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Observed survival benefit of mild therapeutic hypothermia reanalysing the Circulation Improving Resuscitation Care trial

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ABSTRACT

Background Mild therapeutic hypothermia is argued being beneficial for outcome after cardiac arrest.

Materials and methods Retrospective analysis of Circulation Improving Resuscitation Care (CIRC) trial data to assess if therapeutic cooling to 33 ± 1 °C core temperature had an association with survival. Of 4231 adult, out-of-hospital cardiac arrests of presumed cardiac origin initially enrolled, eligibility criteria for therapeutic hypothermia were met by 1812. Logistic regression was undertaken in a stepwise fashion to account for the impact on outcome of each significant difference and for the variable of interest between the groups.

Results Out-of- and in-hospital cooled were 263 (15%), only after admission cooled were 230 (13%) and not cooled were 357 (20%) patients. The group cooled out-of- and in hospital had 98 (37%) survivors as compared to the groups cooled in hospital only [80 (35%)] and of those not cooled [68 (19%)]. After adjusting for known covariates (sex, age, witnessed cardiac arrest, no- and low-flow time, shockable initial rhythm, random allocation, bystander cardiopulmonary resuscitation and percutaneous coronary intervention), the odds ratio for survival comparing no cooling to out-of- plus in-hospital cooling was 0.53 [95% confidence interval (CI): 0.46–0.61, $P < 0.001$], and comparing to in-hospital cooling only was 0.67 (95% CI: 0.50–0.89, $P = 0.006$).

Conclusion Mild therapeutic hypothermia initiated out of hospital and/or in hospital was associated with improved survival within this secondary analysis of the CIRC cohort compared to no therapeutic hypothermia.

Keywords Cardiopulmonary resuscitation, heart arrest, resuscitation, survival, trials.

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Introduction

Mild therapeutic hypothermia is considered beneficial based on meta-analyses from randomised controlled trials comparing therapeutic hypothermia to no cooling [1]. This notion was

recently challenged based on the results from a pragmatic randomised trial that reported a long time to approaching target temperature in the moderate hypothermia group, and no significant difference in survival or neurologic status over time between the mild vs. moderate hypothermia group [2]. The optimal timing for induction of hypothermia is uncertain [3]. The Circulation Improving Resuscitation Care (CIRC) trial determined equivalence between automated load distributing band (LDB) cardiopulmonary resuscitation (CPR) integrated

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with manual CPR (iLDB-CPR) to high quality manual CPR (M-CPR) in survival of out-of-hospital cardiac arrest patients [4]. This large, study cohort allowed for a nonrandomised observational assessments of the effects of mild therapeutic hypothermia on clinically relevant outcomes.

The aim of this study was to explore an association between mild therapeutic hypothermia with particular attention to *out-of-hospital* and/or *in-hospital* initiation and maintenance of therapeutic hypothermia on outcome within the 'chain of survival' [5] in initial survivors of out-of-hospital cardiac arrest from patients enrolled into the CIRC trial [4].

Materials and methods

The CIRC trial was a randomised, controlled 'group sequential' trial of adult out-of-hospital cardiac arrest patients of presumed cardiac origin conducted under exception from informed consent for emergency research and approved by the supervising Institutional Review Boards (three US sites) or Ethics committees (two European sites) at each site [6]. Reporting of the study conforms to STROBE statement [7]. Sites represented a variety of emergency medical service system types and covered populations that ranged from 135 141 to 2 144 491 with response areas between 68 and 888 square miles. The CIRC trial methods paper with the rationale and design of the trial in addition to the statistical analysis plan have been published previously [6].

Study design

Cohort study from patients initially enrolled into the CIRC trial to investigate the effect of therapeutic hypothermia on survival.

Selection of subjects

We analysed all patients, who showed any return of spontaneous circulation (≥ 60 s) and who were not waking up – thus having been potentially eligible for therapeutic hypothermia [8]. Patients were excluded if they were presumed to be pregnant, had a Do Not Resuscitate order, and were a prisoner or were a ward of the state.

