-group	*p*-Value
Sex male (%)	72	72	72	1
Age >80 years (%)	17.7	17.7	17.7	1
Cardiac origin (%)	78.6	78.6	78.6	1
Collapse witnessed (%)	60.6	60.6	60.6	1
Bystander-CPR (%)	30.1	30.1	30.1	1
First rhythm shockable (%)	32.3	32.3	32.3	1
ACD-CPR (%)	45.0	45.0	45.0	1
Location rest home of the elderly (%)	3.4	3.4	3.4	1
Location public/doctor's office (%)	10.2	10.2	10.2	1
Time interval from collapse ≤5 min (%)	56.5	56.5	56.5	1
Time interval from collapse 6–10 min (%)	30.7	30.7	30.7	1
Time interval from collapse ≥10 min (%)	12.7	12.7	12.7	1
Treatment with adrenaline (%)	95.3	95.3	95.3	1
Treatment with amiodarone (%)	35.4	35.4	35.4	1

p-Value calculated by χ^2-test. Patients of the HHS-group received an infusion of 2 ml kg^{-1} body weight of hypertonic saline with hydroxyethyl starch in a 10-min interval during CPR.

Crystalloids were administered in 83.9% and 80.4% of the patients in the HHS- and NON-HHS-group, respectively ($p = 0.258$). The HHS-group received slightly higher volumes of crystalloids than the NON-HHS-group (HHS-group = 718.36 ± 619.69 ml; NON-HHS-group = 603.11 ± 321.96 ml; $p = 0.007$).

4.1. CPR success rates

Predicted ROSC-rate calculated by RACA-score was not different between groups (HHS-group = 44.63%; NON-HHS-group = 43.63%, $p = 0.440$). The achieved ROSC rate in the NON-HHS group was not different from predicted value (NON-HHS predicted = 43.63%; achieved = 42.2%, 95%CI: 36.8–47.6%). In contrast, HHS treatment significantly increased the achieved ROSC rate (HHS predicted = 44.63%; achieved = 59.0%, 95%CI: 53.6–64.4%) (Fig. 2).

In the HHS-group 190 patients achieved ROSC compared with only 136 patients in the NON-HHS group (achieved ROSC-rate: HHS-group = 59.0%; NON-HHS-group = 42.2%; OR 1.97; 95%CI: 1.439–2.693; χ^2: $p < 0.0001$) (Fig. 3, top panel).

In addition the "admission to hospital rate" was significantly higher in the HHS-group. Admission to hospital with spontaneous circulation was achieved in 169 HHS patients and only 108 NON-HHS patients (HHS-group = 52.5%; NON-HHS-group = 33.5%; OR 2.19; 95%CI: 1.592–3.009; χ^2: $p < 0.0001$) (Fig. 3, bottom panel).

For better understanding when and how hypertonic saline/HES solution in CPR might work, we analysed all subgroups – defined by the matching criteria – of the 644 patients our case–control study. These subgroups were drawn from the 322 pairs by excluding those pairs which did not fit to the subgroup criterion. For these subgroups we calculate RACA-ROSC rate, and rate of patients "admitted to hospital with spontaneous circulation" (Table 3 and Fig. 4). In all of these subgroups predicted ROSC-rate by RACA-score were comparable between patients receiving HHS or not, but in all subgroups "admission to hospital rate" were higher in patients receiving HHS. In terms of "hospital admission rate with spontaneous circulation", these differences were significant for the following subgroups: gender female (YES, NO), age of patients > 80 years (YES, NO), cardiac origin (YES, NO), collapse witnessed (YES, NO), bystander-CPR performed (YES, NO), first ECG-rhythm shockable (YES, NO), time interval until arrival of first EMS vehicle ≤ 5 min and 6–10 min (YES, NO), time interval until arrival of first EMS vehicle ≥ 10 min (NO), ACD-CPR performed (NO), administration of adrenaline (YES), administration of amiodarone (YES, NO).

In conclusion the effect of HHS could be detected over all 644 patients and in all subgroups. But HHS might not be as effective if time interval until arrival of first EMS vehicle was too long (≥11 min), location of arrest was "nursing home", administration of adrenaline was not necessary and if ACD-CPR was performed.

