

## **Use of a standardized treatment protocol for post-cardiac arrest treatment**

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## Introduction

For a long time outcome of patients after out-of-hospital cardiac arrest (OHCA) has been extremely poor, with only 5–10% of survivors with good neurological outcome. In recent years, several studies demonstrated an increase in survival of cardiac arrest patients admitted to the intensive care unit (ICU), often surpassing 60% with good neurological outcome [1-6]. Since the introduction of cardiopulmonary resuscitation (CPR) in the early nineteen-sixties by Safar *et al.* (mouth-to-mouth respiration) [7] and Kouwenhoven *et al.* (closed chest-compression) [8], emphasis in resuscitation medicine has been on treatment of cardiac arrest until return of spontaneous circulation (ROSC), with manual CPR and early defibrillation of convertible cardiac rhythms being the two most important items. The general consensus was that improvement of outcome of cardiac arrest patients would solely lie in shortening the period of circulatory standstill, thus minimizing the, mainly neurological, damage. After having restored circulation, treating physicians “could only wait and see what the outcome would be”. However, alongside the processes of recovery and compensation, a pathological state may develop with associated organ failure – the so-called post-resuscitation syndrome. Physicians should be aware of this condition and actively treat its complications to improve the condition of the patient and to increase the chance of a good neurological outcome after cardiac arrest. Induced mild hypothermia is an important factor in approaching this entity and has become an established treatment for the post-cardiac arrest patient. However, induced mild hypothermia is not the sole treatment modality that we should use.

Indeed, Sunde *et al.* [4] reported on the use of a standardized treatment protocol and showed improved outcomes of patients treated with a bundle of strategies with historic controls. This chapter discusses the role of several strategies

in patients after cardiac arrest and details of post–resuscitation care. It provides a rationale for the different treatment steps of a standardized treatment protocol for post–cardiac arrest patients (see table 1).

### **Chain of survival**

The chain of survival as advocated by the various societies of resuscitation, promotes getting help, basic life support (BLS) with manual CPR to buy time, early defibrillation to restart the circulation and advanced life support (ALS) by professionals. In the past, emphasis in resuscitation medicine has mainly been on the first 3 steps of resuscitation: getting help, early and good quality CPR and early defibrillation. The 4<sup>th</sup> step of the chain of survival, ALS, was probably never as well defined as the earlier steps. As early defibrillation is probably the most crucial step in the early phase of cardiac arrest, the use of automated external defibrillators already has most probably led to a better neurological outcome in cardiac arrest patients. Also early coronary interventions have improved outcome.

The 2 landmark studies by the HACA group [9] and by Bernard *et al.* [10] showing benefit of induced mild hypothermia after cardiac arrest have shifted the focus and now there is an increasing interest in post–resuscitation treatment. However, it was not until 2005 before the 4<sup>th</sup> ring of the chain of survival was updated to reflect the importance of post resuscitation care in determining the ultimate outcome following cardiac arrest [12] (Figure 1).

### **The post–resuscitation syndrome**

The post–resuscitation syndrome is defined as a condition after resuscitation following (prolonged) cardiac arrest and therefore whole body ischemia and

reperfusion with multiple–organ dysfunction, most notably of but not limited to the brain. Negovsky, one pioneer of “reanimatology” and therapeutic hypothermia, most probably introduced the concept of the post–resuscitation syndrome [12]. Negovsky found pathophysiological changes after resuscitation that substantially differed from those caused by ischemia and hypoxia. In the brain, redistribution of  $\text{Ca}^{2+}$ , together with the formation of free radicals was observed, causing damage to DNA and organelle membranes, followed by development of progressive autoimmune pathology, reflecting the damage of the blood-brain barrier [12-13]. The post–resuscitation or post–cardiac arrest syndrome is at present believed to be a form of systemic inflammatory response syndrome, caused by ischemia–reperfusion. As this “sepsis–like syndrome” [14] may precede the development to multiple–organ dysfunction syndrome, even after successful and swift restoration of the circulation, a patient after cardiac arrest may ultimately die of the consequences of this post–resuscitation syndrome. On the other hand, this syndrome gives physicians the opportunity to intervene and strive for improvement of outcome by supporting the function of failing organs by ventilation, hemodynamic support or renal replacement therapy, thereby improving the outcome of these patients.