Therapeutic hypothermia

Therapeutic hypothermia was the exposure of interest and categorised according to the initiation of therapeutic hypothermia *out of plus in hospital*, *in hospital* (either emergency department and/or intensive care unit) or *no cooling*. Part of CIRC trial protocol were resuscitation guidelines in place at the time of the study, which directed that all patients receive protection of their airway and artificial ventilation, hemodynamic support, prompt revascularization, monitoring and management of blood glucose levels, antibiotic therapy for infection and other disease-specific interventions. This also included therapeutic hypothermia to be considered without

any delay immediately after return of spontaneous circulation to a target of 33 ± 1 °C core temperature [9]. Available methods for cooling included ice packs, intravenous infusion of cold fluids, water-circulating cooling pads and precooled cooling pads, surface and endovascular cooling according to local protocols. Measurement of the core body temperature was site-specific as were the details of the care pathway.

Data collection

The data for this study were obtained from the emergency medical service and hospital patient care documentation using standardised data abstraction forms. Electronic defibrillator data were also analysed. Data were managed by a Data Coordinating Center at the Medical College of Wisconsin (Milwaukee, WI, USA). Throughout the trial and the protocol development for this cohort analysis access to the study database was restricted to data coordinating centre staff [6]. The out of hospital, emergency room, in hospital and discharge assessments with regard to therapeutic hypothermia focused on key data points within the 'chain of survival' [5,8,10].

Outcome measures

Survival to hospital discharge was chosen as outcome based on its robustness, good coverage and clinical relevance over return of spontaneous circulation or survival to hospital admission. The outcome was dichotomised as being discharged from hospital alive (yes vs. no).

Statistical analysis

Continuous data are presented as median and 25–75% quartiles; categorical data as count and relative frequency. The exposure as the initiation of therapeutic hypothermia at the organizational level was categorised into *out-of- plus in-hospital* cooling (reference), *in-hospital* cooling *alone* and *no cooling* (Fig. 1). Demographic factors and factors related to cardiac arrest and treatment according to the exposure levels were tabulated. To test the null hypothesis of no difference between the exposure levels we used a standard chi-squared test for categorical variables and a non-parametric k-sample test on the equality of medians for continuous variables. A nonparametric score test to test for a trend across ordered categories was used. Logistic regression was then undertaken in a stepwise fashion to account for the impact on outcome of each significant difference and for the variable of interest between the groups (cooling out of and/or in hospital and no cooling on survival to discharge). To allow for the multi-centre design of the study, we calculated the 95% confidence intervals (CI) from robust standard errors based on clustering by study site. Given the observational design and to adjust for potential confounding, we introduced *a-priori* defined candidate variables, which are known to be associated with the exposure and outcome, but not being moderators as covariables into a

multivariable logistic regression model. These variables were all categorised and included sex, witnessed cardiac arrest, bystander CPR, shockable initial rhythm, CIRC treatment allocation, age, 'no-flow' time, 'low-flow' time and percutaneous coronary intervention [10]. In case of missing data, we created 'missing' categories to include the information about missing data in our analysis. Where applicable a category for missing values was included. We tested for linear effects and first level interactions using the likelihood ratio test. We used the Wald test to test the null hypothesis of odds ratio = 1 in the models. Several sensitivity analyses on the exposure classification were performed and yielded virtually the same results. For data management and analyses MS EXCEL and STATA 11 for Mac (Stata Corp, College Station, TX, USA) was used.

Results

Included in the CIRC trial were 4231 patients between 2009 and 2011. There were no important outcome differences between LDB device and manual CPR groups [4].

Participants

Eligibility criteria for therapeutic hypothermia were met by 1812 individuals from within this cohort (Fig. 1). Overall

out-of- plus *in-hospital* cooled were 263 (15%) patients, cooled only *in hospital* were 230 (13%) and not cooled were 357 (20%).

Descriptive data

Patient characteristics are presented in Table 1. Pertinent to exposure status we observed relevant differences in witnessed cardiac arrest, bystander CPR, shockable initial rhythm after cardiac arrest, 'low-flow' time and return of spontaneous circulation. The time from return of spontaneous circulation to start of therapeutic hypothermia was significantly shorter for patients cooled *out of* hospital compared to those receiving therapeutic hypothermia only after hospital admission (19 [9–29] vs. 97 min [60–181]; $P < 0.001$). No significant differences in temperature at admission and time to lowest temperature were found (Table 1).

