Mild therapeutic hypothermia improves outcomes compared with normothermia in cardiac-arrest patients—a retrospective chart review*

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Objective: **Studies showing the effectiveness of therapeutic hypothermia (32–34°C) in postcardiac arrest patients have been criticized because of patients with elevated body temperature (>37.5°C) in the noncooled control group. Thus, the effects of spontaneous normothermia (<37.5°C) compared with mild therapeutic hypothermia were studied.**

Design: **Retrospective chart review from 1991 to 2010.**

Patients: **Witnessed out-of-hospital arrest, presumed to be of cardiac origin, aged 18 to 80 yrs and with a Glassgow Coma Scale score of <8 at admission.**

Interventions: **Patients with sustained restoration of spontaneous circulation who did not receive therapeutic hypothermia and never exceeded 37.5°C during the 36 hrs postcardiac arrest were compared with patients who received mild therapeutic hypothermia.**

Measurements and Main Results: **The primary end point was a favorable neurological outcome, defined as Cerebral Performance Categories 1 or 2; the secondary end point was overall survival to 180 days. Significantly more patients in the hypothermia group had Cerebral Performance Categories 1 or 2 (hypothermia: 256 of 467 [55%] vs. normothermia: 69 of 165 [42%]) and survived for >180 days (hypothermia: 315 of 467 [67%] vs. normothermia: 79 of 165 [48%]). The propensity score adjusted risk ratio for good neurological outcome of patients undergoing hypothermia treatment was 1.37 (confidence interval 1.09–1.72, $p \leq .01$) and for dying within 180 days was 0.57 (confidence interval 0.44–0.73, $p \leq .01$) compared to normothermia.**

Conclusions: **Therapeutic hypothermia is associated with significantly improved neurological outcome and 180-day survival compared to spontaneous normothermia in cardiac-arrest patients. (Crit Care Med 2012; 40: 2315–2319)**

Key Words: cardiopulmonary resuscitation, heart arrest, hypothermia, morbidity, mortality, survival

In the past decade, two large randomized trials have shown a positive effect of mild therapeutic hypothermia (32–34°C for 12 to 24 hrs) in comatose survivors of cardiac arrest by lowering the occurrence rate of poor neurological outcome and reducing mortality (1, 2). A meta-analysis of studies describing hypothermia in postcardiac arrest patients also showed a beneficial effect of mild therapeutic hypothermia in cardiac-arrest patients (3). As a result of these studies, mild therapeutic hypothermia has been established as a treatment to lower the occurrence rate of severe brain damage and mortality after cardiac arrest and resuscitation. The European Resuscitation Council (4) and the American Heart Association (5) recommend mild therapeutic hypothermia of 32–34°C during postresuscitation care.

However, studies showing the effectiveness of therapeutic hypothermia have been criticized (6, 7) because of the relatively high rate of patients with elevated core body temperature in the control groups; this discrepancy has led to a prospective randomized trial (8) comparing normothermic to hypothermic patients. Still, there is evidence of the detrimental effects of postcardiac arrest hyperthermia, caused by infections or thermoregulatory dysfunction, in terms of neurological outcomes (9, 10). Thus, the effect found in the hypothermia trials (1, 2) may have been due to a higher rate of poor outcome in the control groups caused by elevated body temperatures.

Therefore, the aim of this retrospective study was to evaluate the effect of therapeutic hypothermia (32–34°C for 24 hrs) compared to spontaneous normothermia (<37.5°C) on neurological outcome and survival in patients successfully resuscitated from cardiac arrest.

MATERIALS AND METHODS

This retrospective chart review was based on the data of a prospectively designed and conducted registry of patients resuscitated in an urban area and admitted to the emergency department of a tertiary care center. The local ethics committee accredited the registry. Since 1991, data from all postresuscitation patients have been collected according to the Utstein guidelines for reporting cardiac arrest data (11).

Patient Selection. Patients were included if they had a witnessed, out-of-hospital arrest of presumed cardiac origin, were 18 to 80 yrs old, and had a Glasgow Coma Scale score of <8 after restoration of spontaneous circulation (ROSC). Patients with a documented "do not resuscitate" or "allowed natural death" note were excluded.

