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# Mild therapeutic hypothermia after cardiac arrest: mechanisms of action and protocol development

*Hipotermia terapêutica em pacientes pós-parada cardiorrespiratória: mecanismos de ação e desenvolvimento de protocolo assistencial*

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## ABSTRACT

Cardiac arrest is a high mortality event and the associated brain ischemia frequently causes severe neurological damage and persistent vegetative state. Therapeutic hypothermia is an important tool for the treatment of post-anoxic coma after cardiopulmonary resuscitation. It has been shown to reduce mortality and to improve neurological outcomes after cardiac arrest. Nevertheless, hypothermia is underused in critical care units. This manuscript aims to review the hypothermia mechanism of action in cardiac arrest survivors and to propose a simple protocol, feasible to be implemented in any critical care unit.

**Keywords**: Hypothermia, induced/utilization; Heart arrest; Cardiopulmonary resuscitation/standards

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## INTRODUCTION

Cardiac arrest (CA) is a medical emergency defined as sudden and unexpected cessation of vital functions, characterized by absence of heart beats, respiratory movements and unresponsiveness to stimuli.[1] Nevertheless the development of reanimation maneuvers, mortality of cardiac arrest patients remains high.[2,3] Cardiac arrest produces sudden brain blood flow cessation, causing neuronal ischemia.[4] The extension of neurological damage depends on the degree of brain tissues hypoxemia, leading to permanent damage after 5 to 10 minutes of complete blood flow cessation.[5] Persistent vegetative state is the most severe feature of the ongoing ischemia and is characterized by complete unconsciousness and irresponsiveness to stimuli, maintaining the sleep-waking cycle.[6] Between 10 to 30% of cardiac arrest survivors are estimated to progress with vegetative state.[7] The costs related to the care of these patients reach one billion dollars every year.[8]

Several trials have tried to identify prognostic factors able to predict patients with increased risk of persistent vegetative state. Physical neurological examination, electroencephalogram, computed tomography, biochemical neural injury markers, somatosensorial evoked potential, all these methods have their limitations and, to a

greater or lesser extent, provide inaccurate prognosis evaluation.[9-13]

In this context, therapeutic hypothermia (TH) has been shown to be effective in reducing ischemic brain injury in different neurological insults, as head injury, cerebrovascular accidents, subaracnoid hemorrhage and anoxic brain damage.[14-19] Hypothermia reduces brain oxygen demands, promoting protection against ischemia.[20] Several evidences suggest that TH reduces mortality in coma patients surviving after CA.[21] Patients undergoing hypothermia had reduced mortality and increased favorable neurological outcomes as compared to normothermic patients.[22,23] These results have been consistently reproduced.[24,25]

Although highly effective for reducing brain damage after cardiac arrest, TH is underused in ICUs.[26] Thus, this manuscript intends to review hypothermia mechanisms of action and its effects on the critical care patient, aiming to propose a simple and low-cost protocol for TH in low, medium and high complexity ICUs.

For literature review, an extensive non-systematic search was conducted on PubMed: National Library of Medicine and on Scielo database, searching for articles on TH in cardiac arrest survivors using the key words therapeutic hypothermia, cardiac arrest and neurological outcome. In addition, these articles references were also considered. The search was undertaken from October 2009 to January 2010. The articles were included if evaluated adult cardiac arrest survivors, published after 2002. Case reports, letters, animal studies and pediatric studies were excluded. After review, a TH protocol for cardiac arrest survival patients was developed to be used in the ICU at Hospital de Clinicas de Porto Alegre, which is feasible for any Brazilian ICU.

