The impact of delayed therapy on neurologic outcome for post-cardiac arrest patients treated with therapeutic hypothermia

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A. Study Purpose and Rationale:

In February 2002, two landmark trials were published in the New England Journal of Medicine that introduced a simple intervention that, if performed after a patient was successfully resuscitated from cardiac arrest, could prevent devastating anoxic neurologic injury[1, 2]. These trials, conducted in Europe and Australia, showed that deliberately lowering the body temperature of a patient to achieve "mild hypothermia" of 32-34C for 12-24 hr following an arrest could double the patient's chance of walking out of the hospital with limited deficits. They marked the beginning of the era of therapeutic hypothermia, and the practice has gained widespread use across the Western world, dramatically improving neurologic outcomes. There were limitations: hypothermia is much more effective for patients with "cardiac" causes of arrest (ventricular fibrillation or pulseless ventricular tachycardia) than other causes (PEA, asystole, bradycardia) and appears to be more effective in younger, healthier patients than in older, critically ill patients[3-7]. Even in an optimized patient population, 4/10 patients will still have a poor outcome[7]. Still, it represents the only effective therapy for preventing hypoxic-ischemic injury following a cardiac arrest and a dramatically effective therapy, with a NNT=4[2]. Because it is still a new therapy, much of the procedure itself has not been optimized. The optimal target temperature is currently being studied in an ongoing trial (32C vs. 34C), the duration of hypothermia has not been optimized and the length of time that a patient should be rewarmed over in still in dispute. Lurking within these debates is the consensus that a patient should be cooled "as quickly as possible" following an arrest. Practice, however, shows great variability in the time required to achieve hypothermia. This study will elucidate the impact of delayed hypothermia on neurologic outcome.

This question has been previously addressed with results that support the hypothesis that early hypothermia improves outcome, but the results have been neither definitive nor consistent. In 2009, a German group looked at a relatively small prospective cohort of 49 patients and found a large, but not statistically significant difference in time to target temperature between the patients who had a good neurologic outcome and the patients who had a poor neurologic outcome (334 minutes to 450 minutes with a $p = 0.07$)[8]. A recent Finnish study showed time to target temperature had minimal impact on outcome; notably, the mean time to target temperature was markedly shorter than prior studies at 240 minutes[9]. This suggests two points: 1) the Finnish method for admitting and cooling cardiac arrest patients is more efficient than the process used in the rest of the world and 2) there may be a critical period for cooling patients that maximizes their chances for a good outcome.

NewYork-Presbyterian Hospital was an early adopter of therapeutic hypothermia and has been a high volume center for more than five years. Cursory observation, however, reveals considerable variability in how quickly patients are cooled. Possible causes for these delays include equipment availability, different levels of training, prioritization of other procedures such as cardiac catherization and diagnostic tests over cooling, lack of integration of cooling into the ACLS protocol and individual hospital floor policies. This potentially large data set and

potential variability in practice creates a natural experiment and ability to study the impact of cooling time on outcome that could not be ethically done under more controlled circumstances.

B. Study Design and Statistical Analysis:

This will be a retrospective cohort study of all patients who experienced cardiac arrest who were treated with therapeutic hypothermia at NewYork-Prebysterian Hospital (NYP), including NYP/CUMC, NYP/WCMC and NYP/AH, between April 30, 2008 and April 30, 2013. The cohort will include patients who experienced out of hospital arrest and patients who experienced arrest as inpatients at NYP. Once identified, the patients' charts will be reviewed, the time of their arrest will be recorded using best available evidence and the time that they achieved goal hypothermia (T < 34C) will be recorded according to the patients' documented temperature in their vital signs flowsheet. The time of arrest will be subtracted from the time of hypothermia to obtain the time-to-hypothermia (TTH). If the TTH is less than 5.5 hours (330 minutes), the patient will be assigned to the "Early Hypothermia" (EH) group and if the TTH is more than 7.5 hours (450 minutes), the patient will be assigned to the "Late Hypothermia" (LH) group. Patients who achieves hypothermia 5.5-6.5 hours after arrest and 6.5-7.5 hours after arrest will be assigned to "Group A" and "Group B," they will be assessed in a similar manner and data collected from these two groups will be used in a secondary analysis.

