Therapeutic Hypothermia for Comatose Survivors after Cardiac Arrest

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Abstract

Background: Unconscious adults with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32–34°C (ILCOR recommendations, 2003) when the initial rhythm is ventricular fibrillation.

Objectives: To assess the technique, safety and efficacy of mild induced hypothermia in patients after OHCA due to VF.

Methods: Patients were cooled using the MTRE CritiCool™ external cooling system. Cold intravenous fluids were added to achieve faster cooling in 17 patients. Data were collected prospectively and patients were analyzed according to their neurological outcome on discharge, defined by their cerebral performance category.

Results: From February 2002 to September 2006, 51 comatose VF patients with OHCA underwent MIH. Treatment was discontinued early in five because of hemodynamic instability; goal temperature was reached in 98% and maintained for an average of 19.5 hours; 61% had a favorable outcome (CPC 1–2) and 37% died. Improved outcome was observed with longer hypothermia time and possibly when time from collapse to return of spontaneous circulation was < 25 minutes.

Conclusions: MIH, using an external cooling system, is simple and feasible, reduces mortality and protects neurological function. Four major factors seem to influence outcome: age, co-morbidities, duration of hypothermia, and possibly the length of time from collapse to return of spontaneous circulation.

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Cardiac arrest outside the hospital is a major cause of unexpected death, with survival rates ranging from 5 to 35% [1,2]. In patients who are initially resuscitated, anoxic neurological injury is an important cause of morbidity and mortality [3]. Post-cardiac arrest cerebral reperfusion injury and resuscitation probably also contribute to the poor outcome [4]. Induction of hypothermia after return of spontaneous circulation has been associated with improved functional recovery and reduced cerebral histological deficits in various animal models of cardiac arrest [5,6]. Although additional promising preliminary human studies have been performed [7-10], the exact mechanism behind this cerebral beneficial effect is not clear [11,12].

OHCA = out-of-hospital cardiac arrest
VF = ventricular fibrillation
MIH = mild induced hypothermia
CPC = cerebral performance category
ROSC = return of spontaneous circulation

In 2002 two prospective randomized trials compared mild induced hypothermia with normothermia in comatose survivors of out-of-hospital cardiac arrest [13,14]. In patients who were successfully resuscitated after cardiac arrest due to ventricular fibrillation, MIH reduced mortality and increased the rate of a favorable neurological outcome. Based on these studies, the ILCOR (International Liaison Committee on Resuscitation) recommended in 2003 that all unconscious adults with spontaneous circulation after OHCA should be cooled to 32–34°C for 12–24 hours when the initial rhythm is VF [15,16]. Cooling should probably be initiated as soon as possible after ROSC, but appears to be successful even if delayed [14]. The cooling technique, the optimal duration of MIH, optimum target temperature, rates of cooling and rewarming, and the selection of patients are specific questions that remain to be answered.

Patients and Methods

Since February 2002, all comatose patients after cardiac arrest due to VF presumed to result from cardiac origin were treated with MIH in order to compare these results with the normothermic groups from the two prospective randomized studies already published [13,14]. Exclusion criteria for MIH were pregnancy, a terminal illness, cardiogenic shock or life-threatening arrhythmia, or patients with known primary coagulopathy. The patient's family was informed about MIH and three physicians gave signed approval for treatment.

All patients received standard treatment according to intensive cardiac care unit protocols and were mechanically ventilated. All patients were sedated with induction and intravenous infusion of midazolam, and were paralyzed with atracurium besylate to prevent shivering.

The patients were undressed and air conditioning was applied. All patients were cooled by the MTRE Criti Cool™ external cooling system, which enables simultaneous water flow through numerous channels in a body-shaped heat exchange garment (°CureWrap). An infusion of cold intravenous normal saline, 4°C (30 ml/kg, 100 ml/min), was added in the last 17 patients to achieve faster cooling. In patients who underwent primary percutaneous coronary intervention, MIH was started prior to and lasted throughout the procedure. Goal MIH temperature was 32–34°C, goal MIH duration was 24 hours, and goal rewarming rate was 0.5°C/hour.