Outcome data

Outcome data on vital status at hospital discharge were available for 1812 individuals included in this cohort. Discharge data were missing for 12 patients. Among the 263 patients with *out-of-* plus *in-hospital* cooling were 98 (37%) survivors, the 230 with *in-hospital* cooling alone 80 (35%) and those with no cooling 68 (19%) (Table 2). Patients who had no cooling had a 0.53 lower odds of survival (95% CI: 0.46–0.61,

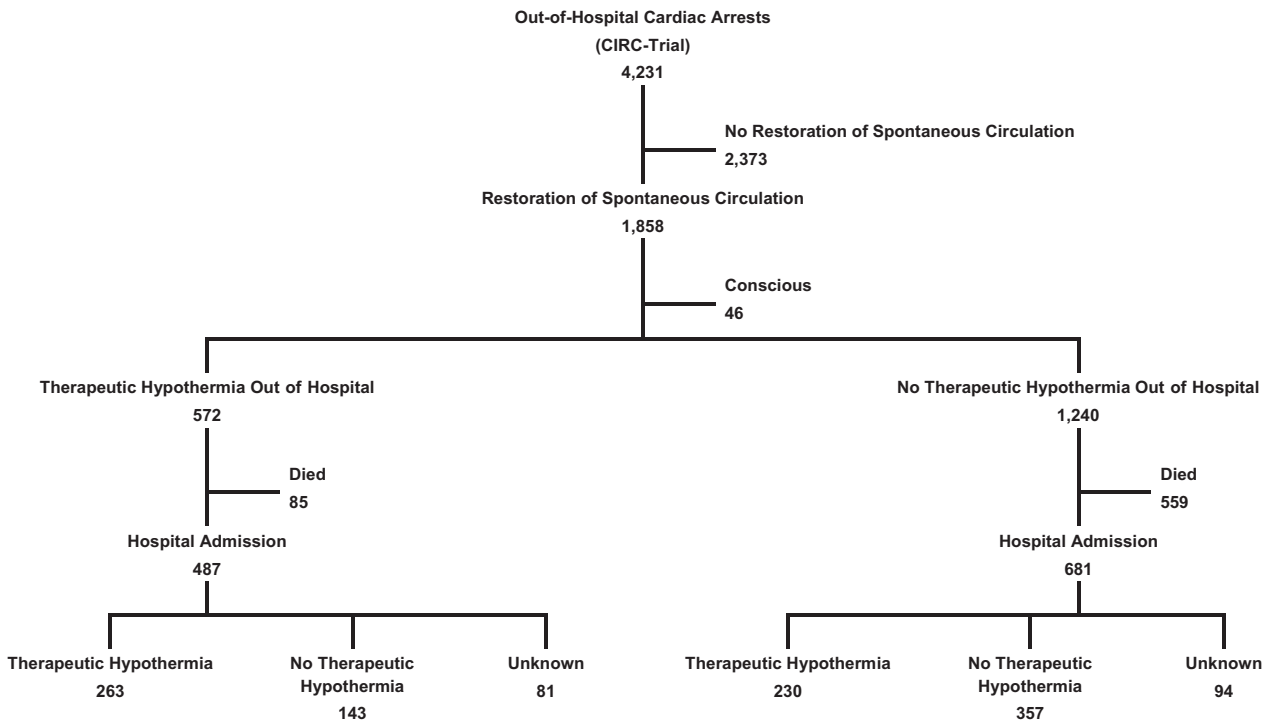


Figure 1 Patient flow chart. Selection of patients and distribution by location of initiation of therapeutic hypothermia.

