196
Evaluation of Rapid Brain Cooling Methods for Induction of Mild Resuscitative Hypothermia

Klain M, Safar P, Sterz F, Tisherman S, Ziao F, Stezoski SW, Li H
International Resuscitation Research Center, University of Pittsburgh
Pittsburgh, Pennsylvania, USA

Objectives: To summarize new data on various methods for lowering brain and total body temperature (T) to 33-35°C within 15 minutes (min) after an insult. To help clinical implementation of rapid, mild cooling, which proved beneficial in animals after cardiac arrest, brain trauma, stroke or shock.
Dog Studies: In more than 80 dogs (18–28 kg), various cooling methods were evaluated during no-flow, low-flow (CPR), or high-flow (spontaneous circulation). Core and tympanic membrane (brain) T were monitored, and sometimes also epidural and deep brain T. The rapidity of cooling to brain T 34°C was 2–5 min with cardiopulmonary bypass or carotid cold flush, 10–15 min with head-neck-trunk surface cooling. The latter could be reduced to 15 min by adding nasopharyngeal and gastric, or esophageal cooling and an intravenous (IV) cold fluid load.
Human Cadavers: In two human cadavers (no-flow), surface cooling by head immersion in ice water lowered deep brain T to 34°C in ±30 min.
Phantom: Calculations of heat transfer from 0°C applied to the "head surface" showed that "deep brain T" of 34°C is achieved after >30 min.
Conclusions: Surface cooling alone is too slow. Clinical trials of surface-combination cooling methods are encouraged.

197
Rapid Induction of Mild Cerebral Hypothermia with Peritoneal Cold Lavage in Dogs

Xiao F, Safar P, Wik L, Sim K, Kuboyama K
International Resuscitation Research Center
University of Pittsburgh
Pittsburgh, Pennsylvania, USA

Introduction: In dogs, it has been shown that mild resuscitative (post-insult) cerebral hypothermia (34°C) immediately for 1–2 hours (h) after prolonged cardiac arrest reduces brain damage. A 15-minute (min) delay in initiation of cooling almost offsets the beneficial effect. Such rapid cooling could be achieved in dogs by blood cooling or cumbersome combinations of external cooling. This study presents a relatively simple alternative using peritoneal lavage with cold fluid.
Methods: Five dogs (23 ±1 kg) under spontaneous circulation, with N_2O:O_2 50:50% - halothane 0.5% anaesthesia and paralysis, with intermittent positive pressure ventilation (IPPV) and controlled normotension, had various temperatures (T) monitored. A catheter was inserted just below the umbilicus into the peritoneal cavity. Two liters of Ringer's solution at 10°C (7–15°C) were instilled rapidly into the peritoneal cavity, retained there for five minutes, and then drained by gravity.
Results: Pulmonary artery T was controlled at 37.5°C before cooling. Other Ts were observed. By the end of peritoneal cold fluid instillation, all Ts had decreased rapidly. Tympanic membrane T (Tty) reflecting brain T reached 34°C at 7–10 min after peritoneal instillation. With dogs at 25°C room T, Tty remained 32–34°C for 60 min, without the need for further surface cooling. Physiologic variables did not change. The rate of peritoneal cooling was significantly more rapid than that observed in previous studies using either an intravenous (IV) fluid load of 10 ml/kg at 4°C; or esophageal, nasopharyngeal, or head-neck surface cooling.
Conclusions: Peritoneal instillation of cold Ringer's solution may be an effective method for rapid induction of mild cerebral hypothermia, and should be tried in comatose patients who could benefit from therapeutic mild hypothermia.

198
A Method for Systematic Evaluation of Novel Cerebral Resuscitation Therapies after Cardiac Arrest (CA)

Sim K, Safar P, Radovsky A, Bircher N, Abramson N, Ebmeyer U
International Resuscitation Research Center
University of Pittsburgh
Pittsburgh, Pennsylvania, USA

Objective: Controversies about the evaluation of new cerebral resuscitation potentials after cardiac arrest have been caused by uncoordinated studies in different laboratories on different species with different models, and the use of often unreliable methods of evaluation. Through years of experience, a systematic sequence of such studies has been developed, including specific requirements for animal outcome models.
Methods: Novel therapeutic potentials were selected on the basis of rationale and promising bench data. Phase I consisted of one or more brain morphologic outcome studies in a rat forebrain ischemia or rat cardiac arrest (CA) model. Significant mitigation of brain damage had to be demonstrated to progress to the next phase. Phase II used normal dogs, without CA, with and without anesthesia, to study side-effects caused by IV infusion (to overdose) of the experimental therapy (shams). In Phase III, the most reproducible CA dog outcome model (with brief CPB for controlled reperfusion) was used to compare a small series of the experimental treatment with a large series of historic controls (which achieved reproducibly poor outcome). If Phase III results suggest benefit, Phase IV was used with the same dog outcome model for a large randomized, placebo blinded study with concurrent controls. If Phase IV shows benefit, Phase V (with a clinically more realistic external CPR dog outcome model) was used to confirm the results of Phase IV. If Phase V shows benefit, Phase VI will be a randomized clinical trial.
Results: Several novel treatment potentials (blood flow promoting measures; calcium entry blocker therapies; mild hypothermia; excitatory amino acid receptor blocker; and other drugs) have been exposed to this process. Data will be summarized.

https://doi.org/10.1017/S1049023X00048305 Published online by Cambridge University Press

Conclusions: Evaluation of novel cerebral resuscitation potentials should not be taken from rat data indirectly to patient trials without systematic evaluation of risks and benefits in reproducible outcome models in a large species.