**Mechanism of action in hypothermia**

Neuronal ischemia after cardiac arrest may persist for several hours after resuscitation. Hypothermia is protective against several harmful biochemical mechanisms, being the first effective therapy for reducing ischemic neurological damage in cardiac arrest survivors. Improved outcomes related to hypothermia were only seen when its mechanisms of action were understood, realizing that mild hypothermia (32ºC to 34ºC), instead of deep hypothermia (≤ 30ºC) was effective for neuroprotection, at lower adverse side effects.[27] This understanding came from the fact that reducing brain metabolic demand is not the only protective mechanism associated to hypothermia, although important. The brain metabolism is reduced by 6 to 10% for each 1ºC temperature reduction. When the temperature drops below 32ºC, the brain metabolic rate is reduced by about 50% of the normal, and the $O_2$ consumption and $CO_2$ production falls proportionally.[28] During the ischemia-reperfusion time which starts soon after cardiac arrest, an important reduction in high energy molecules, such as adenosine triphosphate, takes place. The immediate consequence of this phenomenon is a change in cell metabolism from aerobic to anaerobic. Anaerobic glycolysis increases intracellular phosphate, lactate and hydrogen ions levels, resulting in intra and extra cellular acidosis, which in turn increases the calcium inflow. The calcium inflow is very harmful to the cell, as it causes mitochondrial dysfunction, and disturbs sodium and potassium pumps functioning, leading to cell membranes depolarization and extracellular release of glutamate, an excitatory neurotransmitter. The intracellular acidosis, which stimulates the cell destructive processes and apoptosis, may be evidenced by increased brain lactate levels.[29] Hypothermia inhibits these harmful excitatory effects. Hypoxia accounts for cell membrane changes, determining cytotoxic edema and blood brain barrier disruption. These changes result in intracranial hypertension, leading to a vicious brain ischemia circle. Hypothermia is able to reduce vascular permeability, minimizing cerebral edema.

Ischemia-reperfusion generates large amounts of free radicals, such as hydrogen peroxide, superoxide and peroxynitrite. These molecules are harmful to the cell, as they cause cell membranes peroxydation. Oxidative damage is reduced under hypothermia conditions. There is also an unbalance of pro-inflammatory mediators (TNF-α and interleukin 1) release associated with oxidative damage which is minimized at lower temperatures.[30]

Another mechanism implied in hypothermia neuroprotective effects appears to be the induction of anticoagulant effects, which are seen in temperatures below 35ºC. The activation of coagulation plays an important role on ischemia-reperfusion injury development, forming fibrin and blocking

the microcirculation. Hypothermia also acts on endothelin and tromboxane $A_2$ release, being both potent vasoconstrictors and platelet aggregators.

The epileptic activity suppression is one additional probable beneficial hypothermia effect in the context of anoxic encephalopathy, as convulsive and non-convulsive seizures determine increased brain oxygen consumption. All these mechanisms have different weights on ischemic injury development, as well as are in a greater or lesser extent influenced by TH, depending on the temperatures reached.[31]

**Cooling phases**

Hypothermia causes several physiological effects, and their understanding is essential to achieve a better cooling benefit. They are shown on chart 1. TH has four phases: identification of patients, hypothermia induction, maintenance, and rewarming.

**Chart 1- Hypothermia effects**

| |
|---|
| Reduced cerebral metabolic demands |
| Reduced $O_2$ consumption and $CO_2$ production |
| Intracranial pressure reduction |
| Hemoglobin curve left deviation |
| Shivering |
| Bradycardia |
| Hypotension |
| Arrhythmias |
| PR and QRS interval prolongation |
| Electrocardiogram Osborne waves |
| Cardiac output reduction |
| Ventricular filling pressure drop |
| Reduced gastrointestinal motility |
| Profuse diuresis |
| Insulin resistance |
| Reduced immunity |
| Coagulopathy |
| Potassium, magnesium and calcium cell shifts |
| Drugs pharmacokinetics and pharmacodynamics changes |

**Identification of patients:** since 2003 the ILCOR recommends TH for comatose cardiac arrest survivors, independently of the cardiac arrest rhythm and the event site. Should be excluded: patients reanimated longer than 60 minutes; patients with return of spontaneous circulation after 6 hours; patients with coma previus to cardiac arrest; pregnancy; patients with active bleeding or coagulopathy; major surgery less than 14 days; patients with cardiogenic shock or septic shock; and terminal patients.[32]

**Hypothermia induction phase:** target temperature is 32ºC to 34ºC. Prospective randomized historic control trials have shown the neuroprotective benefits of these temperature levels. This target represents a balance between the clinical benefits and adverse effects, which are very exacerbated at lower temperatures. Cardiac arrhythmias are frequent below 31ºC, and below 28ºC the risk of VF is very high. Additionally, this temperature range (32ºC to 34ºC) is easily reached with non-invasive cooling methods.[33]

Data suggest that TH should be started as early as possible following the return of spontaneous circulation, however a benefit is apparent even when delayed for up to 6 hours. An experimental study tested the impact of the immediate versus one hour delayed TH start after resuscitation on the outcomes of rats submitted to brain anoxia. The findings pointed to a better functional outcome in rats cooled immediately.[34]