Table 1 Characteristics of cardiac arrest study population according therapeutic hypothermia

	Therapeutic hypothermia		
	Out- & In-hospital <i>n</i> = 263	In-hospital <i>n</i> = 230	No <i>n</i> = 357
Age – median (IQR)	63 (53–74)	64 (52–75)	64 (55–76)
Female sex – <i>n</i> (%)	90 (34)	87 (38)	160 (45)
Public location – <i>n</i> (%)	48 (18)	67 (29)	124 (35)
Witnessed cardiac arrest – <i>n</i> (%)			
Bystander	145 (55)	149 (65)	152 (43)
Emergency medical service	32 (12)	26 (7)	72 (20)
Bystander cardiopulmonary resuscitation – <i>n</i> (%)	120 (46)	124 (54)	161 (45)
Shockable rhythm- <i>n</i> (%)	122 (46)	112 (49)	110 (31)
Out-of-hospital return of spontaneous circulation – <i>n</i> (%)	263 (100)	210 (91)	308 (86)
Out-of-hospital rearrest – <i>n</i> (%)	70 (27)	64 (28)	104 (29)
Cardiopulmonary resuscitation at admission – <i>n</i> (%)	13 (5)	39 (17)	84 (24)
Rearrest at emergency department – <i>n</i> (%)	22 (8)	29 (13)	58 (16)
No-flow time* – <i>n</i> (%)			
0–2.9 min	66 (25)	74 (32)	106 (30)
3–11.9 min	42 (16)	48 (21)	26 (7)
12+ min	27 (10)	21 (9)	30 (7)
No values available	128 (49)	87 (38)	195 (55)
Low-flow time [†] – <i>n</i> (%)			
0–13.9 min	67 (25)	53 (23)	60 (17)
14–22.9 min	71 (27)	55 (24)	63 (18)
23+ min	62 (24)	52 (23)	81 (22)
No values available	63 (24)	70 (30)	153 (43)
Emergency medical service response time [‡] (min) – median (IQR)	8 (6–11)	9 (5–12)	8 (0–11)
Emergency department admission temperature (°C) – median (IQR)	35.9 (34.8–36.4)	35.8 (35.1–36.4)	36.1 (35.3–36.8)
Time to therapeutic hypothermia (min) – median (IQR) [‡]	19 (9–29)	97 (60–181)	–
Surface cooling – <i>n</i> (%)	162 (62)	151 (66)	–
Lowest temperature (°C) – median (IQR)	32.7 (32.0–33.0)	32.6 (32.0–33.0)	–
Percutaneous coronary intervention – <i>n</i> (%)	55 (21)	65 (28)	50 (14)

*Time from cardiac arrest until first attempted chest compression.

[†]Time from first attempted chest compression until first return of spontaneous circulation.

[‡]Time from emergency call until start of cardiopulmonary resuscitation by emergency medical service personal (= 0 min if cardiac arrest was witnessed by emergency medical service).

[‡]Time from restoration of spontaneous circulation until target temperature.

$P < 0.001$), and those who had cooling only after hospital admission had a 0.67 lower odds of survival (95% CI: 0.50–0.89, $P = 0.006$) compared to those who had cooling *out of* plus *in* hospital (Table 3).

Discussion

Patients cooled to 33 ± 1 °C for 24 h within this observational cohort study showed an improvement in survival if therapeutic

Table 2 Unadjusted associations of initiation of therapeutic hypothermia effects on survival-to-hospital discharge

	Survival to hospital discharge n/N (%)	Unadjusted odds ratio for survival-to-hospital-discharge (95% CI)*	P-value
Therapeutic hypothermia			
Out- & In hospital	98/263 (37)	Reference	
In hospital	80/230 (35)	0.90 (0.55–1.46)	0.66
No	68/357 (19)	0.41 (0.27–0.64)	< 0.001

*Based on cluster robust standard errors to allow for multicentre design.

hypothermia was applied *out of* hospital and continued *in* hospital compared to those not cooled. Time to therapeutic hypothermia was achieved more rapid if cooling was initiated out of hospital. Moreover, individuals who were cooled only after hospital admission had also better outcome than non-cooled patients.

