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## Therapeutical hypothermia after cardiopulmonary resuscitation: evidences and practical issues

*Hipotermia terapêutica pós-reanimação cardiorrespiratória: evidências e aspectos práticos*

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### ABSTRACT

Cardiac arrest survivors frequently suffer from ischemic brain injury associated with poor neurological outcome and death. Therapeutic hypothermia improves outcomes in comatose survivors after resuscitation from out-of-hospital cardiac arrest. Considering its formal recommendation as a therapy, post-return of spontaneous circulation after cardiac arrest, the objective of this study was to review the clinical aspects of therapeutic hypothermia. Non-systematic review of articles using the keywords “cardiac arrest, cardiopulmonary resuscitation, cooling, hypothermia, post resuscitation syndrome” in the MedLine database was performed. References of these articles were also reviewed. Unconscious adult patients with spontaneous circulation after out-of-hospital ventricular fibrillation or pulseless ventricular tachycardia should be cooled. Moreover, for any other rhythm or in the intra-hospital

scenario, such cooling may also be beneficial. There are different ways of promoting hypothermia. The cooling system should be adjusted as soon as possible to the target temperature. Mild therapeutic hypothermia should be administered under close control, using neuromuscular blocking drugs to avoid shivering. The rewarming process should be slow, and reach 36° C, usually in no less than 8 hours. When temperature increases to more than 35° C, sedation, analgesia, and paralysis could be discontinued. The expected complications of hypothermia may be pneumonia, sepsis, cardiac arrhythmias, and coagulopathy. In spite of potential complications which require rigorous control, only six patients need to be treated to save one life.

**Keywords:** Hypothermia induced/adverse effects; Heart arrest/complications; Heart arrest/therapy; Cardiopulmonary resuscitation/complications; Cardiopulmonary resuscitation/therapy

### INTRODUCTION

Therapeutic hypothermia (TH) is a controlled decrease of the patients' central temperature with pre-established therapeutic objectives. This treatment has been used for more than 50 years in cardiac surgeries<sup>(1)</sup> and more recently in neurological surgeries.<sup>(2)</sup> During the last six years this subject has gained momentum once again and has become one of the well established therapies after a cardiac arrest (CA) in adults.

During a CA, spontaneous circulation stops and vital organs perfusion is interrupted. Chest compressions, if well performed, provide a blood flow of up 30% in relation to the condition. Better perfusion of the vital organs will only take place after spontaneous circulation returns in patients successfully submitted to cardiorespiratory resuscitation (CRR) maneuvers. Main beneficial mechanisms of hypothermia for

comatose patients recovered from CRR are shown in chart 1.

**Chart 1 - Beneficial mechanisms of hypothermia in comatose patients recovered from a cardiorespiratory arrest** <sup>(24-26)</sup>

1. Reduction of cerebral oxygen consumption
2. Suppression of chemical reactions associated to reperfusion injuries
3. Reduction of free radical reactions that increase cerebral damage
4. Reduction of intracellular calcium release
5. Modulation of apoptosis
6. Modulation of anti-inflammatory response
7. Protection of the lipoprotein membranes

**MAIN EVIDENCE FOUND IN MEDICAL LITERATURE**

Patients admitted to the hospital after an out-of-hospital CA, in general, show a significant neurological anoxic injury and high mortality.<sup>(3)</sup> During the last 11 years various studies in experimental models have disclosed that neurological injury after overall severe anoxia is reduced when TH is applied.