5. Discussion

The present study demonstrated that the locally implemented treatment protocol in Göppingen using i.a. hypertonic saline/HES after OHCA is very effective, because achieved ROSC-rate is higher than predicted and 92 out of 704 patients survived with good neurological recovery. In Göppingen the rate of survivors with CPC1 + 2 reached 13.1% or 7.2 per 100,000 inhabitants per year. This survival rate is much more higher than recently reported from the "Resuscitation Outcome Consortium", USA[39,40] (survival: 6–8%, no incidence reported) and from Denmark (2010: 3.7 survivors per 100,000 inhabitants per year).[41]

Second, we verified that short-term survival rates were higher in patients listed in the GRR as receiving HHS. In fact, the matched-pairs analysis in 644 patients demonstrated that the administration of 2 ml kg^{-1} body weight HHS during CPR significantly increased "hospital admittance rate with ROSC" from 33.5% to 52.5% although predicted ROSC-rate was similar in both groups. These results are consistent with previous experimental studies[26,27] and, in

Table 2
Drugs administered.

	Overall	HHS-group	NON-HHS-group	*p*
Adrenaline (mg)	8.87 ± 6.13	8.74 ± 5.75	9.01 ± 6.50	0.587
Vasopressin (U)	39.35 ± 10.33	40.41 ± 9.57	34.64 ± 12.67	0.094
Atropine (mg)	2.66 ± 1.22	2.62 ± 0.81	2.70 ± 1.53	0.612
Thrombolysis (mg)	3997.60 ± 4073.54	3538.13 ± 4047.73	4353.32 ± 4124.06	0.467
Sodium bicarbonate (ml)	99.25 ± 86.02	87.86 ± 42.08	113.25 ± 118.76	0.129
Amiodarone (mg)	296.27 ± 93.50	294.30 ± 91.39	298.25 ± 95.92	0.751
Lidocaine (mg)	108.33 ± 28.87	100.00 ± 0	114.29 ± 37.80	0.424
HHS (ml)		215.11 ± 48.17	Not used	

Mean ± standard deviation; *p*-value calculated by *t*-tests. Patients of the HHS-group received an infusion of 2 ml kg^{-1} body weight of hypertonic saline with hydroxyethyl starch in a 10-min interval during CPR.

Table 3
Subgroups analysis.