This study is a cohort study investigating the effect of therapeutic hypothermia on survival from patients initially enrolled into the randomised CIRC trial [4] with it is major limitation not being a randomised prospective trial. In our opinion even so the data seems to be worth being reported and not hold back from the therapeutic hypothermia resuscitation research interested community, even with risk of selection bias that this study is associated. The primary finding is that there is an association between *out-of-hospital* or *in-hospital* delivery of induced hypothermia with improved survival confirming at least some previous in-hospital cooling trials [11,12]. The initiation and/or continuation of therapeutic hypothermia occurred at the discretion of treating personnel and were likely influenced by perceptions of patients' likelihood of survival and benefitting from the treatment. Resuscitation guidelines in place at the time of the study and the CIRC study protocol directed that all patients receive therapeutic hypothermia without any delay immediately after return of spontaneous circulation. This made the group with therapeutic hypothermia initiated out of hospital and continued in hospital having improved out-of-hospital return of sustained circulation, less ongoing CPR at admission and rearrest at the emergency department. Making it to the hospital with restoration of spontaneous circulation after cardiac arrest in itself is a strong criterion for primary resuscitation success. The groups only cooled or not after hospital admission showed no major cardiac arrest and resuscitation related differences and thus seemed to have quite equal basic conditions for proving that cooling might be effective in improving outcome. The higher rearrest rates (16% vs. 8%) of the group

Table 3 Adjusted estimates of factors for survival-to-hospital discharge from a multivariable logistic regression model

	Adjusted odds ratio for survival-to-hospital discharge (95% CI)*	P-value
Therapeutic hypothermia		
Out- & In hospital	Reference	
In hospital	0.67 (0.50–0.89)	0.006
No	0.53 (0.46–0.61)	< 0.001
Sex (female vs. male)	1.10 (0.89–1.37)	0.36
Age (by quintile)	0.84 (0.69–1.01)	0.07
Witnessed cardiac arrest		
Not witnessed	Reference	
By bystander	2.62 (2.12–3.24)	< 0.001
By emergency medical service	4.56 (2.82–7.36)	< 0.001
No flow time [†]		
0–2.9 min	Reference	
3–11.9 min	0.75 (0.44–1.28)	0.29
12+ min	0.98 (0.68–1.40)	0.90
No values available	0.95 (0.61–1.49)	0.84
Low flow time [‡]		
0–13.9 min	Reference	
14–22.9 min	0.34 (0.23–0.50)	< 0.001
23+ min	0.17 (0.10–0.29)	< 0.001
No values available	0.20 (0.11–0.34)	< 0.001
Shockable initial rhythm (yes vs. no)	2.96 (2.10–4.18)	< 0.001
Random allocation (Circulation Improving Resuscitation Care Trial)	0.96 (0.79–1.17)	0.70
Bystander cardiopulmonary resuscitation (yes vs. no)	2.38 (1.60–3.52)	< 0.001
Percutaneous coronary intervention	3.72 (1.82–7.61)	< 0.001

*Based on cluster robust standard errors to allow for multicentre design.

[†]Time from cardiac arrest until first attempted cardiopulmonary resuscitation.

[‡]Time from first attempted cardiopulmonary resuscitation until first return of spontaneous circulation.

not cooled may reflect the negligible prognoses of these patients and thus no consideration for therapeutic hypothermia. However, this could have also demonstrated early

benefits of cooling with rearrest rates of only 8% in the *out-of-hospital* vs. *in-hospital* cooled patients in addition contradict the postulated potential deleterious effects of cold intravenous fluid administration *out of hospital*, but might also be explained by the high rates of out of hospital applied surface cooling methods (Table 1) [13,14]. Outcome from out-of-hospital cardiac arrest is about much more than just survival – good health related quality of life or functional capacity of survivors is vital. Unfortunately, neurologic outcomes were missing for 28% of the cases in the CIRC trial. This was mainly due to lack of informed consent, which however occurred equally in all groups [4]. Due to the very small numbers of conscious survivors in each group this results are not reported here. Estimates about rates of withdrawal of life sustaining treatment allow the assumption, that there might have been no differences between groups. Therefore, it was unlikely to have introduced any bias into our results. The magnitude of missing data is somewhat high, but did not seem to differ between treatment groups and did not impact on the robustness of our results.