The first of these studies, published by Bernard et al <sup>(4)</sup> in 1997, induced hypothermia (33° C) in 22 victims of out-of-hospital CA admitted to the emergency room. External cooling was performed and maintained for 12 hours in the intensive care unit (ICU). After comparison with historical control, an improved survival was noted for patients submitted to cooling (mortality of 45% versus 77% in groups without TH), with no significant adverse effects related to TH. Next, various publications disclosed the feasibility and safety of TH, in addition to improved neurological outcome, and a suggestion of lower mortality in the group treated with TH.<sup>(4-13)</sup>

Two large clinical trials were published in the same edition of the New England Journal of Medicine, 2002, on this subject.<sup>(5,6)</sup> Both showed the beneficial effects of hypothermia on neurological outcomes – one showed a significant decrease of mortality, leading the International Liaison Committee on Resuscitation (ILCOR) to publish guidelines in July 2003.<sup>(14)</sup> They recommended use of TH (32° C to 34° C) for unconscious patients after out-of-hospital CA, during 12 to 24 hours when the initial rhythm of CA was ventricular fibrillation (VF) and suggested that presumably this technique would be also beneficial for other CA rhythms and for intra-hospital CA.

An Australian study by Stephen Bernard et al.<sup>(5)</sup> was developed in four emergency departments in Melbourne. Patients of the study were comatose survivors of out-of-hospital VF. Exclusion criteria were less than 18 years of age, less than 50 year old women (due to possible pregnancy), cardiogenic shock (defined as systolic arterial pressure under 90mmHg after return of circulation) and possible causes of trauma other than CA itself (for instance, head injury, drug overdose or stroke).

Randomization divided this population into two groups: that of conventional treatment and that of induction to hypothermia. Ice packs were applied to those of the latter group to foster temperature decrease, already at the site of out-of-hospital care. Upon arrival at the hospital, measures for hypothermia were intensified. All patients were submitted to laboratory tests and to mechanical ventilation, in addition to correction of possible hemodynamic instability. After neurological evaluation they were sedated with midazolam and given vecuronium for neuromuscular blockade. Therapy with thrombolytics or heparin was used according to requirements. All were given aspirin and arterial pressure, arterial blood gases (corrected for temperature), glycemia and serum potassium were constantly monitored. The central reference temperature measurement was the tympanic until a Swan-Ganz catheter was introduced. Ice packs were removed when the central temperature reached 33° C. Temperature was maintained for 12 hours, with the patient always sedated and paralyzed. After the 18<sup>th</sup> hour, patients were rewarmed with a blanket with hot air for the next 6 hours.

A good neurological outcome (understood by the authors as discharge to home or rehabilitation physiotherapy) was achieved by 49% of patients. Among patients submitted to normothermia, 26% had a good outcome when the same criteria are used. After adjustments for age and time of CA, the odds ratio for good outcome in the group with hypothermia, when compared to the group with normothermia, was rather significant: 5.25 with p=0.011. There was no difference in the frequency of adverse events, although in the hypothermia group there was, on an average, more vascular systemic resistance, a lower cardiac index and higher glycemias.

An important multicentric European study,<sup>(6)</sup> developed in nine centers of five European countries, included patients victims of VF or pulseless ventricular tachycardia (VT) with ages ranging from 18 to 75

years<sup>(6)</sup>. Patients that had some probable non-cardiac cause for CA, in addition to patients who stayed more than 15 minutes without basic life support or patients who took more than 60 minutes for the return of spontaneous circulation were excluded. Patients who reached the emergency room already with a very low temperature (tympanic temperature less than 30° C), pregnancy, comatose state even before CA, responsive to verbal orders after return of spontaneous circulation, evidence of hypotension, hypoxemia, pre-existing coagulopathy or terminal disease were also excluded from the study. The primary outcome of this study was neurological assessment six months after CA. Patients were ranked according to the Pittsburgh cerebral performance categories: 1 (good recovery), 2 (moderate disability), 3 (severe disability), 4 (vegetative state) and 5 (death).

Of the patients who received therapeutic hypothermia, 55% were classified as 1 or 2 after six months of the event, when compared to 39% of those with conventional treatment, a statistically significant difference. Mortality at six months was of 41% in the hypothermia group, significantly lower than the 55% of the normothermia group. In this study, contrary to what might be expected, complication rates that could result from therapeutic hypothermia did not differ between the two groups.

### WHEN HYPOTHERMIA SHOULD BE INDICATED?

The ILCOR guidelines recommend that TH should be performed in every adult patient that remains unconscious after recovering from a CPR due to a out-of-hospital VF. They must be cooled up to 32 to 34° C for 12 to 24 hours. This technique would be also beneficial for other CA rhythms and for intra-hospital CA.