		Rate of hospital admission with spontaneous circulation [*n* of admission/*n* of patients (%)]			χ^2-Test of HHS vs NON-HHS	Predicted ROSC rate by RACA score [%]	[%]	*t*-Test of HHS vs NON-HHS
		Overall	HHS-group	NON-HHS-group	*p*	HHS	NON-HHS-group	*p*
	All pairs	277/644 (43.0%)	169/322 (52.5%)	108/322 (33.5%)	<0.0001	44.63	46.63	0.440
Subgroups								
(1.)	Gender female = YES	79/180 (43.9%)	49/90 (54.4%)	30/90 (33.3%)	0.004	48.25	45.90	0.326
	Gender female = NO	198/464 (42.7%)	120/232 (51.7%)	78/232 (33.6%)	<0.0001	43.23	42.76	0.757
(2.)	Age of patients > 80 years = YES	39/114 (34.2%)	25/57 (43.9%)	14/57 (24.6%)	0.030	40.76	36.58	0.141
	Age of patients > 80 years = NO	238/530 (44.9%)	144/265 (54.3%)	94/265 (35.5%)	<0.0001	45.46	45.13	0.827
(3.)	Cardiac origin = YES	218/506 (43.1%)	133/253 (52.6%)	85/253 (33.6%)	<0.0001	45.39	43.96	0.346
	Cardiac origin = NO	59/138 (42.8%)	36/69 (52.2%)	23/69 (33.3%)	0.025	41.84	42.44	0.789
(4.)	Collapse wittnesed = YES	190/390 (48.7%)	112/195 (57.4%)	78/195 (40.0%)	<0.001	50.82	49.45	0.383
	Collapse wittnesed = NO	87/254 (34.3%)	57/127 (44.9%)	30/127 (23.6%)	<0.0001	35.13	34.70	0.796
(5.)	Bystander-CPR performed = YES	93/194 (47.9%)	54/97 (55.7%)	39/97 (40.2%)	0.031	52.41	50.99	0.562
	Bystander-CPR performed = NO	184/450 (40.9%)	115/225 (51.1%)	69/225 (30.7%)	<0.0001	41.28	40.47	0.564
(6.)	First ECG rhythm shockable = YES	122/208 (58.7%)	75/104 (72.1%)	47/104 (45.2%)	<0.0001	62.08	60.43	0.187
	First ECG rhythm shockable = NO	155/436 (35.6%)	94/218 (43.1%)	61/218 (28.0%)	<0.001	36.31	35.62	0.559
(7.)	Location of arrest "nursing home" = YES	10/22 (45.5%)	6/11 (54.5%)	4/11 (36.4%)	0.392	38.36	42.45	0.274
	Location of arrest "nursing home" = NO	267/622 (42.9%)	163/311 (52.4%)	104/311 (33.4%)	<0.0001	44.85	44.03	0.532
(8.)	Location of arrest public/doctor's office = YES	33/66 (50%)	19/33 (57.6%)	14/33 (42.4%)	0.218	55.67	50.91	0.272
	Location of arrest public/doctor's office = NO	244/578 (42.2%)	150/289 (51.9%)	94/289 (32.5%)	<0.0001	43.37	42.80	0.669
(9.)	Time interval until arrival of first EMS vehicle ≤5 min = YES	161/364 (44.2%)	96/182 (52.7%)	65/182 (35.7%)	<0.001	45.61	45.10	0.763
	Time interval until arrival of first EMS vehicle ≤5 min = NO	116/280 (41.4%)	73/140 (52.1%)	43/140 (30.7%)	<0.0001	43.36	41.74	0.406
(10.)	Time interval until arrival of first EMS vehicle 6–10 min = YES	82/198 (41.4%)	55/99 (55.6%)	27/99 (27.3%)	<0.0001	45.51	44.12	0.534
	Time interval until arrival of first EMS vehicle 6–10 min = NO	195/446 (43.7%)	114/223 (51.1%)	81/223 (36.3%)	0.002	44.24	43.42	0.603
(11.)	Time interval until arrival of first EMS vehicle ≥ 11 min = YES	34/82 (41.5%)	18/41 (43.9%)	16/41 (39.0%)	0.654	38.17	36.00	0.553
	Time interval until arrival of first EMS vehicle ≥ 11 min = NO	243/562 (43.2%)	151/281 (53.7%)	92/281 (32.7%)	<0.0001	45.57	44.75	0.544
(12.)	ACD-CPR performed = YES	136/290 (46.9%)	76/145 (52.4%)	60/145 (41.4%)	0.060	43.28	43.00	0.877
	ACD-CPR performed = NO	141/354 (39.8%)	93/177 (52.5%)	48/177 (27.1%)	<0.0001	45.74	44.16	0.375
(13.)	Administration of adrenaline = YES	257/614 (41.9%)	158/307 (51.5%)	99/307 (32.2%)	<0.0001	44.00	43.35	0.619
	Administration of adrenaline = NO	20/30 (66.7%)	11/15 (73.3%)	9/15 (60.0%)	0.439	57.68	49.55	0.223
(14.)	Administration of amiodarone = YES	124/228 (54.4%)	73/114 (64.0%)	51/114 (44.7%)	0.003	50.68	48.65	0.363
	Administration of amiodarone = NO	153/416 (36.8%)	96/208 (46.2%)	57/208 (27.4%)	<0.0001	41.32	40.89	0.774

Subgroup analysis. Subgroups were defined by the used matching criteria, those pairs were excluded which did not fit to the specified criterion. Absolute numbers of admissions and patients, percentage; *p*-value calculated by χ^2-test or *t*-test. Patients of the HHS-group received an infusion of 2 ml kg^{-1} body weight of hypertonic saline with hydroxyethyl starch in a 10-min interval during CPR.