Follow-up of all patients, including data collection from the surveillance monitors and patient charts, neurological evaluation by the Glasgow Coma Scale (12) and the Cerebral Performance

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Category (CPC) (13) of the patients, were performed at least up to 6 months after ROSC (11). Of the included normothermic patients, intensive care unit charts and monitoring data were searched for recorded temperatures for the following time intervals post-ROSC: 0, 15 and 30 mins and 1, 2, 3, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 hrs.

Treatment. All patients were stabilized if necessary and treated with standard intensive-care procedures (14). For sedation analgesia, midazolam, and fentanyl were administered; paralysis was performed with pancuronium or rocuronium. For temperature monitoring, an esophageal or a bladder-temperature probe was used. Patients who received active therapeutic hypothermia of any method were coded in the hypothermia group and were cooled to 32–34°C for 24 hrs. Patients who were not actively cooled and never reached a temperature > 37.5°C during the 36 hrs after ROSC were coded in the spontaneous normothermia group. The 36-hr time period was chosen based on the length of the standard hypothermia procedure (24 hrs of cooling, followed by 12 hrs of rewarming).

Outcome. The primary end point for this study was favorable neurological recovery within 180 days after ROSC, defined as CPC 1 (good recovery) or 2 (moderate disability) on a 5-point category scale. Other categories were CPC 3 (severe disability), 4 (vegetative state), or 5 (death). Patients in CPC categories 3–5 and patients who died during general anesthesia were classified as not having reached a good neurologic outcome. The best CPC ever reached by each patient during follow-up was used for this analysis. The secondary end point was overall mortality at 180 days after ROSC. Furthermore, a combined end point called "good survival" was defined as a patient with good neurological outcome and survival for 6 months. Outcomes were assessed by clinical follow-up.

Statistical Analysis. Continuous data are presented as mean ± sd if not otherwise specified. Categorized data are presented as count and relative frequency. We aimed at assessing the effect of mild therapeutic hypothermia on 180-day mortality and functional neurological outcome. Specifically we were interested in assessing to what extent cooling might act by influencing the frequency of uncontrolled hyperthermia.

As hyperthermia can only be observed in patients not cooled, we can restrict the control group to patients who did not develop hyperthermia, but this cannot directly be done for patients who received cooling. We therefore calculated the propensity of getting hyperthermia from the set of noncooled patients using a multivariable logistic regression model. The dependent variable was hyperthermia, covariates were clinical and demographic factors that were available at admission. The most influential factors for the propensity of getting hyperthermia were age, shockable rhythm during cardiopulmonary resuscitation, arrest time ("no-flow time"), whether basic life support was performed, seizures at admission, and whether patients needed catecholamines at admission. Based on this model we calculated propensity scores for getting hyperthermia in patients who received cooling. Because approximately half of the patients in the control group experienced hyperthermia we chose to classify patients in the cooling group with a propensity score above the median value as having a high risk of getting hyperthermia.

Next, we calculated the propensity of receiving mild therapeutic hypothermia to adjust for potential confounding by indication. Again we used a multivariable logistic regression model. The dependent variable was cooling, covariates were clinical and demographic factors that were available at admission. The most influential factors for the propensity of receiving cooling therapy were age, sex, shockable rhythm during cardiopulmonary resuscitation, arrest time (no-flow time), whether basic life support was performed, and periods of calendar time (1992–1997, 1998–2004, and 2005–2010). Based on the estimates from this model we calculated propensity scores for getting mild therapeutic hypothermia in patients admitted to the emergency department after cardiac arrest.

We used generalized linear models with a log-link function to calculate risk ratios (RRs) with 95% confidence intervals (CIs) for the mortality and functional neurological outcome, including cooling as a covariate as well as the propensity score for cooling therapy. We performed this analysis for (1) all cooled patients vs. patients not having received cooling (2), all cooled patients vs. patients not having received cooling, excluding those who got hyperthermic (3), all cooled patients at low risk of getting hyperthermic vs. patients not having received cooling, excluding those who got hyperthermic, and (4) all cooled patients at high risk of getting hyperthermic vs. patients not having received cooling who got hyperthermic. We tested for first-order interactions using a likelihood ratio test and compared the propensity score adjusted models with standard models including all covariables separately as a sensitivity analysis.