### **Early coronary intervention**

Early revascularization after myocardial infarction improves outcome after myocardial infarction. As compared with thrombolytic therapy, primary coronary intervention (PCI) results in a higher rate of patency of the infarct–related coronary artery, lower rates of stroke and re–infarction, and higher long-term survival rates [15]. Induced mild hypothermia in combination with PCI is feasible and safe in patients resuscitated after cardiac arrest due to acute myocardial infarction [16]. In patients with cardiac

arrest due to ST–elevation myocardial infarction (STEMI), it may be acceptable to use thrombolytic therapy as the reperfusion strategy of first choice. This applies especially in hospitals where immediate PCI is not available [17]. The diagnosis of STEMI can be established in the field immediately after ROSC in most patients. This may enable an early decision about reperfusion therapy, i.e., immediate out–of–hospital thrombolytic therapy or targeted transfer for PCI [18]. In view of the existing evidence, PCI after cardiac arrest due to STEMI should be the preferred mode of treatment in regions and situations where this is applicable.

### **Induced mild hypothermia**

Since the landmark publications by the HACA group [9] and Bernard *et al.* [10], many studies have been published using a non–randomized design or matched historical controls, all showing a profound improvement of outcome since the implementation of therapeutic hypothermia (Figure 2). The two original studies provided us with the evidence for treating patients with mild hypothermia if these fulfilled the criteria for inclusion (HACA study: witnessed cardiac arrest, ventricular fibrillation or ventricular tachycardia as the initial cardiac rhythm, presumed cardiac origin of the arrest, age between 18–75 years, estimated interval of 5–15 minutes from the patient’s collapse to the first attempt at resuscitation by emergency medical personnel, and an interval of no more than 60 minutes from collapse to restoration of spontaneous circulation). These inclusion criteria must have led to exclusion of many cardiac arrest patients. Indeed, out of 3551 patients assessed for eligibility in the HACA study, 3246 did not meet these inclusion criteria. There is accumulating evidence, however, that induced mild hypothermia is probably also valuable for patients not strictly fulfilling these criteria, such as patients with asystole or pulse–less electrical activity [19-20] or

patients above 75 years of age [21]. It seems reasonable to consider induced mild hypothermia for all patients admitted to the ICU after cardiac arrest, which is supported by the ILCOR statement on therapeutic hypothermia [22].

Why should all patients after circulatory arrest and ROSC receive induced hypothermia? Therapeutic hypothermia affects brain metabolism, lowering the metabolism with 40–50% when temperature decreases from 38°C to 32°C, thereby decreasing oxygen demand. Moreover, the level of inflammation is attenuated and intracranial pressure decreases [19]. However, we might view mild hypothermia not so much as a neuro-protective strategy alone, but as an active treatment strategy to improve the function of the brain as well as other organs. Apart from improving brain function, therapeutic hypothermia may (or can) improve function of other organs: studies suggest positive effects in cardiogenic shock, seizures, acute respiratory distress syndrome, nephropathy, hepatic failure, or arrhythmias [20]. These strategies remain to be proven however. A non-significant reduction of infarct size in myocardial infarction has also been reported [23].