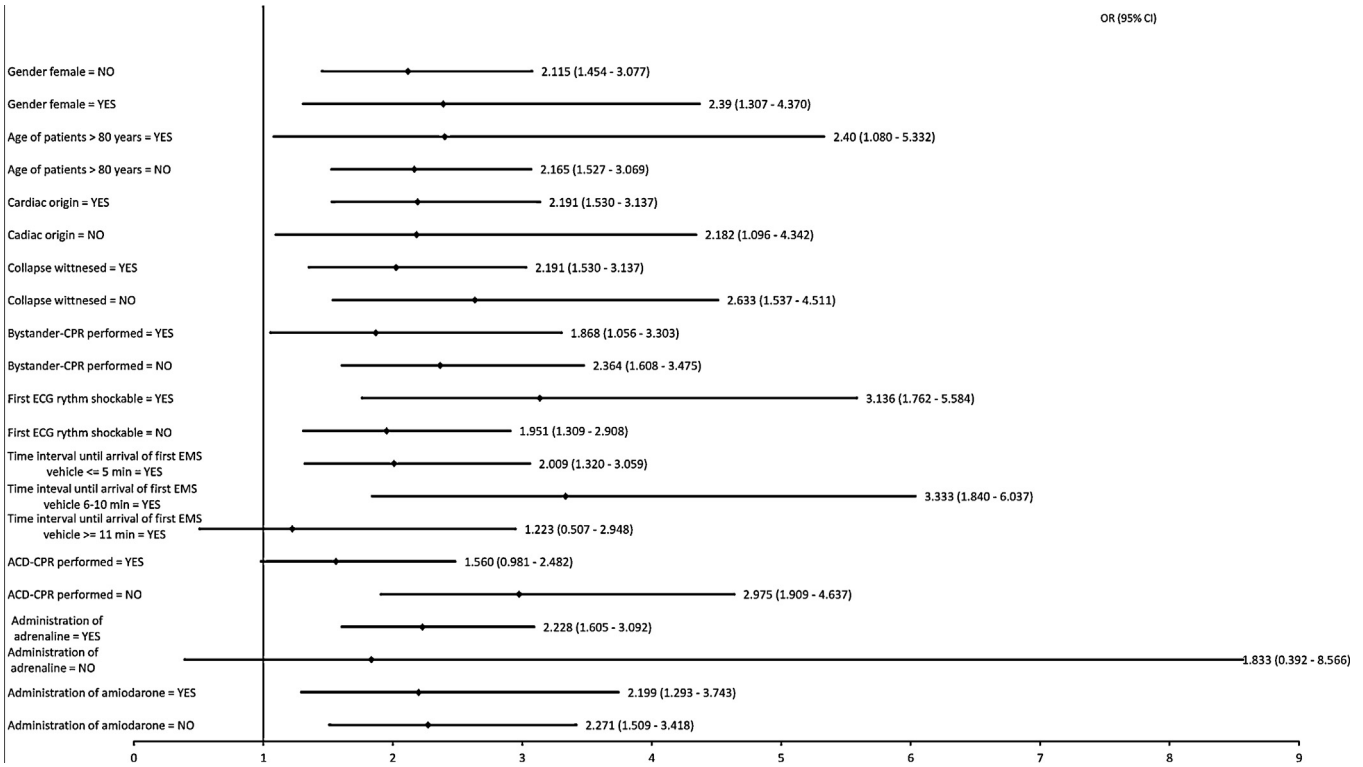

Fig. 4. Subgroup analysis using forest plot for the endpoint "hospital admission with spontaneous circulation". Subgroups were defined by the used matching criteria, those pairs were excluded which did not fit to the specified criterion. Patients of the HHS-group received an infusion of 2 ml kg^{-1} body weight of hypertonic saline with hydroxyethyl starch in a 10-min interval during CPR.

part, with our RCT,[31,32] which demonstrated an improvement in neurological outcome at discharge from hospital. In that RCT administration of HHS increased the number of patients with "good cerebral performance or only moderate cerebral disability at discharge" from 5% to 13% (χ^2: $p < 0.05$; OR 2.9, 95%CI: 1.004–8.5).[32]

While the current study did not address any mechanisms that might be involved in the improved short-term survival after HHS treatment in OHCA patients, results from previous studies offer possible explanations. In experimental studies[22,26–28,42] and in the RCT[32] HHS application during CPR led to an increase of serum sodium concentration; this osmotic gradient was shown to reduce endothelial cell swelling and increase capillary diameter in shock models, caused by a fluid shift from intracellular to intravascular space.[24] Also, in several experimental studies of CA using different techniques to assess organ blood flow, the administration of hypertonic saline improved myocardial and cerebral blood flow during CPR.[22,25–28] In these studies it was demonstrated that improved myocardial reperfusion increases short term survival.[26–28] A final possibility is that, the better neurological recovery with application of hypertonic saline after CA and forebrain ischaemia[30,32] could be the result of a reduced no-reflow-phenomenon[22,43] and an increased reperfusion of the brain in the first hours after CPR[25,28,42] as was indicated by a reduced protein-S100 release after CPR.[29]

The application of 2 ml kg^{-1} body weight HHS increases serum sodium level for a short period.[32] This leads to fluid shift from the endothelium and the perivascular cells to the intravascular compartment and improves microcirculatory blood flow. However, administration of hypertonic saline/HES during CPR does not cause a pronounced volume expansion and haemodilution[32] so this could not be the key mechanism of improved short-term survival with small volume resuscitation during CPR.