Initial patient monitoring should include continued electrocardiogram, fluid balance, invasive blood pressure measurement, and central temperature measurement by either vesical catheter, esophageal thermometer or pulmonary artery catheter. Intra-arterial blood pressure monitoring is important because hypotension development is common during TH, frequently requiring vasoactive drugs. Hypovolemia is also quite a rule in this scenario, as hypothermia accounts for profuse diuresis.[35]

Laboratory tests should include complete blood count, platelets, coagulation, electrolytes, arterial gasometry, to be collected at baseline and every 6 or 12 hours. Mild coagulation changes are seen in hypothermia conditions. Major bleedings are not associated with mild hypothermia.[36] Blood oxygenation and ventilatory settings are better evaluated using arterial gasometry, because pulse oxymetry is not a suitable parameter during TH due to the hypothermia induced cutaneous vasoconstriction. Hypothermia causes potassium, magnesium, calcium and phosphorus cell inflow, and may cause severe arrhythmias. Electrolyte replacement is recommended to be started during the induction phase, and to be discontinued during rewarming.[33]

Appropriate sedation and analgesia are funda-

mental during TH induction. Shivering is a normal physiological response, attempting to maintain the body temperature. It is counter-productive, as it generates heat and delays the cooling process, in addition to increase oxygen demand and intracranial pressure. Midazolam and phentanyl are routine drugs. Neuromuscular blockers are frequently required, attempting to reduce shivering.

The ideal cooling method is one that is able to induce rapid hypothermia, without overcooling risk; to keep the desired temperature without wide fluctuations; to provide a controlled and slow rewarming; to be minimally invasive and affordable.[37] Heat removal may be invasive or non-invasively induced. The non-invasive or conventional methods include use of ice packs, thermal blankets, surface cooling devices, and infusion of cold solutions. These methods are quite effective to induce hypothermia, however the rate of temperature changes is less accurate and there is a higher overcooling risk, in addition to a more difficult rewarming. Associations of these methods have been used in several TH studies, showing good results. Infusion of cold fluids at a 30 to 40 mL/kg dose, either peripheral or centrally, is able to induce a temperature drop by 2ºC to 4ºC,[38] with the advantage of feasible use even pre-hospital.[39] Large cold saline volumes do not seem to be associated with severe adverse effects in cardiac arrest survivors, with no pulmonary edema shown in these patients.[40] Along with the use of cold saline, ice packs over the neck, axillas and groins surfaces is a simple and easy way to keep cooling. The external ice packs should be changed when melted, and attention should be paid to cold induced skin injuries. No correlation is apparent between the body surface and the time to hypothermia induction.[41] Ice packs together with thermal blankets are the most affordable way to induce TH, however studies have shown that overcooling is almost a rule, with potential severe complications if very deep or prolonged.[42] Overcooling is less common with surface cooling devices. These devices are made of pads covered with thermal gel, connected to a thermoregulator unit. The system either increases or reduces the circulating water temperature in response to both the target temperature and the patient's temperature. The mean elapsed time to reach the target temperature is about 1.4ºC/hour. This is a safe and effective method, as the temperature range is better controlled both during induction and rewarming.[43]

Currently, the most effective method to induce hypothermia is the use of endovascular catheters that provide optimized temperature control for induction, maintenance or rewarming. It is very fast for hypothermia induction, reducing the temperature by 2ºC to 2.5ºC/hour. This system uses a special coated metal central venous catheter where water circulates from an external cooler system. The catheter may be installed either via femoral, subclavia or jugular accesses. The experience with these devices is still limited as they are more expensive but, on the other hand, less troublesome to the team than conventional methods.[37]

**Hypothermia maintenance phase:** the temperature should be constantly measured, aiming to be kept between 32ºC and 34ºC over 24 hours.[5] An important aspect for these patients care involves hemodynamic parameters. Mean blood pressure levels above 80 mmHg are recommended for cardiac arrest survivors, and volume replacement and vasopressors may be required to keep these values. The most commonly used vasopressor during TH is norepinephrine.

Hypothermia causes insulin resistance. Blood glucose monitoring should be performed with venous blood measures, as skin vasoconstriction may change the results. Laboratory tests may be scheduled every 6 or 12 hours, depending on previous results, and include the same tests as during the induction phase. Pulse oxymetry is not a suitable parameter during hypothermia, and the mechanic ventilation parameters should be set based on gasometry values.

Feeding is not indicated during TH, as stomach emptying is delayed in these patients. Additionally, there is an increased mechanic ventilation associated pneumonia (VAP) risk for possible aspiration during CA. Strict VAP prevention measures are thus recommended.