We then calculated the absolute risk for getting the outcomes by multiplying the adjusted RR with the baseline risk which we derived from the respective contingency tables. For data management and analysis we used Microsoft Excel (Microsoft Corp., Redmond, WA) for Mac 2011 and Stata 11 (Stata Corp, College Station, TX). Generally a two-sided p .05 was considered statistically significant.

RESULTS

From December 1991 to May 2010, 3,952 patients were included in the registry. Of these patients, 3,124 patients did not match the inclusion criteria and were excluded. Of the remaining 828 patients, 467 patients were cooled with various methods and were thus coded to the hypothermia group. Of the remaining 361 patients, 165 never exceeded 37.5°C and were thus coded in the normothermia group; the remaining 196 were coded in the hyperthermia group. Details are shown in the flow chart in Figure 1. Baseline variables of the hypothermia and spontaneous normothermia groups are shown in Table 1. Patients in the spontaneous normothermia group were significantly older, received less basic life support, were less likely to have a primary rhythm of ventricular fibrillation, and had a shorter time interval from collapse to ROSC than patients in the hypothermia group.

Overall, 493 patients (60%) survived for a period of 180 days after ROSC. A significantly higher percentage of patients in the hypothermia group survived a period of 180 days compared to patients in the spontaneous normothermia group (Table 2). The RR of death within 180 days was 0.57 (CI 0.44–0.73, $p < .01$) in favor of therapeutic hypothermia (Fig. 2).

Overall, a CPC score of 1 or 2 was found in 410 patients (50%). A significantly higher percentage of patients in the therapeutic hypothermia group scored an overall CPC score of 1 or 2 compared to patients in the spontaneous normothermia group (Table 2). In the multivariate logistic regression with cooling and the propensity score for cooling therapy as covariates, the RR for good neurological outcome in favor of therapeutic

hypothermia was 1.37 (95% CI 1.09–1.72, $p < .01$) (Fig. 2).

Overall, 396 patients (48%) survived for 180 days post-ROSC and had a favorable neurological outcome (Table 2); they were thus categorized as good survivors. Patients treated with therapeutic hypothermia were more likely to achieve good survival than spontaneously normothermic patients with a RR of 1.40 (95% CI 1.10–1.78, $p < .01$) for cooling (Fig.2).

DISCUSSION

Our findings indicate that therapeutic hypothermia is associated with good neurological outcomes and higher survival rates compared to spontaneously normothermic patients, and that normothermia is a risk factor for unfavorable neurological outcome and mortality in patients successfully resuscitated from cardiac arrest.

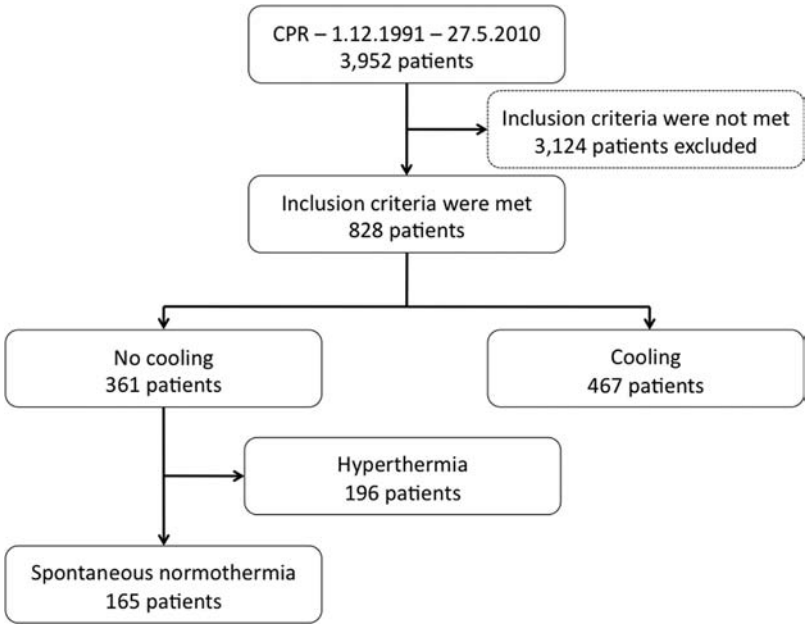

Figure 1. Flow chart of patient selection. *CPR*, cardiopulmonary resuscitation.