Data on all consecutive patients who underwent therapeutic hypothermia due to VF from February 2002 until September 2006 were collected prospectively. Patients were analyzed according to their neurological outcome on discharge, defined by their Pittsburgh cerebral performance category on a five-point scale [17]: favorable outcome (CPC 1 = good cerebral function, 2 = moderate neurological disability) or unfavorable outcome (CPC 3 = severe neurological disability, 4 = coma, 5 = death). Data were compared to the normothermic and hypothermic groups from previous randomized studies [13,14].

The ROSC was estimated according to the written time of patient evacuation, number of advanced cardiac life support cycles, and the report of the paramedics to the medical team who admitted the patient to the emergency room or ICCU.

When comparing patients with favorable and unfavorable outcome, categorical variables were presented as percentages and compared by two-tailed chi-square or two-tailed Fisher's exact test. Continuous variables were presented as mean ± SD and were compared by the *t*-test.

Results

Patient characteristics

Fifty-one consecutive patients were treated with MIH from February 2002 to September 2006. The patients were stratified as favorable (n=31, 61%) or unfavorable (n=20, 39%) outcome. Nineteen patients (37%) died.

In five patients, treatment was discontinued prematurely due to hemodynamic instability in three and death during cooling in two. Goal temperature was achieved in four of them. All five patients were included in the analysis.

Baseline characteristics according to outcome are presented in Table 1. Patients in the poor outcome group were older and had a higher rate of severe co-morbidities (i.e., three or more risk factors for ischemic heart disease, IHD or its equivalent, chronic renal failure, or moderate to severe left ventricular dysfunction)].

Among patients with acute ischemia there was a higher rate of primary PCI in the favorable compared to the unfavorable outcome group, due to a higher rate of ST elevation myocardial infarction.

Baseline characteristics compared to previous randomized studies are shown in Table 2, with our patients showing a similarity to those published in the literature [13,14]. The rate of ischemic patients, however, could not be compared due to unavailable data in the two referenced studies.

Acute event characteristics and cooling

Table 3 shows the acute event characteristics in patients with favorable and unfavorable outcomes. Despite the fact that no difference in time from collapse to ACLS was found, there was a trend toward a better outcome when time duration from collapse to ROSC was < 25 minutes, while a worse outcome was noted in patients who presented to the emergency department with hypotension. Table 4 presents the cooling characteristics. There was no difference between the groups in time duration from collapse, ACLS or ROSC to MIH, and from collapse, ACLS or ROSC to goal temperature (< 34°). There was no difference in time from arrival at the emergency room to MIH. There was, however, a difference in total duration of hypothermia, with longer treatment in the favorable outcome group. Another difference was the higher rate of seizures and the need for catecholamine treatment in the unfavorable group compared to the favorable one. In patients with CPC 1-2, median monitoring time was 36 hours (range 11–170) after the cessation of MIH, and extubation date was on day 2.8 ± 1.1 to hospitalization.

Table 1. Baseline characteristics

	Favorable outcome (n=31) (60.8%)	Unfavorable outcome (n=20) (39.2%)	*P*
Gender (% male)	80.6	80	NS
Age (yrs)			
Average	57.8 ± 10.6	65 ± 12.5	0.03
Median & range	59 (33–76)	64 (42–86)	
Severe co-morbidities*	55%	85%	0.035
EF < 35%	16%	55%	< 0.01
IHD	45%	65%	NS
DM	13%	25%	NS
CRF	6%	15%	NS
HTN	52%	70%	NS
Smoking	39%	45%	NS
Dyslipidemia	52%	65%	NS
CVA	16%	25%	NS
COPD/asthma	3%	15%	NS
PVD	3%	15%	NS
Location of cardiac arrest (% OHCA)	29 (93.5%) **	20 (100%)	NS
BLS (CPR) by bystander (%)	58%	45%	NS
Ischemic cause (AMI & ACS)	67.7%	45%	NS
STEMI	21/31 (67.7%)	8/20 (40%)	0.06
PCI among ischemic cases			
Primary	86%	44.4%	0.03
Non-primary (during hospitalization)	9.5%	0	NS

* At least three risk factors for IHD/IHD or CVA or PVD/CRF/EF ≤ 35%.