Another fundamental aspect for this phase management is sedation and analgesia. In addition to continued midazolam and phentanyl infusions, additional doses may be needed to maintain appropriate sedation. A better sedation control is suitable using sedation scores or the BIS (Bispectral Index). Seizures activity may be masked by sedation and muscular blockade, so continued electroencephalogram is indicated, if available. BIS

and electroencephalogram uses are protocol refinements, and are not indispensable. Convulsive seizures and shivering require aggressive therapy in any phase, as they increase metabolic oxygen demands. Neuromuscular blockers should be reevaluated after 12 hours and stopped if there is no evidence of shivering.[44]

Severe arrhythmias and bleeding during this phase require cooling discontinuation. Continued electrocardiogram monitoring is fundamental during the entire treatment period. Bradycardia or Osborne waves do not indicate TH discontinuation.[30] If the patient has any signs of awaking, hypothermia is stopped and spontaneous rewarming allowed.

**Rewarming fase:** this phase takes place 24 hours after cooling was started, and should be slow, by 0.2ºC to 0.4ºC/hour, for 12 hours, until a temperature between 35ºC and 37ºC is reached. Rewarming may be either passive or active. Passive rewarming up to a 35ºC central temperature usually takes about 8 hours.[45] If a thermal blanket is used, it should be removed when the temperature reaches 35ºC. If commercial external cooling devices or endovascular catheters are used, the rewarming speed is setted. This is one of the main advantages of these devices, a better control of the rate of temperature changes.[37]

Hemodynamic instability, with peripheral vasodilation and hypotension is part of post-reperfusion syndrome, and is very common as the temperature increases. It may require higher vasopressor doses. Another concern during rewarming is hyperkalemia, as the potassium cell inflow during hypothermia now flows out. This may cause arrhythmias. All potassium- or magnesium-containing solutions should be discontinued. Insulin infusion is also discontinued due to hypoglycemia risk.

When 35ºC is reached, sedation is discontinued. After the TH protocol ends, aggressive fever (if occurring) therapy is recommended, as it is associated with unfavorable outcomes after cardiac arrest.[46]

Based on the above information, we propose a simple protocol, that is easy to perform and can be immediately implemented in either low, medium or high complexity ICUs. The protocol is shown on appendix 1, and a suggested medical flow sheet is on appendix 2.

## DISCUSSION

**S**evere adverse effects of deep hypothermia has limited its use to very specific procedures in operating rooms for more than 30 years. During this time, animal studies progressed, showing that even small reductions in body temperature could minimize the harmful ischemia-reperfusion injury and associated brain damage.[47]

It is currently known that the brain works appropriately in a constant temperature and pH ranges, and is very sensitive to minimal temperature changes, particularly after neuronal injury. Injured brain areas are even more hyperthermic than the non-injured areas.[30,48] This is due to a range of destructive mechanisms following brain hypoflow. Mild hypothermia is able to modulate cell processes involving oxidative stress, excitatory amines release and cell necrosis and apoptosis induction, besides to reduce neuronal oxygen consumption. Neuroprotection takes place by several mechanisms.[49]

In a randomized clinical trial of 77 comatose patients who survived a VF or VT cardiac arrest, Bernard et al compared a group undergoing mild hypothermia (33ºC) induced after return of spontaneous circulation and kept for 12 hours, with a normothermic group. Forty nine per cent of the hypothermia patients survived and were discharged from the hospital with good neurological outcome, while only 26% of the normothermic patients had the same outcome.[23] Similar statistically significant results were demonstrated in a multicenter European trial that included 273 cardiac arrest survivors from shockable rhythms who underwent mild hypothermia (32ºC – 34ºC) for 24 hours. In the TH group, 55% of the patients had favorable six months neurological outcome, versus 39% in the normothermic group. Mortality was reduced in the hypothermia group (55% versus 41%; p=0.02).[27] Storm et al. also suggest that the hypothermia survival benefit persists after two years follow-up.[50] Sufficient evidence is available on the hypothermia neuroprotective effects to make it a standard therapy for anoxic encephalopathy after cardiac arrest. The high mortality associated with cardiac arrest is related to the progression to persistent vegetative state, and this progression is clearly reduced with therapeutic hypothermia use. Currently, not submitting car-

diac arrest comatose survivors to therapeutic hypothermia means not offering them the best available therapy for post-resuscitation syndrome. The NNT (number needed to treat) for reducing one death is six.[51] This is much better than the most treatments used in intensive care, in addition to be affordable and feasible in any ICU. In a cost-effectiveness study, Merchant et al. have shown that TH is comparable to the economically accepted medical interventions.[52]