We further analyzed the overall effect of cooling vs. noncooling; the noncooling group included normothermic and hyperthermic patients. Here we also found a beneficial effect of cooling in terms of survival rates and neurological outcome. This analysis resembles a sequel of the Hypothermia After Cardiac Arrest (HACA) trial (2); the inclusion criteria of our study differed by including patients with initial nonshockable rhythm and patients up to the age of 80 yrs. Time from cardiac arrest to first resuscitation attempts and ROSC were not evaluated for exclusion as it was in the HACA trial. Overall, only 13 patients had a no-flow time >15 mins and 46 patients were resuscitated for >60 mins; these patients would not have been included in the HACA trial. RRs for survival and neurological outcome of the HACA trial were comparable with our findings (HACA 180-day survival: RR 0.74, 95% CI 0.58–0.95 vs. RR 0.67, 95% CI 0.56–0.80; HACA CPC 1 or 2: RR 1.40, 95% CI 1.08–1.81 vs. RR 1.27, 95% CI 1.09–1.48). By excluding the hyperthermic patients and thus comparing normothermic patients to cooled patients RRs further improved to 0.57 (95% CI 0.44–0.73) for 180-day mortality and 1.37 (95% CI 1.09–1.72) for good neurological outcome in favor of mild therapeutic hypothermia.

We further tried to evaluate cooled patients for potential hyperthermia if they would not have been cooled. We searched

Table 1. Baseline characteristics

	All Patients	Normothermia	Hyperthermia	Cooling	Cooling—Probably Normothermic	Cooling—Probably Hyperthermic
n	828	165	196	467	212	255
Age (yrs)—median (IQR)	58 (50–67)	61 (53–69)	57 (50–66)	58 (49–66)	64 (54–73)	53 (45–61)
Female— n./total n (%)	203/828 (25%)	46/165 (28%)	49/196 (25%)	108/467 (23%)	43/212 (20%)	65/255 (25%)
Height (cm), median (IQR)	175 (170–180)	175 (168–180)	175 (170–180)	175 (170–180)	175 (170–180)	175 (170–180)
Weight (kg)—median (IQR)	80 (75–90)	80 (70–90)	80 (75–90)	80 (75–90)	80 (75–90)	80 (75–90)
"No-flow" time— median (IQR)	2 (0–7)	1 (0–6)	2 (0–7)	3 (1–8)	1 (0–6)	5 (1–10)
"Low-flow" time— median (IQR)	17 (10–27)	15 (6–25)	15 (9–25)	18 (11–28)	19 (12–30)	18 (10–26)
Ventricular fibrillation/ventricular tachycardia[a]—n/total n (%)	653/828 (79%)	110/165 (67%)	150/196 (77%)	393/467 (84%)	158/212 (75%)	235/255 (92%)
Basic life support performed—n./total n (%)	334/828 (40%)	53/165 (32%)	72/196 (37%)	209/467 (45%)	74/212 (35%)	135/255 (53%)
Seizures at admission —n./total n (%)	11/828 (1%)	4/165 (2%)	7/196 (4%)	0/467 (0%)	0/212 (0%)	0/255 (0%)
Hypertension at admission—n/total n (%)	55/828 (7%)	14/165 (8%)	19/196 (10%)	22/467 (5%)	7/212 (3%)	15/255 (6%)
Hypotension at admission—n/total n (%)	443/828 (53%)	94/165 (57%)	112/196 (57%)	237/467 (51%)	126/212 (59%)	111/255 (44%)
Vasopressor at admission—n/total n (%)	98/827 (12%)	4/164 (2%)	1/196 (<1%)	93/467 (20%)	93/212 (44%)	0/255 (0%)
Initial Po_2 (mm Hg)—median (IQR)	244 (113–428)	240.5 (111–383)	221.5 (112–418)	256 (113–441)	214 (97.4–432)	296.5 (124–449)
Initial Pco_2 (mm Hg)—median (IQR)	40.1 (34.3–47)	37.5 (33.2–45.8)	38.9 (32.2–45.9)	41.7 (35.8–49.2)	43.3 (37.3–50.7)	40 (33.7–47.6)
Coronary intervention —n/total n (%)	127/828 (15%)	4/165 (2%)	4/196 (2%)	119/467 (25%)	74/212 (35%)	45/255 (18%)

IQR, interquartile range.
[a]Shockable rhythm.