The dosage of HHS that we used in the matched pairs study and the RCT was 2 ml kg^{-1} body weight infused in 10 min during CPR. A higher dosage of 4 ml kg^{-1} body weight – that is recommended for haemorrhagic shock – was not more effective than 2 ml kg^{-1} body weight after experimental CA.[26] We therefore recommend 2 ml kg^{-1} body weight hypertonic saline/HES for treatment of OHCA.

Emergency physicians in Germany are well trained i.a. in endotracheal intubation and establishing i.v. access. In the current study, hypertonic saline/HES was administered early in the CPR algorithm during chest compressions, a short time after establishing an i.v. access. This was also the situation in our earlier RCT pertaining to the Bonn EMS system; infusion of hypertonic saline/HES was started 14.8 ± 6.9 min after collapse and ALS-measures began 12.0 ± 6.6 min after collapse.[32]

In the presented data adrenaline was given to 95.3% of both the HHS and NON-HHS groups in a mean dosage of 8.87 mg. Adrenaline administration has been shown to increase short-term survival in previous RCTs. In the study by Olasveengen et al.[7] "hospital admission rate" after OHCA significantly increased from 20.6% to 31.8% (OR 1.8; 95%CI: 1.322–2.462) in patients receiving intravenously administered drugs, mainly adrenaline. Jacobs et al.[8] demonstrated that adrenaline administered during CPR significantly increases hospital admittance rate from 13.0% to 25.4% (OR 2.3; 95%CI: 1.4–3.6). In the current matched pairs analysis we reported that including the administration of HHS during CPR to subjects already receiving adrenaline significantly increased hospital admittance rate from 33.5% to 52.5% (χ^2: $p < 0.0001$; OR 2.19; 95%CI: 1.592–3.009). Looking at these data, one is tempted to conclude that adrenaline and hypertonic saline/HES have an additive positive impact on short-term survival after OHCA. Further studies need to be completed before such a conclusion can be made, however. In addition, we must highlight that pharmacological treatment with adrenaline and – most likely – hypertonic saline/HES is only effective when "basic life support" is performed at a high level of quality.[44]

Negative side effects of small volume resuscitation after CA of cardiac origin were not observed and seem unlikely since we saw a higher admission rate in the current matched pairs study and the higher survival rates with good neurological recovery after hypertonic saline/HES in our previous RCT.[32] In fact some clinical studies demonstrate that the infusion of even a large volume of cold saline solution (up to 30 ml kg^{-1} body weight) for the induction of hypothermia after CPR is safe and feasible,[45,46] suggesting that small volume resuscitation has a negligible effect. Nevertheless, safety aspects of the administration of hypertonic saline/HES after CPR from OHCA should be closely followed.

5.1. Limitations

First, this is a case–control study and not a randomized clinical trial. We therefore cannot exclude that influencing factors which are not documented in the GRR or we did not know will have influenced the results. But the method we used – a matched pairs study based on the RACA-score – will have minimize the risk of an important selection bias. This argument is supported by our finding, that the predicted ROSC rate – calculated by the RACA score – did not differ significantly between the two groups (HHS-group = 44.63%; NON-HHS-group = 43.63%, $p = 0.440$).

Second, the patients of both groups were matched using all influencing factors that were quantified in the logistic regression analysis for the definition of the RACA-score. In addition, the patients were matched for those therapeutic measures with statistically significant impact on short-term survival, i.e., ACD-CPR, adrenaline and amiodarone. However, in Germany the measurement of CPR quality after OHCA is not routinely used. For that reason, it is possible that patients receiving HHS get better CPR than patients in the NON-HHS group. To avoid this influence we matched our patients for the use of ACD-CPR, which was equally distributed to both groups and therefore ACD-CPR cannot explain the better survival rates in the HHS-group.