An observational trial, with historical controls, analyzed the impact of TH use on the ICU time of stay in post-cardiac arrest patients. In addition to beneficial neurological effects, a shorter time of stay in the ICU was found in TH treated patients (mean 14 days versus 21 days). The same authors suggest that hypothermia could be an independent predictor of mechanic ventilation time.[53]

Despite all favorable evidence for the use of hypothermia, it is estimated that less than 30% of the patients with indication for this therapy are effectively treated.[54] Recent literature reports agree that institutional TH protocols implementation is relevant due to its ability to increase the use of this therapy.[55,56] The ILCOR and European Resuscitation Council support the use of TH in comatose cardiac arrest survivors from VF and VT rhythms, with a level I evidence.[32,57,58] Level IV evidence (historic studies, non-randomized cohorts, or case-controls trials) suggest that intra-hospital cardiac arrest survivors with non-shockable rhythms may also benefit from therapy, however this is still an open issue. Initial asystolia or pulseless electrical activity patients have a survival rate lower than those with VF or VT, probably because they are more severely ill and because of an increased low flow time (VF usually degenerates to asystolia). Due to the dismal prognosis of these patients, TH remains uncertain in these situations.[45,59]

## FINAL REMARKS

Therapeutic hypothermia is so far the only therapy consistently shown to reduce mortality and improve neurological outcomes in cardiac arrest survivors. Despite its low costs and known benefits, the implementation of therapeutic hypothermia protocols has been slow worldwide. Understanding the beneficial mechanisms of action of hypothermia is part of a well succeeded protocol, in order to minimize adverse events. Therefore, those involved with the care of these patients should support the adoption of therapeutic hypothermia in Brazilian ICUs.


## RESUMO

A parada cardiorrespiratória é um evento de alta mortalidade. A isquemia cerebral difusa relacionada ao hipofluxo cerebral frequentemente leva à injúria neurológica grave e ao desenvolvimento de estado vegetativo persistente. A hipotermia terapêutica representa um importante avanço no tratamento da encefalopatia anóxica pós-parada cardíaca. Seus efeitos neuroprotetores têm sido amplamente demonstrados em várias situações de isquemia neuronal. Apesar de ser um procedimento associado com redução de mortalidade nesses pacientes, a hipotermia ainda é um tratamento subutilizado no manejo da síndrome pós-ressuscitação. Nosso objetivo é revisar aspectos referentes aos mecanismos de ação da hipotermia e seus efeitos em pacientes críticos reanimados pós- parada cardiorrespiratória e propor um protocolo assistencial simples, que possa ser implantado em qualquer unidade de terapia intensiva.