199
Mild Cerebral Hypothermia after Cardiac Arrest Mitigates Brain Damage in Dogs

Safar P, Sterz F, Leonov Y, Weinrauch V, Kuboyama K, Radovsky A
International Resuscitation Research Center
University of Pittsburgh
Pittsburgh, Pennsylvania, USA

Objective: To summarize the results of a logical sequence of four cardiac-arrest outcome studies.
Methods: The standardized ventricular fibrillations (VF) 10 or 12.5 min (no-flow) outcome models in dogs were used. In studies #1, #3 and #4, reperfusion was with brief cardiopulmonary bypass (CPB). In study #2, reperfusion was with external CPR. The use of intermittent positive pressure breathing (IPPV) was to 20 h and intensive care with outcome evaluation to 72 or 96 h. Outcome was determined as overall performance, neurologic deficit, and brain histologic damage scores. Mild hypothermia (34°C) was induced from reperfusion to 1–2 h; in study #2, a combination of external cooling methods was started after restoration of spontaneous normotension.
Results: In all four studies, cerebral functional and morphologic outcomes were significantly better in the mild hypothermia groups compared with normothermic concurrent controls. Mild hypothermia was more beneficial than was post-arrest moderate (30°C) or deep hypothermia (15°C), which worsened cardio-vascular variables. When start of cooling was delayed by 15 min after reperfusion, histologic but not functional improvement occurred.
Conclusions: These dog data and others' rat data justify clinical development and evaluation of rapid mild brain cooling methods for use in EMS and hospitals.

200
Mild Protective and Resuscitative Cerebral Hypothermia Improves Outcome after Asphyxial Cardiac Arrest in a New Rat Model

Xiao F, Ebmeyer U, Safar P, Radovsky A, Katz, L, Neumar R, Sim KM, Stezoski SW
International Resuscitation Research Center
University of Pittsburgh
Pittsburgh, Pennsylvania, USA

Objective: To explore in cardiac arrest (CA) the ability of mild hypothermia (Hth), tympanic temperature (Tty) 34°C, for protection (cooling before the insult) or resuscitation (cooling after restoration of spontaneous circulation (ROSC), to improve functional and morphologic cerebral outcome in this rat model of eight minutes (min) asphyxiation, to thereby confirm that the model's insult is in the treatable range.
Methods: Twenty-seven rats were randomized into normothermic control Group A (n = 10), resuscitative Hth Group B (n = 9), and protective Hth Group C (n = 8). Cooling was by external means. After eight min asphyxiation (CA 5 min), return of spontaneous circulation (ROSC) was with external CPR, epinephrine intravenous (IV), $NaHCO_3$ IV, and intermittent positive pressure ventilation (IPPV) to one hour (h). Evaluation to 72 h was in terms of neurologic deficit scores (NDS 0–100%), overall performance categories (OPC, 1–5), and whole brain histopathologic damage scores (of at least four coronal slides).
Results: The NDSs were lower (better) in Groups B and C compared with Group A ($p < .05$). Compared with Group A, OPCs were better numerically in group B and significantly better ($p < .05$) in Group C. Total ($p < .05$) and regional (numerical) histologic damage score were lower in Group C and correlated with ND ($r = 0.83$) and OPC ($r = 0.79$).
Conclusions: This rat model, with eight-minute asphyxiation (CA 5 min), is suitable for treatment trials as it responds to protective mild hypothermia. Mild resuscitative cerebral hypothermia in rats seems to improve outcome not only in models with incomplete forebrain ischemia (as shown by others previously), but also in a model of total body circulatory arrest.

201
Cardiogenic Shock and Multiple-Organ Failure

Oohama N, Yamanaka I, Imaki S, Ogawa T
St. Marianna University School of Medicine
Yokohama City Seibu Hospital Emergency Center
Yokohama, Japan

Introduction: Multiple-organ failure (MOF) is becoming one of the most important problems during anti-shock therapy of patients suffering from cardiogenic shock. Cardiogenic shock (CGS) was studied and its prognosis was evaluated.
Methods: All patients who were admitted to the emergency center with cardiovascular disease from 1 January 1991 through 31 December 1992 were studied.
Results: The total number of patients studied was 301. Of 301 patients, 30 were found to have cardiogenic shock. They con-

https://doi.org/10.1017/S1049023X00048305 Published online by Cambridge University Press