Third, due to our long review period, patients were resuscitated according to two different guidelines (2000 and 2005). The number of patients within the time periods was equally distributed in both groups and recent studies showed no difference in outcome if patients were treated according to different guidelines.[39,47] But due to the fact, that our sample period ended in March 2011 we do not know the effect of hypertonic saline/HES infusion during CPR when the 2010 ERC guidelines were implemented.

Fourth, rate of vasopressin application and amount of crystalloid infusion differed between the HHS and NON-HHS group significantly. However, since neither vasopressin[48,49] nor crystalloid infusion influence short-term survival, it is unlikely that this affected our results.

5.2. Conclusions

In conclusion, our method of a "matched pairs analysis" of subjects retrieved from the GRR controlled most of the obviously known predictors of outcome after CPR. For this reason ROSC-rate predicted by the RACA-score did not differ between the HHS- and NON-HHS-group. Our study clearly demonstrated that patients receiving hypertonic saline/HES while being resuscitated achieved significantly higher "ROSC" and "hospital admission rates" compared with those being resuscitated conventionally. To the best of our knowledge the administration of hypertonic saline/HES during CPR is an easy, feasible, and safe measure to improve short-term survival after CA of non-traumatic aetiology. It could be a new pharmacological approach to improve microcirculatory reperfusion of the heart and brain during CPR. Further clinical trials are recommended to verify the effect of this measure on long-term survival with good neurological recovery as demonstrated in the RCT by Breil et al. in 2012.[32]

Conflict of interest statement

The authors declare that they have no competing interests.

Role of funding source

This study has no funding source.

Author contributions

CH, JTG and MF have made substantial contributions to conception and design, and drafted the manuscript. SS provided statistical support.

JCS, MB, MM, JTG, JW, SS and AB contributed data to the GRR and helped to revise the manuscript. JTG, SR and MF have been involved in the final revising the manuscript critically for important intellectual content, and have given final approval of the version to be published.

Acknowledgements

The authors are indebted to all active participants of the GRR who registered OHCA patients on a voluntary basis. The registry is organized and funded by the German Society of Anaesthesiology and Intensive Care Medicine. Further, the authors would like to thank all professionals involved in prehospital emergency medical care and intensive care at the following 23 emergency physician-staffed emergency medical systems (Study Group of the German Resuscitation Registry): Berlin (Schmittbauer W), Bonn (Heister U), Dortmund (Lemke H, Schniedermeier U), Dresden (Haacke W), Erlangen (Schüttler J, Birkholz T, Meyer M), Esslingen (Immrich W, Kerner M), Eutin (Knacke P), Göppingen (Fischer M, Messelken M), Gütersloh (Strickmann B), Heidelberg (Russ N, Bernhard M), Kaiserslautern (Madler C, Kumpch M), Lüneburg (Zeng T), Lünen (Franz R), Malchin (Hanff T), Marburg (Kill C), Meiningen (Walther M), Münster (Bohn A, Lukas R), Ostfildern (Kehrberger E, Gmyrek M), Remscheid (Bachus T), Rendsburg-Eckernförde (Dörges V, Gräsner JT), Straubing (Mrugalla R, Thiel C), Trier (Schmitz CS, Carl L), and Tübingen (Fischer H).

The investigators also thank Nancy Alsip, PhD, for editing and reviewing the manuscript (Office of Clinical Research Services and Support, University of Louisville).

References

1. Berdowski J, Berg RA, Tijssen JG, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: systematic review of 67 prospective studies. Resuscitation 2010;81:1479–87.
2. Nichol G, Thomas E, Callaway CW, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. JAMA 2008;300:1423–31.
3. Herlitz J, Bahr J, Fischer M, Kuisma M, Lexow K, Thorgeirsson G. Resuscitation in Europe: a tale of five European regions. Resuscitation 1999;41:121–31.
4. Fischer M, Fischer NJ, Schuttler J. One-year survival after out-of-hospital cardiac arrest in Bonn city: outcome report according to the 'Utstein style'. Resuscitation 1997;33:233–43.
5. Lukas RP, Grasner JT, Seewald S, et al. Chest compression quality management and return of spontaneous circulation: a matched-pair registry study. Resuscitation 2012.
6. Wik L, Kramer-Johansen J, Myklebust H, et al. Quality of cardiopulmonary resuscitation during out-of-hospital cardiac arrest. JAMA 2005;293:299–304.
7. Olasveengen TM, Sunde K, Brunborg C, Thowsen J, Steen PA, Wik L. Intravenous drug administration during out-of-hospital cardiac arrest: a randomized trial. JAMA 2009;302:2222–9.
8. Jacobs IG, Finn JC, Jelinek GA, Oxer HF, Thompson PL. Effect of adrenaline on survival in out-of-hospital cardiac arrest: a randomised double-blind placebo-controlled trial. Resuscitation 2011;82:1138–43.

