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The Neuroprotective Effects of Targeted Temperature Management in Post Cardiac Arrest Patients

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Abstract
- Novel methods of ensuring survival following cardiac arrest and resuscitation are of supreme importance to the medical community.
- Targeted temperature management (TTM) has become increasingly utilized pre-hospital, in emergency departments, and within intensive care units to increase the probability of survival. TTM has further been used to attempt to improve neurological functioning. The efficacy and mechanism behind TTM remains poorly understood.
- In several patient populations it also remains unproven. The purpose of this study is to assess the physiological mechanism, survival, neurological recovery and methodology behind TTM.
- Literature review was utilized to assess the physiological mechanism by which TTM elicits its effects. The literature on neuroprotective effects on neurological outcomes and survival rates were further examined. Finally, the proposed method to safely and efficiently induce and maintain TTM in appropriate patients was also assessed through literature review.

Methods
- To acquire relevant research PubMed, Clinical Key, Cochrane review and Cochrane Collaboration were referenced.
- Search terms included: targeted temperature management, therapeutic hypothermia, cardiac arrest, return of spontaneous circulation (ROSC) and MTR. These terms were used in several combinations to obtain appropriate research materials.
- Dynamic and the American Heart Association (AHA) were further assessed for recommendations on patient selection, implementation, and methodology behind TTM.
- Striking of the potential benefits in cardiac arrest (OHCA) as well as out-of-hospital cardiac arrest (OHCA) were included to assess the use of TTM pre-hospital. Furthermore, TTM use in pediatric patients as well as in vulnerable and non-shockable rhythms was assessed through literature review.

Statement of Problem
- Targeted temperature management is a poorly understood intervention.
- It is believed to confer benefit to survival and neurological outcome, though the mechanism is still under research. The magnitude of potential benefit to survival and neurological functioning also remains under scrutiny.
- Finally, the method of TTM induction remains poorly standardized. Assessment into the methods and procedures of several studies may yield a more effective and efficient method to confer the greatest benefit to survival and neurological function.

Research Questions
- By what proposed mechanisms does targeted temperature management improve survivability and neurological functioning following cardiac arrest and resuscitation?
- Do studies evaluating the benefit of targeted temperature management demonstrate statistically significant improvements in survival to hospital discharge as well as improvements in cognitive function following resuscitation?
- What is currently agreed upon method of inducing targeted temperature management and what is its ease of implementation?

Clinical Applicability
- TTM is most effectively accomplished by rapidly decreasing core body temperature to 33-36 degrees Celsius, though fever and shivering are monitored and treated for. FH 1-2, 9% eT1-1.145.
- Damped recommendations rapidly induction to target temperature 32-36 degrees Celsius and followed by rewarming over 1-2.44 hours. The Yu et al. (2017) study further suggests that earlier implementation is effective in preserving neurological function.
- Per Wulff (2017) recommends that TTM should be induced in patients who remain unresponsive following OHCA with ROSC and a presenting shockable rhythm, or if a non-shockable rhythm was converted to ROSC following ROSC with non-shockable rhythms or following IHCA. Core body temperature should be decreased to 33-34 degrees Celsius and maintained for 24 hours.
- The AHA does not currently endorse routine pre-hospital cooling methods. TTM can be readily applied in rural ER practice and maintained for transport to a higher level of care by EMS, decreasing the time to therapeutic effect.

Literature Review
- Pathophysiology
  - Fan et al. (2017) utilized a rat model to show increased DRP-1 and CYT-C as TTM proceeds. Further, Dr. Li Xia et al. (2017) demonstrated a decrease in cerebral edema and mitochondrial apoptosis of neuronal cells with TTM application. Serum biomarkers of brain injury and dysfunction of the endothelium constituting the brain blood barrier (BBB) have also been found to be decreased in patients undergoing TTM.
  - Finally, assay of antioxidants demonstrates a decrease in oxidative damage and increase in antioxidant protection following resuscitation.

- Study Designs
  - Patients who underwent an out-of-hospital cardiac arrest (OHCA) had a 12% likelihood of surviving to discharge (Chan, Mon, Tarm & Kattan, 2014). OHCA demonstrates improved good neurological function in 8.5% (Buck et al., 2018).
  - Targeted temperature management has become a mainstay within hospital systems to improve neurological function in patients after cardiac arrest.
  - Proponents further suggest that implementation improves survival to hospital discharge.
  - This includes improved neuroprotective mechanism, improvements in survival and neurological functioning, and recommendations for implementation were assessed through literature review.

Discussion
- Animal studies performed by Fan et al. (2017) and Chan et al. (2017) demonstrate inhibition of mitochondrial-induced cellular apoptosis through alteration of mediators of mitochondrial pore opening such as CYT-C, DRP-1, and ANT-1. Furthermore, the rate and extent of apoptosis were decreased in all cardiac arrest groups (P < 0.05), suggesting decreased mitochondrial induced neuronal apoptosis (P < 0.05).
- Hackenthal et al. (2017) performed a study focused on reactive oxygen species (ROS) development. TTM was effective in decreasing reactive oxygen species (P < 0.05).
- Jahandiez, et al. (2017) performed studies using rabbits to model cardiac arrest. A decrease in mitochondrial apoptosis was noted (P < 0.05).
- Jeben et al. (2017) performed a series of porcine studies assessing the effects of TTM. TTM demonstrated a decrease in the examination of neuroprotective methodologies, and diminished serum biomarkers of brain injury and dysfunction of the endothelium further evaluated the damaged vascular endothelium. The serum ANG-1 and ANG-2 ratio was found to be increased in TTM patients with mitochondrial dysfunction suggesting minimized damage to vascular endothelium (P < 0.1).
- Chen et al. (2017) performed controlled studies using endothelial cells of laboratory rats. Ischemic cells in the TTM group demonstrated a decrease in apoptosis (P < 0.0083). The CYT-C precursor Bax as well as caspase 3 were elevated to a lesser degree in the TTM cohort (P < 0.05).
- Survival and cognition improvements
  - Fan, et al. (2017) performed an experiment performing TTM on lab rats. Improvements were noted in the TTM group in survival and neurological function (P < 0.05).
  - Heager et al. (2017) utilized data obtained from the Circulation Improving Resuscitation Care Trial (CIRCIT). The results suggest that survival to discharge is superior in patients who receive prehospital/hospital TTM (P < 0.006).
  - Miller et al. (2017) performed a study to determine the efficacy of TTM for pediatric patients who experience IHCA. No significant difference was found in survival, nor was there difference in cognitive function (P = 0.50), suggesting increased survivability.
  - Pernet et al. (2015) used retrospective analysis to determine the effectiveness of TTM who present with a non-shockable rhythm (asystole/PEA). Both cohorts enjoyed improved neurological functioning and survivability to discharge regardless of the location of arrest (P = 0.001, respectively).
- Method of implementation
  - Casamento et al. (2016) utilized review of patient records to assess varying methodologies of TTM. In several TTM patients undergoing TTM to 32 or 36 degrees, greater likelihood of complications was found in the 32-34 degree group (P < 0.01).
- They also note an increased discharge to home rate in the 36-degree group (P = 0.02).
- Yu et al. (2017) performed a porcine study on the effects of early versus delayed administration of TTM. CPC scores demonstrated improved neurological function in the early TTM group (P = 0.012).

References