** One patient collapsed in the emergency room and one in the hospital area; ACLS was provided by the ER crew.

DM = diabetes mellitus, HTN = hypertension, PVD = peripheral vascular disease, BLS = basic life support, CPR = cardiopulmonary resuscitation, AMI = acute myocardial infarction, ACLS = advanced cardiac life support, ACS = acute coronary syndrome, STEMI = ST elevation myocardial infarction, ER = emergency room.

Outcome and complications

Patients' outcome on hospital discharge shows that the treatment is efficient [Tables 2 and 3]: 61% of patients demonstrated a favorable outcome, with a 37% death rate, similar to that reported in the literature [13,14]. It took a median of 3 days

ICCU = intensive cardiac care unit
IHD = ischemic heart disease
PCI = percutaneous coronary intervention
ACLS = advanced cardiac life support

Table 2. Comparison with previous studies

	Sheba	HACA*	Bernard**
No. of hypothermia patients	51	137	43
Age (yrs)			
Median	61	59	67
Range	33–86	51–69	49–89
Male (%)	80	76	58
VF (%)	100	97	100
Ischemic cause (AMI & ACS)	30/51 (59%)	N/A	N/A
Revascularization among ischemic cases			
Primary PCI	22/30 (73%)	N/A	2 patients
All PCI during hospitalization	24/30 (80%)	N/A	N/A
Thrombolysis	0	27 patients	1 patient
CABG	3/30 (10%)	N/A	N/A
BLS by bystander	53%	43%	49%
ROSC from collapse (min)	51% < 25 min 49% > 25 min	Median 21 (15–28)	26.5 ± 12.9
ROSC to MIH (median) (hr)	2.9 (0.6–12.2)***	1.75 (1–3.2)	In ambulance
ROSC to target temperature (hr)	8.2 (3.2–20.4)***	8 (4–16)	2
Rate of cooling (°C/hr)	0.7 (0.14–1.44)****	0.3	0.9
Duration of hypothermia (hr)			
Start to cessation	19.5	Median 24 (12–29)	18
Start to 36°C	23.5		
Time at goal temperature	14.8		12
Favorable outcome on discharge*****	60.8%	55% (vs. 39% in normothermia)	49% (vs. 26% in normothermia)
Death	37%	41% (vs. 55% in normothermia)	51% (vs. 67.6% in normothermia)

* Hyperthermia After Cardiac Arrest study group [14].
** Bernard et al. [13].
*** Estimated ROSC. See text.
**** Rate of external cooling: 0.65 ± 0.3°C/hr; rate of external cooling + IV cold saline: 0.8 ± 0.3 °C/hr (P = 0.13).
***** CPC1-2 = good cerebral function or moderate neurological disability.
VF = ventricular fibrillation, PCI = primary coronary intervention, CABG = coronary artery bypass graft, ROSC = return of spontaneous circulation.

(range 1–120 days) to reach a neurological plateau in the favorable outcome group, while in the unfavorable group 85% of patients were comatose until death. All patients but one died in this group. Median time of death was day 5 of hospitalization (range 1–27 days). The primary cause of death was cardiogenic shock in 12 patients (one of whom also had rupture of the left ventricular free wall). The remaining deaths resulted primarily from severe neurological injury (11 patients) and septic shock (7 patients). Among the unfavorable outcome group, 11 patients had combined causes of death.

The rate of complications is shown in Table 3. There was no difference in the rate of pneumonia, bleeding and acute renal failure between the two groups. However, the unfavorable group had a higher rate of sepsis, cardiogenic shock and seizures.

In the favorable group elective PCI was performed in 29% during the same hospitalization and implantable cardioverter defibrillator was implanted in 45%. None of these procedures was performed in the unfavorable group.

