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Clinical paper

Time to start of cardiopulmonary resuscitation and the effect of target temperature management at 33 °C and 36 °C☆

Josef Dankiewicz[a,b,*], Hans Friberg[a,b], Jan Bělohlávek[c], Andrew Walden[d], Christian Hassager[e], Tobias Cronberg[a,b], David Erlinge[a,b], Yvan Gasche[f], Jan Hovdenes[g], Janneke Horn[h], Jesper Kjaergaard[i], Michael Kuiper[j], Thomas Pellis[k], Pascal Stammet[l], Michael Wanscher[m], Jørn Wetterslev[n], Matthew Wise[o], Anders Åneman[p], Niklas Nielsen[b,q]

[a] Department of Intensive and Perioperative Care, Skåne University Hospital, Lund, Sweden
[b] Department of Clinical Sciences, Lund University, Lund, Sweden
[c] 2nd Department of Cardiovascular Internal Medicine, First Medical Faculty, Charles University, Prague and General Teaching Hospital of Prague, Prague, Czech Republic
[d] Department of Intensive Care, Royal Berkshire Hospital, Reading, United Kingdom
[e] Department of Cardiology, The Heart Centre, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
[f] Department of Intensive Care, Geneva University Hospital, Geneva, Switzerland
[g] Department of Anesthesiology, Rikshospitalet, Oslo University Hospital, Oslo, Norway
[h] Department of Intensive Care, Academic Medical Centre, Amsterdam, The Netherlands
[i] Department of Cardiology, The Heart Centre, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
[j] Department of Intensive Care, Leeuwarden Hospital, Leeuwarden, The Netherlands
[k] Department of Intensive Care, Santa Maria degli Ángeli, Pordenone, Italy
[l] Department of Anesthesiology and Intensive Care, Centre Hospitalier de Luxembourg, Luxembourg City, Luxembourg
[m] The Heart Centre, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
[n] Copenhagen Trial Unit, Centre of Clinical Intervention Research, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
[o] Adult Critical Care, University Hospital of Wales, Cardiff, United Kingdom
[p] Department of Intensive Care, Liverpool Hospital, Sydney, NSW, Australia
[q] Department of Anesthesiology and Intensive Care, Helsingborg Hospital, Helsingborg, Sweden

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ABSTRACT

Introduction: The optimal temperature during targeted temperature management (TTM) for comatose patients resuscitated from out-of-hospital cardiac arrest is unknown. It has been hypothesized that patients with long no-flow times, for example those without bystander CPR would have the most to gain from temperature management at lower temperatures.
Methods: We analysed data from an international clinical trial randomizing cardiac arrest patients to targeted temperature management at 33 °C and 36 °C for an interaction between no-flow time and intervention group, with neurological function at six months after cardiac arrest as the primary outcome. A cerebral performance category (CPC) score of 1 or 2 was considered a good outcome.
Results: No-flow time (min) was associated with poor neurological outcome (OR 1.13, 95% confidence interval 1.06–1.20, $p < 0.001$). There was no statistically significant interaction between no flow-time and intervention group ($p = 0.11$), which may imply that the non-superior effect of 33 °C was consistent for all no-flow times. Bystander CPR was not independently associated with neurological function.
Conclusions: TTM at 33 °C compared to 36 °C was not associated with an increased probability of a good neurological function for patients with longer no-flow times.

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* Corresponding author at: Skåne University Hospital, Department of Intensive and Perioperative Care, 22185 Lund, Sweden.
E-mail address: josef.dankiewicz@gmail.com (J. Dankiewicz).

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Introduction

Targeted temperature management (TTM) after cardiac arrest is currently recommended by international guidelines for both shockable and non-shockable rhythms based on two trials from 2002.[1–3] Following the publication of the TTM-trial, which showed no difference in survival or neurological outcome between 33 °C and 36 °C,[4] an update from the International Liaison Committee on Resuscitation (ILCOR) preceding a formal consensus statement stressed that target temperature management remains an important aspect of post-resuscitation care, and stated that target temperatures of 33 °C and 36 °C were both acceptable options. [5]

Since the adoption of TTM more than a decade ago efforts have been made to elucidate which patients gain most benefit from TTM. Subgroups that have been investigated include different age groups, shockable and non-shockable rhythms as well as patients with in-hospital cardiac arrest.[3,6–8] Based on the classification of cardiac arrest into three stages by Weisfeld and Becker it has been suggested that patients in the metabolic phase of arrest, which include those with more than 10 min of no-flow time (time from cardiac arrest to start of cardiopulmonary resuscitation (CPR) would be particularly responsive to TTM.[9,10] This hypothesis is to some extent supported by animal studies showing that ischemia persisting beyond 8 min is progressively associated with worse neurological outcomes.