This treatment strategy seems to be quite efficient and only 6 patients need to be treated to save one life, that is to say a number needed to treat (NNT) of 6. Therefore there is no reason not to use this therapy as a routine.

TH should not be performed on patients under cardiac shock, after return of spontaneous circulation or in patients with primary coagulopathy or pregnant women. Thrombolytic therapy is not a contraindication for performance of TH and it is important to mention this because coronary diseases are the basic cause of many of the CA attended.<sup>(15,16)</sup>

### HOW TO COOL THE PATIENT?

There are various tested cooling techniques: ice packs, extracorporeal circulation, iced infusions in the carotid artery, cape containing quite iced solutions (-30°C), nasal lavage, gastric lavage, bladder lavage, peritoneal lavage, pleural lavage, cooling catheters, infusion of iced liquids, blanket with circulating cold air among others.<sup>(17-21)</sup> Ideal cooling procedures must quickly and practically reach the target temperature, without causing injuries.

One of the techniques for rapid temperature decrease is immersion in ice water that reduces about 9.7°C per hour, on the average, however this strategy is not very practical for routine use, An even faster decrease may be achieved, if it is possible to keep this ice water circulating and in contact with the patient's skin. Extracorporeal circulation is also one of the methods of quickly reaching the target temperature,<sup>(17)</sup> however it is a highly invasive and unpractical treatment.

A promising method uses an intravascular catheter capable of cooling blood by means of an internal circuit permitting circulation of iced liquid and constant temperature exchange with the blood, reducing central temperature about 1.4°C per hour.<sup>(18)</sup> Application of ice packs has proven efficient, reducing on the average 0.9° C per hour of application.<sup>(19)</sup>

Probably, the most practical and agile method is intravenous infusion of iced fluid (at 4°C). Rajek et al.<sup>(20)</sup> administered iced saline solution (4°C) to volunteers at a speed of 40 mL/kg, 30 minutes by means of central catheter and it was possible to safely achieve a 5°C reduction of central temperature per hour. Bernard et al.<sup>(21)</sup> cooled patients who returned to spontaneous circulation by using Ringer lactate at 4°C in an infusion of 30mL/kg for 30 minutes, achieving a temperature decrease at an average speed of 3.2°C per hour, also in a safe way. Infusion of iced liquid, probably is the most promising, as it is fast, practical, safe and low cost.

Some topics related to cooling must still be defined and future studies are required to answer them. Perhaps cooling measures should begin already during cardiopulmonary resuscitation (CPR) or only after return of spontaneous circulation? At what ideal temperature should the patient be kept? For how long should patients, ideally, be maintained cooled to achieve maximum benefits with minimum risk? Which is the quickest form of cooling that is safe? At what speed should patients be rewarmed?

## HOW TO REWARM THEM?

The ideal temperature for maintenance of therapeutic hypothermia in patients who recovered spontaneous circulation is unknown. ILCOR recommendations follow the first two main works: from 12 to 24 hours. Rewarming may be passive (about 0.5°C per hour) or active (using a thermal blanket for approximately 1°C per hour). Eventually, a slightly warmed saline solution infusion may be called for.<sup>(22)</sup> Maybe patients who are able to reach the target temperature more quickly and soon after CA require less time of hypothermia, however this hypothesis has to be conveniently studied.

## MONITORING OF CENTRAL TEMPERATURE

The ideal temperature measurement would be measuring the cerebral intraventricular temperature, which is unfeasible in post-CA patients. Studies have shown that there are no significant differences between jugular vein, subdural, tympanic membrane, pulmonary artery temperatures and bladder temperature. Rectal temperature is inferior for monitoring of central temperature. Axillary temperature cannot be used under any circumstances as a parameter to decide for cooling or warming.

The two largest studies on TH post-CA, at some point of monitoring, used tympanic and bladder temperature.<sup>(5,6)</sup> For this reason, together with esophageal temperature, they are the more often used monitoring modalities.