Data from surveys in Europe and the United States suggest that rates of use among physicians of induced mild hypothermia in post-cardiac arrest patients may be as low as 30–40% [24]. A recent e-mail-invitation guided anonymous web-based survey was held amongst ICUs in the Netherlands. Thirty-seven ICUs (50%) mentioned always to treat these patients with therapeutic hypothermia, 42% only treat patients when CPR fulfilled several criteria, such as ventricular fibrillation as presenting cardiac rhythm at arrival of ambulance (82%) and duration of time to return of spontaneous circulation (55%). Six ICUs (8%) never induced hypothermia. The most important reason for not inducing hypothermia was lack of equipment. Surface cooling (86%) and cold intravenous fluids (71%) were most frequently used

to reach the target temperature. Hemodynamic instability was most cited as a reason to discontinue treatment with therapeutic hypothermia. Thus, in the Netherlands, therapeutic hypothermia after CPR is implemented in almost all ICUs, which is compared to previous reports of other countries, exceedingly high [unpublished data]. Nevertheless, despite varying acceptance and implementation across the world, lack of scientific evidence for the use of induced mild hypothermia after cardiac arrest may no longer be used as an argument for not implementing this treatment.

### **Cerebral blood flow and mean arterial blood pressure**

Initially, shortly after ROSC, there is a change in cerebral blood flow, which in the later stage, after 72 hours, normalizes [25]. The mean flow velocities, as assessed using trans-cranial Doppler are lowered, while oxygen extraction was initially normal but decreased after time. This latter effect was significantly more pronounced in non-survivors.

After cardiac arrest, cerebral autoregulation is disturbed, but not completely absent [26]. As this mechanism regulates the cerebral blood flow to maintain a steady oxygen delivery to the brain during changes in blood pressure, this means that cerebral blood flow is highly pressure dependent during impairment of the autoregulation and therefore a high mean arterial blood pressure (MAP) is most probably needed. There is no clinical evidence for a specific limit for the mean arterial blood pressure, but as the intracranial pressure following CPR is not necessarily elevated, and in general remains below 15 mm Hg [27], maintaining the MAP > 75 mm Hg and thus a cerebral perfusion pressure of > 60 mm Hg, is justifiable. The optimal MAP for post-cardiac arrest patient may even be higher [28]. Of note, the MAP in the Bernard study [10] was approximately 90 mmHg in both the hypothermia

as well as in the normothermia group. In patients with severe myocardial dysfunction after cardiac arrest, these values may be difficult to obtain, and a balance needs to be found between the optimal blood pressure for cerebral blood flow and the burden for the myocardium to meet this demand.

### **Hemodynamic support and monitoring**

Hemodynamic monitoring is warranted to optimize circulation and balance the oxygen supply with the demand. Heart rate, blood pressure, cardiac output, SvO<sub>2</sub> or ScvO<sub>2</sub>, lactate, and arterial blood gasses need to be monitored. While all of these methods of monitoring the circulation have their own obvious limitations, monitoring may prevent severe misbalances between oxygen delivery and oxygen consumption. Cardiac output during hypothermia may be 20–30% lower and therefore be accepted below normal limits. The use of ScvO<sub>2</sub> or SvO<sub>2</sub> measurements to monitor oxygen balance and maintaining ScvO<sub>2</sub> > 70% is probably a reasonable approach. Volume, inotropics and/or vasopressors will often be necessary to reach these goals. We may need to consider the use of an intra-aortic balloon pump (IABP) in patients with (refractory) cardiogenic shock due to myocardial infarction or myocardial stunning.

In line with guidelines for pharmacological prevention of peri-operative cardiac complications in high risk patients undergoing non-cardiac surgery aiming to maintain adequate oxygen delivery, while preventing myocardial ischemia, the heart rate needs to be maintained between 60–100/minute, using volume, sedation, beta-blockers or a pacemaker to obtain this. As hypothermia often leads to relative bradycardia, beta-blockers are rarely needed, however. Anti-arrhythmic drugs may be needed to maintain sinus rhythm. In patients who come to survive but who are prone to arrhythmias, implantable cardiac defibrillators can be considered. Close

monitoring of the circulation is warranted in order to balance oxygen demand and supply, while at the same time taking care of relieving the myocardial burden and preventing secondary myocardial ischemia.

## **Ventilation**

In post–resuscitation patients, the use of controlled ventilation as opposed to a support mode of ventilation is rational, as this in most cases decreases oxygen consumption [29]. The use of tidal volumes of 6 ml/kg predicted or ideal bodyweight (IBW) is advocated to diminish the occurrence of acute lung injury (ALI) as there is accumulating and convincing clinical and preclinical evidence that ventilation with tidal volumes of 6 ml/kg predicted or ideal bodyweight prevents the development of ALI [30].