9. Dorian P, Cass D, Schwartz B, Cooper R, Gelaznikas R, Barr A. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. N Engl J Med 2002;346:884–90.
10. Kudenchuk PJ, Cobb LA, Copass MK, et al. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. N Engl J Med 1999;341:871–8.
11. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346:549–56.
12. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557–63.
13. Grasner JT, Meybohm P, Caliebe A, et al. Postresuscitation care with mild therapeutic hypothermia and coronary intervention after out-of-hospital cardiopulmonary resuscitation: a prospective registry analysis. Crit Care 2011;15:R61.
14. Wnent J, Seewald S, Heringlake M, et al. Choice of hospital after out-of-hospital cardiac arrest – a decision with far-reaching consequences: a study in a large German city. Crit Care 2012;16:R164.
15. Tomte O, Andersen GO, Jacobsen D, Draegni T, Auestad B, Sunde K. Strong and weak aspects of an established post-resuscitation treatment protocol – a five-year observational study. Resuscitation 2011;82:1186–93.
16. Chase PB, Kern KB, Sanders AB, Otto CW, Ewy GA. Effects of graded doses of epinephrine on both noninvasive and invasive measures of myocardial perfusion and blood flow during cardiopulmonary resuscitation. Crit Care Med 1993;21:413–9.
17. Behmanesh S, Kempski O. Mechanisms of endothelial cell swelling from lactacidosis studied in vitro. Am J Physiol Heart Circ Physiol 2000;279:H1512–7.
18. Kempski O, Behmanesh S. Endothelial cell swelling and brain perfusion. J Trauma 1997;42:S38–40.
19. Lin PJ, Chang CH, Hsiao CW, et al. Continuous antegrade warm blood cardioplegia attenuates augmented coronary endothelium-dependent contraction after cardiac global ischemia and reperfusion. J Thorac Cardiovasc Surg 1997;114:100–8.
20. Caceres MJ, Schleien CL, Kuluz JW, Gelman B, Dietrich WD. Early endothelial damage and leukocyte accumulation in piglet brains following cardiac arrest. Acta Neuropathol 1995;90:582–91.
21. Jehle D, Fiorello AB, Brader E, Cottington E, Kozak RJ. Hemoconcentration during cardiac arrest and CPR. Am J Emerg Med 1994;12:524–6.
22. Fischer M, Hossmann KA. Volume expansion during cardiopulmonary resuscitation reduces cerebral no-reflow. Resuscitation 1996;32:227–40.
23. Nolte D, Bayer M, Lehr HA, et al. Attenuation of postischemic microvascular disturbances in striated muscle by hyperosmolar saline dextran. Am J Physiol 1992;263:H1411–6.
24. Mazzoni MC, Borgstrom P, Intaglietta M, Arfors KE. Capillary narrowing in hemorrhagic shock is rectified by hyperosmotic saline-dextran reinfusion. Circ Shock 1990;31:407–18.
25. Jameson SJ, Mateer JR, DeBehnke DJ. Early volume expansion during cardiopulmonary resuscitation. Resuscitation 1993;26:243–50.
26. Fischer M, Dahmen A, Standop J, Hagendorff A, Hoeft A, Krep H. Effects of hypertonic saline on myocardial blood flow in a porcine model of prolonged cardiac arrest. Resuscitation 2002;54:269–80.
27. Breil M, Krep H, Sinn D, et al. Hypertonic saline improves myocardial blood flow during CPR, but is not enhanced further by the addition of hydroxy ethyl starch. Resuscitation 2003;56:307–17.
28. Krep H, Breil M, Sinn D, Hagendorff A, Hoeft A, Fischer M. Effects of hypertonic versus isotonic infusion therapy on regional cerebral blood flow after experimental cardiac arrest cardiopulmonary resuscitation in pigs. Resuscitation 2004;63:73–83.
29. Krieter H, Denz C, Janke C, et al. Hypertonic–hyperoncotic solutions reduce the release of cardiac troponin I and s-100 after successful cardiopulmonary resuscitation in pigs. Anesth Analg 2002;95:1031–6 [table of contents].
30. Noppens RR, Christ M, Brambrink AM, Koerner IP, Heimann A, Kempski O. An early bolus of hypertonic saline hydroxyethyl starch improves long-term outcome after global cerebral ischemia. Crit Care Med 2006;34:2194–200.