Table 3. Acute event characteristics and outcome

	Favorable outcome (n=31) (60.8%)	Unfavorable outcome (n=20) (39.2%)	*P*
Time from collapse to ACLS (min)	6.8 ± 4.5	8 ± 6.3	NS
SBP < 90 mmHg in ER (% patients)	0	15%	0.05
ROSC within 25 min from collapse	61%	35%	0.09
Death	0	95%	< 0.0001
Date of death (day of hospitalization)		Median 5 (1–27)	
Pneumonia	55%	50%	NS
Sepsis	13%	40%	0.04
Cardiogenic shock	6.5%	55%	0.001
Need for platelet infusion	0	0	
Any bleeding	19%	10%	NS
Acute renal failure	19%	15%	NS
Pancreatitis	3%	0	NS
Pulmonary edema	13%	5%	NS
Seizures	3%	40%	0.002
Significant prolonged or lethal arrhythmia	13%	5%	NS

ACLS = advanced cardiac life support, SBP = systolic blood pressure, NS = not significant.

Discussion

According to ILCOR recommendations [15], and according to resuscitation guidelines [16], unconscious adults with spontaneous circulation after OHCA should be treated with MIH when the initial rhythm is VF. We assessed the feasibility and safety of these guidelines in the "real world" in a single referral center. Our study shows that MIH, using an external cooling system, is feasible, safe, reduces mortality and protects neurological function.

In a meta-analysis of randomized controlled studies of MIH treatment in the above setting, where a temperature of 35°C is applied within 6 hours of arrival to the emergency room, MIH was shown to improve short-term neurological recovery and survival [18]. It appears that improved favorable long-term neurological survival up to 6 months after the event is also achieved. This beneficial effect appears to be independent of the method used to induce MIH, and despite relatively slow cooling.

In our patient population we found a statistically significant relationship between age and clinical outcome. We also found that co-morbidities might influence the final outcome. There was a tendency toward better outcome when the duration time from collapse to ROSC was < 25 minutes, similar to findings in a recent study [19]. Improved outcome was also observed with longer hypothermia time, similar to findings in animal studies [20].

According to the meta-analysis [18], MIH might be associated with increased risk of hemorrhagic complications and a

ILCOR = International Liaison Committee on Resuscitation

Table 4. Cooling characteristics

	Favorable outcome (n=31) (60.8%)	Unfavorable outcome (n=20) (39.2%)	*P*
Time from collapse to hypothermia (min)	234 ± 103.7	262 ± 138.7	NS
Time from ACLS to hypothermia (min)	229.6 ± 101.3	253 ± 139	NS
Estimated time from ROSC to MIH (min)	206 ± 102	226 ± 141.8	NS
Time from ER to hypothermia (min)*	182.4 ± 103	195.4 ± 140	NS
Time from hypothermia to goal temperature (min)	302 ± 204.3	238.6 ± 141.5	NS
Time from collapse to goal temperature (min)	538 ± 236.6	496.5 ± 220.8**	NS
Time from ACLS to goal temperature (min)	528 ± 238	487.7 ± 221.3**	NS
Estimated time from ROSC to goal temperature (min)	509.6 ± 236.5	460 ± 222**	NS
Rate of cooling (°C/hr)	0.7 ± 0.37	0.7 ± 0.26	NS
Median rate of warming (°C/hr)	0.57 (0.22–3.6)	0.5 (0.26–1.32)	NS
Total duration of hypothermia (hr)	***	****	
Start to cessation	21 ± 7.2	17 ± 5	0.046
Start to rewarming to 36°C	24.8 ± 7.4	21 ± 6.3	0.097
Time at goal temperature	15.5 ± 6.5	13.6 ± 5**	NS
Complications during hypothermia			
A change in vital signs***** (% of patients)	25.8%	35%	NS
Arrhythmia (AF/NSVT/VT)	35.5%	10%	0.05
Seizures	3%	30%	0.01
Symptoms of heart failure	22.5%	40%	NS
Need for catecholamines	0	40%	0.0002
Duration of monitoring after cessation of hypothermia (hr)	Median 36 (11–170)	Until death/ discharge	

* ER or ICCU – if brought there initially.