As the metabolic rate drops 5–8% per each degree °C, there is a concomitant drop in oxygen consumption and carbon dioxide production. Ventilator settings need to be adjusted accordingly to prevent hyperventilation and thus hypocapnia. Hypocapnia leads to cerebral vasoconstriction and diminished cerebral blood flow and oxygen delivery. Blood gasses need to be repeatedly checked to be able to maintain normoventilation.

While there is no discussion about the need to treat and prevent hypoxia, this invariably leads to hyperoxia, which may be detrimental in it self, especially after a period of hypoxia. While there is preclinical evidence to promote the use of a limited fraction of inspired oxygen ( $FiO_2$ ), there is no evidence for limiting  $FiO_2$  in humans. Striving for a an peripheral oxygen saturation ( $SpO_2$ ) of 95–98% would seem reasonable to prevent hypoxemia and hyperoxemia, but while hyperoxemia is

potentially detrimental after ischemia, especially out beyond 5 minutes, hypoxemia is obviously worse.

### **Blood glucose and electrolyte monitoring**

As hypothermia can decrease insulin sensitivity as well as reduce insulin secretion by pancreatic islet cells, patients who are cooled have a high risk of developing hyperglycemia. Control of blood glucose using insulin therapy is therefore necessary. While there is no clinical outcome study showing benefit in a strictly defined subgroup of post cardiac arrest patients, there is sufficient evidence for controlling blood glucose using insulin from the van den Berghe studies [31-32] to include this strategy in the post–resuscitation treatment.

Electrolyte disturbances are to be expected in patients treated with hypothermia because of changes in renal function, combined with electrolyte shifts to the intracellular compartment. Especially hypomagnesemia can easily occur and is associated with increased risks for adverse outcome. As magnesium has a pivotal role in many central nervous and cardiovascular processes, it is advisable to early start magnesium supplementation. Administering magnesium helps prevention of hypokalemia, hypophosphatemia, hypocalcemia, and hyponatremia, so controlling magnesium facilitates the control of other electrolytes. During hypothermia hypokalemia may also occur, especially in patients with increased urine production. It is beyond the scope of this paper to discuss all possible effects of electrolyte disturbances during induced mild hypothermia. It is generally advised to keep magnesium, potassium and phosphate in the normal to high-normal range, and to keep sodium in the normal range. [33]

Patients after cardiac arrest will have a lowered pH, due to increases in pCO<sub>2</sub> and lactate. As the patient is mechanically ventilated, the pCO<sub>2</sub> will often not pose a problem and normalize, and restoration of the circulation will most often lead to clearance of lactate, reducing these levels and normalizing the pH. As a low pH induces a pro-inflammatory state, and because many enzyme mediated processes are compromised in case of a pH lower than 7.20–7.25, measures need to be taken to maintain a pH > 7.20. Sunde et al. showed that using a goal directed, standardized approach in the treatment of post resuscitation patients leads to a significantly less negative base excess, and therefore a higher pH, without changes in pCO<sub>2</sub> [4].

In patients with electrolyte disturbances, low pH and/or acute kidney failure, one might consider using a form of continuous renal replacement therapy (CRRT), as continuous veno-venous hemofiltration (CVVH). CVVH may aid in maintaining a normal acid–base and electrolyte balance.

### **Thrombolytic therapy aiming at improvement of brain perfusion**

Fischer *et al.* have shown in a cat model that thrombolytic therapy with recombinant tissue type plasminogen activator and heparin after cardiac arrest and successful cardiopulmonary resuscitation reduces the non-perfused brain areas and improves microcirculatory reperfusion [34]. In a retrospective study, Richling *et al.* found a trend towards better neurological outcome using thrombolytic therapy compared to PCI in patients with cardiac arrest due to STEMI [17]. At the moment however, there are insufficient clinical data to support this strategy.