**Descritores:** Hipotermia induzida/utilização; Parada cardíaca; Ressuscitação cardiopulmonar/normas

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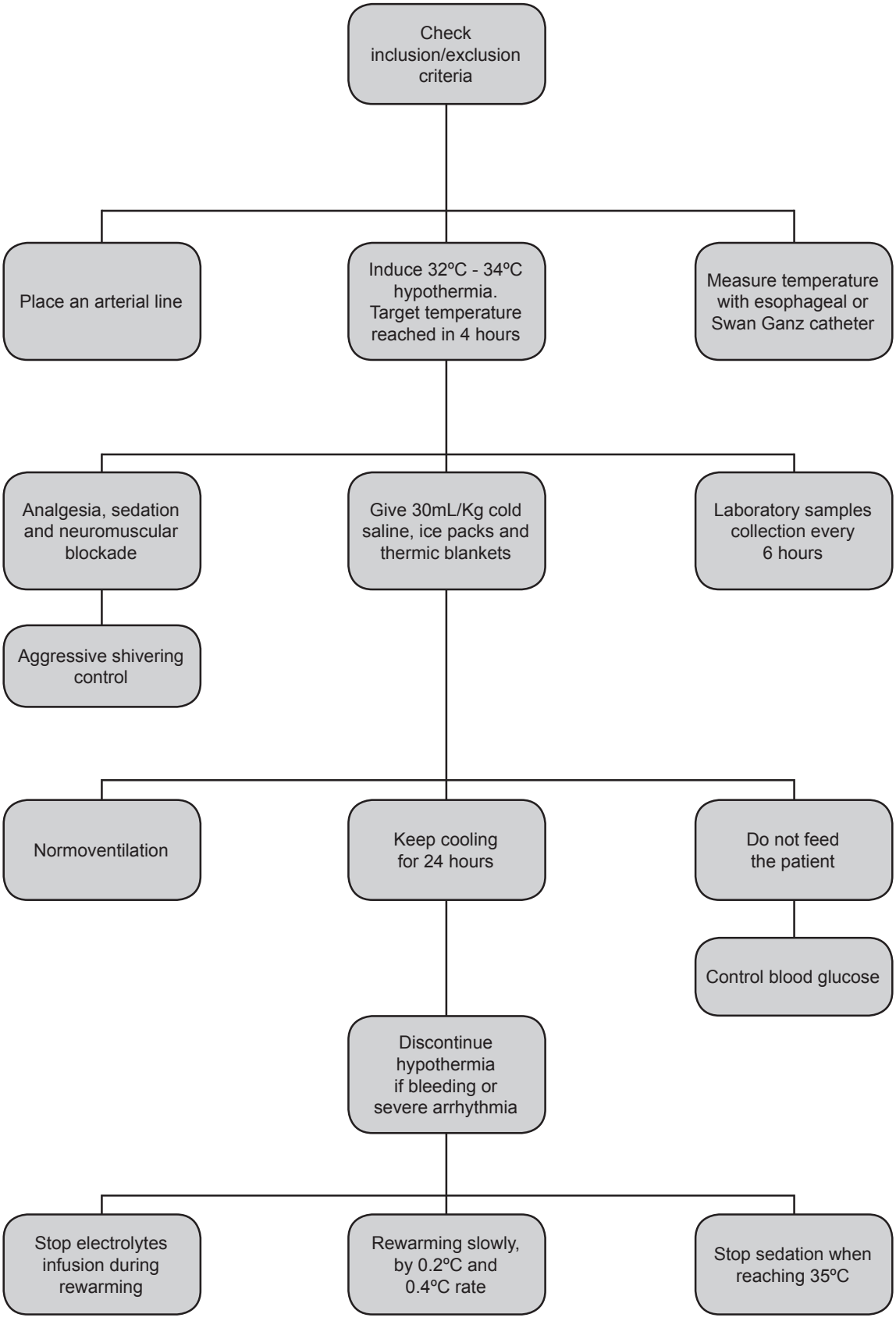
**Appendix 1- Therapeutic hypothermia protocol**



**Appendix 2 - Medical chart suggestion**

Patient's name: _____ Gender: _____
Admission date: _____ Cardiac arrest date: _____
Age: _____ Weight:_____ Height: _____
Site of cardiac arrest: In-Hospital ( ) Out of Hospital ( )
Rhythm:_____ Estimated time: _____ min
Estimated time between arrest and protocol start:_____ min
Suspected cause: _____ Glasgow: _____
Initial temperature:_____ at_____hours Initial heart rate: _____ Blood glucose: _____
Temperature measurement: Swan Ganz catheter ( ) Esophageal catheter ( )
Cooled room: Yes ( ) No ( )
Cooling methods: Thermal blanket ( ) Ice packs ( ) Cold saline ( )
Cold saline volume: _____ mL
Drugs for analgesia and sedation:
BIS used?: Yes ( ) No ( ) Arterial line? Yes ( ) No ( )
Initial laboratory tests drawn at _____ hours
Ht _____ PT_____ Potassium _____
Hb _____ KTTP _____ Magnesium _____
Platelets _____ Arterial blood gas_____ Calcium_____ Sodium_____
Time to target-temperature: _____ Lower temperature: _____
Hypothermia duration: _____ hours
Norepinephrine: Cooling dose _____ Maintenance dose
Early discontinuation: Yes ( ) No ( ) Cause? _____
Laboratory during hypothermia: _____hours
Rewarming time: _____ hours Rewarming rate: _____ ºC/hour
Outcome: Discharge ( ) Death ( ) Transference ( ) Glasgow:_____

**Cooling and rewarming temperature**

| | | | |
|---|---|---|---|
| 1st h | 8th h | 15th h | 22nd h |
| 2nd h | 8th h | 16th h | 23rd h |
| 3rd h | 10th h | 17th h | 24th h |
| 4th h | 11th h | 18th h | 25th h |
| 5th h | 12th h | 19th h | 26th h |
| 6th h | 13th h | 20th h | 27th h |
| 7th h | 14th h | 21st h | 28th h |