31. Bender R, Breil M, Heister U, et al. Hypertonic saline during CPR: feasibility and safety of a new protocol of fluid management during resuscitation. Resuscitation 2007;72:74–81.
32. Breil M, Krep H, Heister U, et al. Randomised study of hypertonic saline infusion during resuscitation from out-of-hospital cardiac arrest. Resuscitation 2012;83:347–52.
33. Grasner JT, Meybohm P, Fischer M, et al. A national resuscitation registry of out-of-hospital cardiac arrest in Germany – a pilot study. Resuscitation 2009;80:199–203.
34. Grasner JT, Meybohm P, Lefering R, et al. ROSC after cardiac arrest – the RACA score to predict outcome after out-of-hospital cardiac arrest. Eur Heart J 2011;32:1649–56.
35. Jacobs I, Nadkarni V, Bahr J, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries. A statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa). Resuscitation 2004;63:233–49.
36. Neukamm J, Grasner JT, Schewe JC, et al. The impact of response time reliability on CPR incidence and resuscitation success: a benchmark study from the German Resuscitation Registry. Crit Care 2011;15:R282.
37. Wolcke BB, Mauer DK, Schoefmann MF, et al. Comparison of standard cardiopulmonary resuscitation versus the combination of active compression–decompression cardiopulmonary resuscitation and an inspiratory impedance threshold device for out-of-hospital cardiac arrest. Circulation 2003;108:2201–5.
38. Aufderheide TP, Frascone RJ, Wayne MA, et al. Standard cardiopulmonary resuscitation versus active compression–decompression cardiopulmonary resuscitation with augmentation of negative intrathoracic pressure for out-of-hospital cardiac arrest: a randomised trial. Lancet 2011;377:301–11.
39. Bigham BL, Koprowicz K, Rea T, et al. Cardiac arrest survival did not increase in the Resuscitation Outcomes Consortium after implementation of the 2005 AHA CPR and ECC guidelines. Resuscitation 2011;82:979–83.
40. Aufderheide TP, Nichol G, Rea TD, et al. A trial of an impedance threshold device in out-of-hospital cardiac arrest. N Engl J Med 2011;365:798–806.
41. Wissenberg M, Lippert FK, Folke F, et al. Association of national initiatives to improve cardiac arrest management with rates of bystander intervention and patient survival after out-of-hospital cardiac arrest. JAMA 2013;310:1377–84.
42. Krep H, Bottiger BW, Bock C, et al. Time course of circulatory and metabolic recovery of cat brain after cardiac arrest assessed by perfusion- and diffusion-weighted imaging and MR-spectroscopy. Resuscitation 2003;58:337–48.
43. Fischer M, Hossmann KA. No-reflow after cardiac arrest. Intensive Care Med 1995;21:132–41.
44. Pytte M, Kramer-Johansen J, Eilevstjonn J, et al. Haemodynamic effects of adrenaline (epinephrine) depend on chest compression quality during cardiopulmonary resuscitation in pigs. Resuscitation 2006;71:369–78.
45. Bernard SA, Smith K, Cameron P, et al. Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: a randomized controlled trial. Circulation 2010;122:737–42.
46. Kamarainen A, Virkkunen I, Tenhunen J, Yli-Hankala A, Silfvast T. Prehospital therapeutic hypothermia for comatose survivors of cardiac arrest: a randomized controlled trial. Acta Anaesthesiol Scand 2009;53:900–7.
47. Deasy C, Bray JE, Smith K, et al. Cardiac arrest outcomes before and after the 2005 resuscitation guidelines implementation: evidence of improvement? Resuscitation 2011;82:984–8.
48. Gueugniaud PY, David JS, Chanzy E, et al. Vasopressin and epinephrine vs. epinephrine alone in cardiopulmonary resuscitation. N Engl J Med 2008;359:21–30.
49. Wenzel V, Krismer AC, Arntz HR, et al. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. N Engl J Med 2004;350:105–13 [see comment].