## **Brain monitoring**

We may consider monitoring the brain using an (continuous) EEG. A study evaluating the use of continuous EEG monitoring after cardiac arrest showed in 26 out of 94 evaluated cardiac arrest patients development of electrographic status epilepticus during therapeutic hypothermia, and this status epilepticus correlated with poor outcome [35]. The continuous EEG monitoring provides the opportunity to treat electrographic status epilepticus in absence of clinical signs (non-convulsive status epilepticus) in patients treated with hypothermia, sedation and paralyzing agents, which prevent the clinical signs and symptoms to become overt. As electrographic status epilepticus is known to increase oxygen consumption of the brain, it seems reasonable to try to terminate the electrographic status epilepticus. Anti-convulsant drugs as well as sedatives can be used to prevent and/or treat this status epilepticus. While reasonable, there are yet no convincing data on outcome to support this strategy.

## **Prevention of infection**

Therapeutic hypothermia increases the risk on infections due to immune suppression. A retrospective cohort study of patients after cardiac arrest treated with mild hypothermia showed an increased incidence of lower respiratory tract infections of 88% [36]. Sunde *et al.* compared a prospective cohort treated with hypothermia with a retrospective cohort before the use of therapeutic hypothermia [4]. They found no increase in the rate of pneumonia as a result of hypothermia, but their reported percentage of pneumonia was also high: 57 % in the cardiac arrest patient cohort before implementing therapeutic hypothermia compared with 48% of in the cohort treated with therapeutic hypothermia. This is most probably a detrimental factor as

ventilator-associated pneumonia (VAP) is known to increase mortality and also because infections may cause fever, which is harmful for the compromised nervous system. There are various options to decrease the possibility of an infection to occur, one of these being the use of selective decontamination of the digestive tract, which is a well-proven strategy to prevent VAP and mortality in ICU patients [37-38].

### **Use of sedation, analgesia and paralyzing agents**

Use of sedation in comatose post cardiac arrest patients is rational, as it not only facilitates the use of hypothermia and controlled ventilation, but also reduces oxygen consumption. The use of analgesics is rational as well: a state of post-anoxic coma does not eliminate the need for anesthesia and/or analgesia [13]. Patients with an acute myocardial infarction may experience pain, which may even be aggravated by prolonged periods of chest compressions, necessitating the use of analgesic agents, which on their own can reduce oxygen consumption. Sedation and analgesia are also used to avoid shivering during hypothermia. Shivering greatly increases oxygen demand and needs to be diagnosed and treated. If sedation and analgesia are not sufficient to abolish shivering, magnesium may be used, as well as meperidine (pethidine®). As the patient still shows signs of shivering, a paralyzing agent needs to be added to the treatment.

The choice of sedatives is not always considered crucial. It needs mentioning that the protocol of the Bernard study [10] demanded the use of midazolam, while in the HACA study [9] the combination of midazolam and fentanyl was used. If we prefer the use of other sedatives or analgesics, we need to consider the potential drawbacks of these drugs. Propofol for instance, often used as a sedative for patients with neurological critical care disorders, has a more profound negative inotropic

effect than midazolam, thereby possibly compromising the circulation and thus negatively affecting the prognosis. Shivering was treated with paralyzing agents as vecuronium in the Bernard study [10] and pancuronium in the HACA trial [9].

**Slow, passive or active re-warming and the prevention of fever.**

Re-warming after therapeutic hypothermia needs to be slow and controlled (0.2–0.5°C/h). Rapid re-warming in patients with traumatic brain injury and in the peri-operative setting has resulted in worse outcome than slow re-warming [19]. Animal studies have shown that rapid re-warming can adversely affect outcome and that slow re-warming preserves the benefits of cooling [39]. Rapid re-warming might cause regional or general imbalances between cerebral blood flow and oxygen consumption and thus cause hypoxia, leading to additional ischemic neuronal damage [19]. In clinical studies, rapid re-warming also increases the risk of electrolyte shifts and especially of hyperkalemia. Re-warming also affects the sensitivity of the cell to insulin; so during re-warming the glucose should closely be monitored.