** One patient did not reach goal temperature.

*** MIH was discontinued early in one patient.

**** MIH was discontinued early in four patients due to hemodynamic instability.

***** Bradycardia, hypotension or hypoxemia.

NS = not significant, AF = atrial fibrillation, NSVT = non-sustained ventricular tachycardia, VT = ventricular tachycardia.

higher rate of severe infection. In our study the rate of sepsis was significantly higher, without excess of hemorrhagic complications, in patients with unfavorable outcome compared to the favorable outcome group, as were the rates of cardiogenic shock and seizures; but this was probably related to a worse baseline cardiac and neurological status. However, the overall beneficial effect was not offset by the complications.

Based on recent publications advocating cooling with cold intravenous fluids [21,22], we added IV cold fluids to the external cooling method in our last 17 patients in order to achieve faster cooling. We found no difference in the rate of achieving goal temperature with or without cold IV fluids. However, the small size of the IV fluid group might have influenced this result.

Our study has all the limitations of a non-randomized trial. We did not compare our data to our historical controls but rather to normothermic groups that had already been reported in the literature in a similar setting but in other centers. Nevertheless, knowing the low rate of survival and high rate of neurological damage in this setting in previous reports [1-3] and the advantage of MIH in controlled randomized studies, our results, using an external cooling system, are encouraging and show the feasibility, safety and efficacy of such treatment in daily clinical practice.

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To love oneself is the beginning of a lifelong romance

Oscar Wilde (1854-1900), Irish playwright and humorist

Capsule

Folic acid and risk of facial clefts

Wilcox and collaborators studied the role of folic acid supplements, dietary folates, and multivitamins in the prevention of facial cleft in infants born in 1996–2001 in Norway. The work included 377 infants with cleft lip with or without cleft palate, 196 infants with cleft palate alone, and 763 controls. The results suggested that folic acid supplementation during early pregnancy (400 µg/day) was associated with a reduced risk of isolated cleft lip with or without cleft palate after adjustment for multivitamins, smoking, and other potential confounding factors (adjusted odds ratio 0.61, 95% confidence interval 0.39–0.96). Independent of supplements, diets rich in fruits, vegetables and other high folate-containing foods reduced the risk somewhat (adjusted odds ratio 0.75, 0.50–1.11). The lowest risk of cleft lip was among women with folate-rich diets who also took folic acid supplements and multivitamins (0.36, 0.17–0.77). Folic acid provided no protection against cleft palate alone (1.07, 0.56–2.03). The researchers conclude that folic acid supplements during early pregnancy seem to reduce the risk of isolated cleft lip (with or without cleft palate) by about a third. Other vitamins and dietary factors may provide additional benefit.

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Capsule

Prolactin and cardiac damage

Postpartum (or peripartum) cardiomyopathy (PPCM), which occurs up to a few months after delivery (or late in pregnancy), is associated with an acute onset of heart failure in women with no history of heart disease. Hilfiker-Kleiner et al. have linked cardiomyocyte STAT3 (signal transducer and activator of transcription 3) to PPCM. Normally, pregnancy is associated with cardiac hypertrophy and increased capillary density – physiological changes that also were found to occur in mice lacking cardiac STAT3. However, postpartum mice lacking cardiac STAT3 lost the increased capillary density. These mice suffered an attenuated increase in cardiac manganese superoxide dismutase, which led to excessive levels of reactive oxygen species, which led, in turn, to an increased abundance of the proteolytic enzyme cathepsin D. Furthermore, the STAT3-deficient mice exhibited enhanced cleavage of full-length prolactin, which is a cathepsin D substrate, into a shorter, anti-angiogenic form. Increasing the amount of circulating prolactin stimulated cardiac damage in mice that over-expressed cardiac cathepsin D. In contrast, pharmacological inhibition of prolactin secretion prevented PPCM. A preliminary study suggested that inhibiting prolactin release by administering bromocriptine was protective of cardiac function in women at high risk of PPCM. Thus, the authors suggest that cardiac STAT3 is critical to postpartum cardiac function and propose that inhibiting prolactin release may be a viable approach to PPCM treatment.

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