## LATEST EVIDENCES

In the scenario of intensive care medicine, a prospective study by Storm C. et al.<sup>(23)</sup> assessed 52 patients, with a mean age of 62 years, submitted to hypothermia after return of spontaneous circulation post-CA; their data were compared to a historical cohort (n=74) treated before formal recommendation of use of hypothermia. The group submitted to hypothermia had a significantly shorter length of stay in the ICU and of time on mechanical ventilation as well as better neurological outcome in up to one year.

## CONCLUSION

The evidence shows a benefit of using TH for recovery of post-CA patients. Most studies were carried out in patient survivors of out-of-hospital VF/VT, that is why at this rhythm of CA therapeutic hypothermia is definitely indicated. In patients victims of CA at other rhythms or intra-hospital CA, the same amount of data is not available on application of TH. Therefore we are not able to assertively state the benefit of this therapy for these subgroups. Nevertheless, there is a theoretical rationale and a few short works that lead us to suppose that TH may be also useful at other rhythms or in victims of intra-hospital CA.

The units must establish a protocol of induced hypothermia to optimize treatment for this profile of patients, for instance that available in chart 2.

**Chart 2 – Protocol for induction of hypothermia after cardiorespiratory arrest**

<b>Protocol for induction of hypothermia after cardiorespiratory arrest</b>
<p><b>Stock of material</b></p> <ol style="list-style-type: none"> <li>1. Saline solution at 0.9% (or other crystalloid) – bags of 1000 mL – at 4°C</li> <li>2. Ice packs</li> <li>3. Clean bandages</li> <li>4. Thermal mattress</li> <li>5. Kit for Swan – Ganz or central venous access and invasive arterial pressure or esophageal thermometer</li> <li>6. Multiparameter monitor</li> <li>7. Drugs for sedation, analgesia (fentanyl, midazolam and propofol) and neuromuscular blocker (atracurium, cisatracurium or parracuronium)</li> <li>8. Foley probe</li> <li>9. Evaluate topic skin protectors and eye drops for protection of the cornea.</li> <li>10. Prophylaxis of venous thromboembolism</li> <li>11. Prophylaxis of acute injury of the gastric and duodenal mucosa</li> </ol>

Continue...