Table 2. Patients treated with hypothermia exhibit better overall outcome compared with patients treated with normothermia

	All Patients	Normothermia	Hyperthermia	Cooling	Cooling—Probably Normothermic	Cooling—Probably Hyperthermic
Cerebral Performance Category good[a]	410/828 (50%)	69/165 (42%)	85/196 (43%)	256/467 (55%)	103/212 (49%)	153/255 (60%)
180 day mortality	335/828 (40%)	86/165 (52%)	97/196 (49%)	152/467 (33%)	86/212 (41%)	66/255 (26%)
Good survival	396/828 (48%)	65/165 (39%)	80/196 (41%)	251/467 (54%)	101/212 (48%)	150/255 (59%)

[a]Cerebral Performance Category score of 1 or 2.

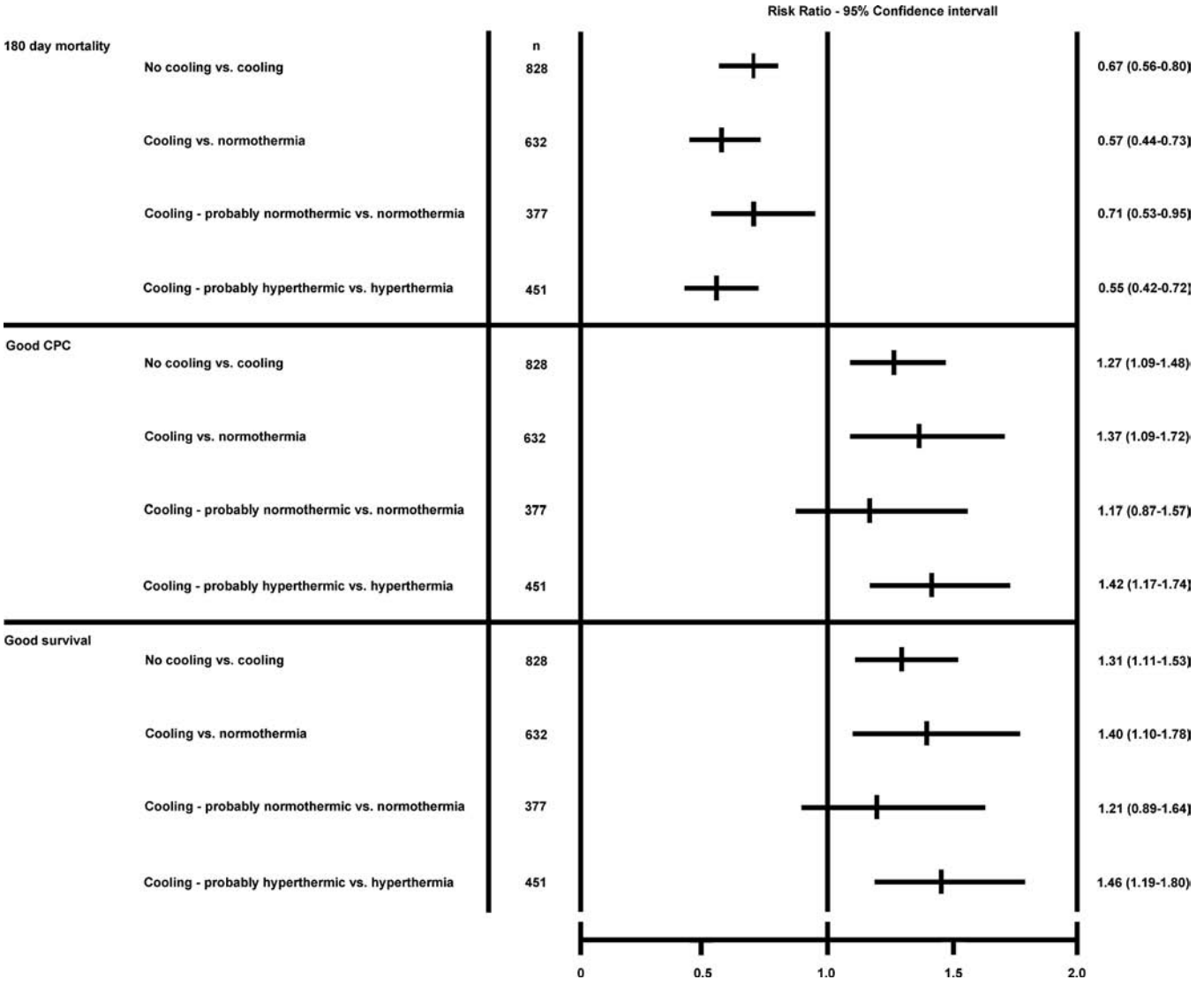

Figure 2. Forest plot—risk ratios—95% confidence interval. *CPC*, Cerebral Performance Category.