A systematic review of ten observational studies described lower in-hospital mortality among patients treated with therapeutic hypothermia (33 ± 1 °C) [11,12,15]. These and our results challenge a study comparing cooling to 33 or 36 °C [2] and three cohort studies including a total of 1034 patients [16–18]. Testori *et al.* [17] have shown a benefit in mortality at 6 months similar to our findings at discharge from hospital. There is a lack of information available comparing different durations and time of initiation of targeted temperature management [19,20]. Seven trials with a total of 2237 patients demonstrate no overall difference in mortality for patients treated with out-of-hospital cooling compared to those who did not receive out-of-hospital cooling [3,21–24]. These studies provided additional insight into the relationship between earlier cooling and outcomes, although this is complicated by issues related to variation in the methods of cooling and further in-hospital targeted temperature management. Further studies found that patients who were cooled to 33 °C more quickly had a better outcome [25–28].

There is an urgent need to further elucidate the optimal components of targeted temperature management. Many different sedation, analgesia and relaxation protocols were used not only in general clinical practice but also in our cohort study. Unfortunately, we were not able to get detailed information regarding postresuscitation critical care and therefore are not able to report on symptoms and clinical details such as shivering during cooling [29].

Due to the difficulties in carrying out randomised clinical trials on using therapeutic hypothermia throughout the chain of survival after cardiac arrest, observational studies are

becoming more popular to investigate the relationship between cooling and outcomes [27,30–35]. In our retrospective cohort study, we defined the selected group of people with or without therapeutic hypothermia from the CIRC trial who were followed up to determine incidence of mortality from out-of-hospital cardiac arrest of presumed cardiac origin. Even with our limited control about the cooling procedures and something possible fundamentally different about those who were cooled compared to those not cooled, which could also be related to survival (i.e., they rearrest and never came back, or they were somehow deemed unlikely to survive, etc.), we think, that we are able to draw conclusion based on collected cooling-related data (i.e., target temperature of 33 ± 1 °C for 24 h) with no loss to follow-up for mortality data in the CIRC trial. Nonetheless, this retrospective analysis of the CIRC trial had some limitations. It was not feasible to blind patients or providers about whether hypothermia was initiated and maintained; however, the outcome assessors in relation to therapeutic hypothermia were blinded. Secondly, it was impossible to standardise hospital-based postresuscitation care, and we were not able to control hospital treatment. Therefore, adjusting for percutaneous coronary intervention as post-exposure factor which could correlate with outcome might be a limitation. Patients were frequently discharged alive before consent for ongoing participating could be obtained, limiting the amount of modified Rankin Scale data we were allowed to collect.

More people can survive sudden cardiac arrest when a particular sequence of events occurs as rapidly as possible. The descriptive ‘chain of survival’ communicates this understanding in a useful way. While separate specialised programmes are necessary to develop strength in each link, all of the links must be connected. Weakness in any link lessens the chance of survival and condemns the efforts of an emergency medical services system to poor results. This holds especially true for therapeutic hypothermia, where standard principles of system management are often missing. It emphasises that there are no easy, single-step, cooling approaches to improve survival from cardiac arrest [2,3,5,28,36,37].

Conclusion

The results of our observational study suggest that there is an association between *out-of-hospital* or *in-hospital* delivery of induced hypothermia with improved survival after cardiac arrest.

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Competing interests

The principal investigator for CIRC, Lars Wik was also sponsored by ZOLL Medical Corporation, for a hemodynamic study by PhysioControl (Ideon Science Park, 22370 Lund, Sweden) and has a patent licensed by ZOLL Medical Corporation. Jan-Aage Olsen is partly funded by unrestricted grant from Norwegian Health Region South-East and partly by a research grant from ZOLL Medical Corporation paid to the Norwegian Center for Prehospital Emergency Care (NAKOS), Oslo University Hospital. Ulrich R. Herken is an employee of ZOLL Medical Corporation (Chelmsford, MA, USA) which manufactures and sells the AutoPulse. All other authors' institutions received funding from ZOLL Medical Corporation for their participation in the trial. The other authors have no other relevant financial conflicts of interest to report.

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