## Chart 2 – Continuation

Protocol for induction of hypothermia after cardiorespiratory arrest	
<b>Purpose of the protocol</b>	
<ol style="list-style-type: none"> <li>1. Ascertain that there are no exclusion criteria</li> <li>2. Initiate sedation, analgesia and neuromuscular blockade</li> <li>3. Induction of hypothermia ice packs and crystalloid solution 30-50ml/Kg</li> <li>4. Maintenance of central temperature at 32 to 34°C for 12 to 24 hours</li> <li>5. Speed of slow rewarming – Maintain sedation and neuromuscular blockade</li> <li>6. Monitor potential complications</li> </ol>	
<b>Inclusion criteria</b>	<b>Exclusion criteria</b>
<ol style="list-style-type: none"> <li>1. Post-CA with return of spontaneous circulation (specially pulseless VF or VT)</li> <li>2. More than 18 years of age. Women at fertile age must have negative pregnancy test</li> <li>3. Comatose patients after return of spontaneous circulation</li> <li>4. Mechanical ventilation</li> <li>5. Arterial systolic pressure must be kept above 90 mmHG spontaneously or by using volume pressors and/or vasopressors</li> </ol>	<ol style="list-style-type: none"> <li>1. Other reason for comatose state (drug overdose, brain injury, stroke, status epilepticus)</li> <li>2. Pregnancy</li> <li>3. Initial temperature &lt; 32°C</li> <li>4. Coagulopathies or previous bleeding</li> </ol>
<b>Sedation and paralysis</b>	
<ol style="list-style-type: none"> <li>1. Fentanyl – attack dose – 1 to 2 mcg/kg + maintenance dose – 1 to 4 mcg/kg/hour</li> <li>2. Midazolam – attack dose – 2 to 6 mg + maintenance dose – 1 to 2mg/hour</li> <li>3. Propofol – begin with 5 mcg/kg/min</li> <li>4. Pancuronium – 1 ampoule - 4mg followed by 0.1 to 0.2 mg/kg every 1 to 2 hours</li> </ol>	
<b>Start cooling</b>	<b>Start rewarming</b>
<p>Interventions during cooling – Interpret ECG and determine need to perform cineangiography or thrombolysis. Check battery of laboratory tests.</p> <ol style="list-style-type: none"> <li>1. Infuse 30 to 50 ml/kg of SS 0.9% or RL at 4°C for 30 minutes to induce hypothermia</li> <li>2. Keep patient naked, under mechanical ventilation, with damp compresses</li> <li>3. Keep ice on the regions of skin folds such as neck, inguinal regions, axillae, lower limbs, trunk and abdominal region.</li> <li>4. Monitor MAP, CVP and central temperature.</li> <li>5. Monitoring of temperature may be by esophageal, tympanic temperature or by Swan-Ganz catheter.</li> <li>6. Target temperature between 32 and 34°C – if needed repeat infusion of crystalloid at 4°C, if the patients did not reach 34° C in 4 hours</li> </ol>	<ol style="list-style-type: none"> <li>1. Start rewarming programmed 18 hours after induction of hypothermia. Speed of rewarming must be of 0.5°C/hour</li> <li>2. Attention to need of fluids during rewarming</li> <li>3. Assess interruption of potassium replacement when appropriate</li> <li>4. Maintain sedation and neuromuscular blockade until patient reaches 36°C</li> </ol>
<b>Monitoring potential complications</b>	
<ol style="list-style-type: none"> <li>1. Arrhythmias</li> <li>2. Infections</li> <li>3. Coagulopathies</li> <li>4. Status epilepticus</li> <li>5. Rebound hypothermia</li> </ol>	

CA – cardiac arrest; VF – ventricular fibrillation; VT – ventricular tachycardia; S – stroke; ECG – electrocardiogram; SS – saline solution; RL – ringer lactate; MAP – mean arterial pressure; CVP – central venous pressure.

## RESUMO

Os sobreviventes de parada cardiorrespiratória freqüentemente apresentam lesão cerebral isquêmica associada a piores desfechos neurológicos e óbito. A hipotermia terapêutica melhora os desfechos entre os sobreviventes comatosos após manobras de reanimação. Considerando sua recomendação formal para emprego terapêutico pós-recuperação da circulação espontânea na parada cardiorrespiratória, o objetivo deste estudo foi rever os principais aspectos clínicos relativos à hipotermia terapêutica. Foi feita revisão através de pesquisa não-sistemática de artigos através das palavras-chave "parada cardiorrespiratória, resfriamento, hipotermia, síndrome pós-reanimação" na base de dados MedLine. Adicionalmente, referências destes artigos foram igualmente avaliadas. Pacientes adultos inconscientes com circulação espontânea após parada cardiorrespiratória extra-hospitalar devem ser resfriados quando o ritmo inicial for fibrilação ventricular ou ta-

quicardia ventricular. Este resfriamento pode ser benéfico para os outros ritmos e para o ambiente intra-hospitalar. Existem várias formas diferentes de induzir a hipotermia. O sistema de resfriamento deve atingir a temperatura alvo o mais rápido possível. O reaquecimento para 36° C deve ser realizado em não menos do que 8 horas. Quando a temperatura aumenta para mais de 35° C, sedação, analgesia e paralisia podem ser descontinuadas. As complicações esperadas da hipotermia terapêutica podem incluir pneumonia, sepse, disritmias cardíacas e coagulopatias. Apesar de potenciais complicações que necessitam de cuidadosa monitoração, apenas seis pacientes precisam ser tratados com hipotermia induzida pós-parada cardiorrespiratória para salvar uma vida.

**Descritores:** Hipotermia induzida/efeitos adversos; Parada cardíaca/complicações; Parada cardíaca/terapia; Ressuscitação cardiopulmonar/complicações; Ressuscitação cardiopulmonar/terapia

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