the documented hyperthermic patients for factors associated with hyperthermia. Associated factors for getting hyperthermic were age, shockable rhythm during cardiopulmonary resuscitation, arrest time (no-flow time), whether basic life support was performed, seizures at admission, and whether patients needed vasopressors at admission. When we compared cooled patients with no risk for hyperthermia, meaning they could have stayed normothermic spontaneously, with spontaneously normothermic patients we also found a significant beneficial effect of cooling in terms of 180-day survival rates in favor of hypothermia. In terms of good neurological outcome results also indicated a beneficial effect of hypothermia, although these results were not statistically significant. This might be due to the relatively low number of patients in this analysis.

Furthermore, we compared hyperthermic patients with cooled patients who were at risk of getting hyperthermic if they would not have been cooled. This analysis also showed a beneficial effect of mild therapeutic hypothermia on 180-day survival and good neurological outcome.

When the principles of mild therapeutic hypothermia were evaluated for clinical feasibility, researchers compared patients actively cooled to patients with no active temperature control (1, 2). Criticism arose over the fact that some of the patients in the control group had an elevated body temperature; thus, these studies were more correctly comparing mildly hypothermic patients to hyperthermic patients. For instance, in the control group of the HACA trial (2) the median bladder temperature rose to >37.5°C during the first 12 hrs and remained elevated during the 48-hr study period.

Additionally, elevated body temperature in patients after cardiac arrest leads to decreased neurological function. Zeiner et al (9) showed a significant association between elevated body temperature and poor neurological outcome. For each degree Celsius > 37°C, the risk of unfavorable neurologic outcome increases with an odds ratio of 2.66 (95% CI, 1.24–4.12). Another study described an elevated risk of clinical brain death associated with elevated body temperature in postcardiac-arrest patients. Patients with a body core temperature >39°C had a significantly higher risk of developing clinical brain death within 72 hrs than patients with a body core temperature < 39°C (10). A recent study showed a significant association of hyperthermia and poor long-term clinical outcome in patients with acute ischemic stroke (15). Because of the similar underlying pathological mechanism of hypoxic-ischemic neuronal damage, these findings could also apply to cardiac-arrest patients.

The methodological limitations of this study include its retrospective nature and single-center characteristic without a random group allocation. The final decision of whether a patient underwent mild therapeutic hypothermia was typically left to the discretion of the physician in charge. Because of the introduction of therapeutic hypothermia, the number of normothermic patients has decreased over the time period of this study, and most of the normothermic patients were from the early years of this study. From 1991 to 2010, therapeutic schemes and measurements in postresuscitation care have been changed; hence, state-of-the-art postresuscitation care is more often provided to hypothermic patients.

In a rat model of asphyxial cardiac arrest and resuscitation (16) the alternate therapeutic hypothermia level of 35°C had similar beneficial effects on neurological recovery as compared with the standard 33°C temperature level. Whether other levels of targeted temperature regulation, as evaluated in our study, have similar effects must be investigated in future trials. Additionally, whether normothermia and hyperthermia both worsen neurologic outcome to the same degree or if there is a stepwise increase of neurological damage associated with elevated body temperature should be further investigated.

Although patients in the normothermia group were significantly older, had a nonshockable initial electrocardiography rhythm, and regained ROSC faster than the hypothermic patients, the findings were statistically robust. Furthermore, the primary outcome was supported by most secondary clinical outcomes in a multivariate analysis, where, after adjusting for the probability of receiving cooling, cooling decreased the risk of death and increased the chance of both good CPC and good survival.

CONCLUSIONS

Mild therapeutic hypothermia (33°C) was associated with improved long-term neurological outcome and reduced mortality compared with spontaneous normothermia in this retrospective single-center chart review. Therefore, our findings additionally support the recommendation of the recent guidelines of resuscitation and emergency cardiac care (4, 5) to cool postcardiac arrest patients for the protection of neurologic function and improved survival.

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