The primary endpoint of this study will be neurologic outcome at time of discharge from the hospital. The patient's neurologic status will be determined as the time of discharge from the hospital or death according to the Cerebral Performance Category scale (CPC), which has been the assessment of choice for evaluating post-anoxic patients[10]. The scale operates as follows:

CPC 1	Good cerebral performance: conscious, alert, able to work. Possible mild neurologic deficit.
CPC 2	Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life (iADL). Able to work in a sheltered environment.
CPC 3	Severe cerebral disability: conscious, dependent on others for daily support of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.
CPC 4	Coma or vegetative state: any degree of coma without brain death. Unawareness, even if appears awake, no interaction with environment, may have spontaneous eye opening and sleep/wake cycles. Cerebral unresponsiveness.
CPC 5	Death

For the purposes of this study, a "Good Neurologic outcome" (GNO) will be defined as a CPC score of 1 or 2 and a "Poor neurologic outcome" (PNO) will be defined as a score of 3, 4 or 5 as has been previously used in the literature[1, 9]. The patient's neurologic status will be determined by review of the patients' discharge summaries, neurology consult notes, social work notes and (when appropriate) death notes.

The following additional information will be collected for each patient in the study: age, time from arrest to return of spontaneous circulation (ROSC), type of arrest ("shockable" ie ventricular fibrillation and pulseless ventricular tachycardia vs. "nonshockable" ie pulseless electrical activity and asystole), location at the time of arrest (in hospital vs. out of hospital), post

arrest shock, as measured by vasopressor requirement following resuscitation, and blood lactate, all of which have been shown to be independently associated with neurologic outcome in prior studies[1, 3, 4, 9].

The proportion of the patients in the "Early Hypothermia" group with a "Good neurologic outcome" will be compared to the proportion of the patients in the "Late Hypothermia" group using Chi-squared analysis. For the purposes of statistical analysis, the null hypothesis will be "there is no difference in neurologic outcomes between patients achieving hypothermia early following arrest and late." A study conducted on a population similar to our study population (all cardiac arrest patients including shockable and nonshockable rhythms, in hospital and out of hospital arrest) which compared hypothermia vs. normothermia treatment showed good neurologic outcomes in 56% of patients treated with hypothermia and 26% of patients treated with normothermia. It is our hypothesis that the patients in the EH group will achieve similar rates of GNO to the patients treated with hypothermia in this study, as the full benefit of the treatment is available to them and that patients in the LH group would experience 50% of the benefit from the therapy as a result of the delay. Based on the expected proportions of 0.56 and 0.41 in the GNO category for the two groups, 186 patients should be identified for each group in order to assess a statistically significant difference with statistical significance pre-determined to be a < 0.05 and a Power = 0.8.

The potential confounders, delineated above, will be controlled for using a stepwise, forward logistical regression. The data from EH, LH, Group A and Group B will be used in a stepwise forward regression in order to attempt to establish a critical window for cooling.

C. Study Procedure:

Study data will be extracted and collected from the electronic and paper medical records at NYP/AH, NYP/CUMC and NYP/WCMC from April 30, 2008 to April 30, 2013. No study subjects will be contacted as a result of their involvement with this study.

D. Study Drugs:

No drugs or medications will be evaluated as part of this study.

E. Medical Device:

No medical devices will be evaluated as part of this study.

F. Study Questionnaires:

No questionnaires will be used as part of this study.

G. Study Subjects:

Candidates for this study are patients who were treated for or following cardiac arrest at NYP between April 30, 2008 and April 30, 2013, were determined to be candidates for therapeutic hypothermia and who had therapeutic hypothermia initiated. Candidates will be excluded as study subjects if their time to return of spontaneous circulation (ROSC) was greater than 25 minutes, if they were not cooled to < 34C or if their baseline function would indicate a pre-arrest CPC of 3 or 4.

H. Recruitment of Subjects:

Candidates for this study will be identified using monthly resource utilization records from the emergency departments and the relevant intensive care units with the assistance of the neurocritical care division of the department of Neurology, who are required to evaluate each potential candidate for hypothermia.

I. Confidentiality of Study Data:

Each candidate subject will be assigned a unique identification number (ID) that will be recorded with the patient's medical record number (MRN) in a separate, secure file. Following assessment and data collection, the patient will be referred to only by their ID number and no further identifying information will be recorded.

J. Potential Conflict of Interest:

There are no potential conflicts of interest.

K. Location of the Study:

This study will be conducted at all campuses of NewYork-Presbyterian Hospital (NYP) including NYP/Columbia University Medical Center, NYP/Allen Hospital and NYP/Weill Cornell Medical Center.

L. Potential Risks:

Exposure of the personal, confidential and medical information of the study subjects to unintended parties is a potential risk of this study.

M. Potential Benefits:

The study subjects will not benefit from their involvement in this study. Rather, any benefits from delineating the optimum time course for therapeutic hypothermia, including improvements in procedures and use of new technology, would be experienced by future patients.

N. Alternative Therapies:

Not applicable.

O. Compensation to Subjects:

The subjects in this study will not be compensated.

P. Costs to Subjects:

There will be no additional costs to the subjects as a result of this study.

Q. Minors as Research Subjects:

No minors will be used as subjects in this study.

R. Radiation or Radioactive Substances:

This study will not involve exposure to radiation.

References:

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