There have been concerns regarding the generalizability of the results of the TTM-trial because a high proportion of patients received bystander-CPR (73%) and a median time to start of basic life support (for patients with bystander-CPR) of 1 min (interquartile range (IQR) 0–2 min, range: 0–25 min).[11,12]

The aim of this study was to explore any potential interaction between temperature and no-flow time to investigate whether patients with longer periods of cerebral ischemia had a better response to the lower target temperature of 33 °C in the TTM-trial.

Methods

Patients

This study is a post hoc analysis of the TTM-trial, an investigator-initiated, multicentre, randomized, parallel group, and assessor-blinded clinical trial (NCT01020916).[3] The TTM-trial included adult patients (≥18 years) resuscitated from OHCA of presumed cardiac cause, irrespective of the initial rhythm, who remained unconscious (Glasgow coma scale <8) after sustained (>20 min) return of spontaneous circulation (ROSC). The main exclusion criteria were unwitnessed arrest with asystole as the primary rhythm, an interval from ROSC to screening of >240 min and a state of refractory shock, defined as a systolic blood pressure (SBP) of <80 mm Hg despite fluid loading, vasopressors, inotropes and/or treatment with mechanical assist devices that could not be reversed within the inclusion time window.[3]

This post hoc analysis included all patients in the trial with available data on no-flow time. No-flow time was defined as the reported time from cardiac arrest to the start of bystander CPR. For patients who did not receive bystander CPR, no-flow time was defined as time between the cardiac arrest and initiation of CPR by a medical provider. Low-flow time was defined as time with active CPR by a bystander and/or a medical provider. Therefore, low-flow time equalled time to ROSC minus no-flow time.

Outcome

Primary outcome was the neurological function at six months assessed by the cerebral performance category (CPC) scale.[13] A CPC of 1–2 was considered a good neurological outcome and a CPC of 3–5 was considered a poor neurological outcome. As an additional outcome, mortality at six months was assessed.

Table 1
Characteristics of the study population.

Characteristic	TTM 33 (n = 473)	TTM 36 (n = 464)
Bystander CPR	344 (73)	339 (73)
Age–median (IQR)	65 (57–73)	65 (56–73)
Male sex–no (%)	393 (83)	367 (79)
Shockable rhythm–no (%)	375 (79)	376 (81)
No-flow time–median (IQR)	1 (0–6)	1 (0–5)
Low-flow time–median (IQR)	23 (14–35)	21 (13–35)
Shock on admission–no (%)	70 (15)	67 (14)
Site[a]–no (%)	110 (23)	108 (23)

TTM: target temperature management; IQR: inter-quartile range.
[a] Patients from the two sites with the highest number of randomized patients. All other sites comprise the reference category.

Statistical analysis

Comparisons between groups were assessed by the Mann–Whitney U test for continuous variables and the chi-squared test for categorical variables. Logistic regression was used to analyse six-month neurological outcome and mortality at six months providing odds ratios (OR) with 95% confidence intervals (CI). Variables included in the models were bystander CPR and the design variables from the TTM-trial (age, gender, initial rhythm, time to ROSC, circulatory shock at admission and site) with time to ROSC subdivided into no-flow and low-flow time.[14] To avoid multicollinearity, continuous variables were centred. The low-flow variable was also included as a squared variable. No-flow time was studied as a continuous variable and in a separate model as a categorical variable. The categories used were the same as those proposed by Testori et al.[9] An interaction between no-flow time and the intervention group (36 °C) was included in both models. To study the effect of temperature at different no-flow times, adjusted predictions at representative values were made using the STATA command margins. These calculations were performed, as the interpretation of the odds ratio of an interaction can be misleading. Variables other than treatment group were left at their actual values while the effect of managing the entire study population at 33 °C and 36 °C was studied. Average probability of a poor neurological function and mortality was calculated at 2-min intervals from 0 min of no-flow time to 20 min of no-flow time. In the categorical analysis the average probability of a poor outcome was calculated for each category. To test the statistical significance of the difference between the estimated average probabilities at different no-flow times we used the STATA command margins (dydx), as overlapping confidence intervals can be too conservative.[15] p-values < 0.05 were considered significant. STATA 13.1 (StataCorp, College Station, Texas, USA) was used for all analyses.

Results

Study population

The modified intention to treat population of the TTM-trial included 939 patients with 473 patients randomized to targeted temperature management at 33 °C and 466 at 36 °C. Exclusions and withdrawals of patients before and after randomization, as well as the main results of the trial have been reported previously.[4] Patient characteristics are shown in Table 1. There were no significant differences in baseline variables between intervention groups.