Increasing evidence suggests that fever is harmful to the injured brain, and it seems reasonable to maintain normothermia in most patients with neurological injuries who have decreased consciousness (especially in those previously treated with hypothermia) for at least 72 h after injury [19].

Passive re-warming cannot be strictly controlled; as slow re-warming and prevention of fever are of the utmost importance, it is reasonable to choose for slow, active and controlled re-warming.

## **Prognostication**

Unpublished data of the PROPAC study [40] by Zandbergen *et al.* on differences in outcome of patients after cardiac arrest related to early do-not-resuscitate (DNR) orders after admittance suggest that installing treatment limitations within the first 24 hours leads to an decreased chance of survival.

Pupillary light response, corneal reflexes, motor responses to pain, and somatosensory evoked potential studies can reliably assist in accurately predicting poor outcome in comatose patients after cardiopulmonary resuscitation for cardiac arrest [41]. Myoclonus status epilepticus, which also is regarded as a reliable predictor of unfavorable outcome, is most probably not as useful as previously thought. Myoclonus status epilepticus is rare and should not be confused with the more frequent myoclonus that can be elicited by touch or noise. As mild hypothermia mandates the use of analgesics, sedatives and sometimes of paralytic agents, and as the pharmacokinetics of these drugs are changed due to hypothermia, resulting in a reduced clearance, the utmost care needs to be taken when performing a neurological assessment of these patients. Often a longer period is needed before prognostications can be made.

While an absent cortical response (N20) of the SEP has been demonstrated to have a positive predictive value of 100%, the presence of a N20 does not in any way predict good outcome.

Serum neuron-specific enolase (NSE) has also been suggested as a predictable parameter in establishing prognosis after cardiac arrest, but recent studies in patients treated with hypothermia show higher serum NSE values than previously reported in patients surviving with good neurological outcome. [42] This probably limits the usefulness of NSE in establishing a reliable prognosis.

Prognosis cannot be based on circumstances of CPR itself. Witnessed or not witnessed, BLS or no BLS, and time to ROSC do not reliably predict outcome in an individual patient. For prognostication we should only use established predictors. Poor outcome in post anoxic coma can be reliably predicted with good neurological assessment after three days and with somatosensory evoked potentials in a substantial number of patients. Installing DNR orders within the first 24 hours after cardiac arrest leads to a decreased chance of survival of the post resuscitation patient.

### **Future perspectives**

While we now witness a great leap forward in the treatment of post cardiac arrest patients, many possible treatment modes are under investigation to further improve outcome.

1) During ALS, a device for automated chest compressions is potentially useful in assisting and improving CPR. We have yet to await convincing clinical data before widespread use can be advocated. Impedance threshold devices to produce negative intra thoracic pressure during ventilation in CPR can be used to improve preload and thereby hemodynamics and cerebral blood flow during CPR [43]. On-site cooling after OHCA has been shown to be feasible [44]. No clinical data are yet available to show survival benefit.

2) Cardio-cerebral or chest compression-only resuscitation has been advocated by Ewy *et al.*, claiming substantial outcome benefit after cardiac arrest [45]. On March 31 of 2008, the American Heart Association issued a statement that recommended to perform chest-compression-only CPR if the rescuer is a bystander without CPR training or "previously trained in CPR but not confident in his or her

ability to provide conventional CPR, including high-quality chest compressions (ie, compressions of adequate rate and depth with minimal interruptions) with rescue breath." [www.americanheart.org]. This recommendation has not been adopted by the European Resuscitation Council.

3) Coenzyme Q10 (CoQ10) is an essential mitochondrial cofactor that has been shown to possess neuroprotective qualities in neurodegenerative disorders and may also have a cardioprotective effect in cardiosurgery. Combining CoQ10 with mild hypothermia immediately after CPR may improve survival and may improve neurological outcome in survivors. [46].

4) Erythropoietin (Epo) is suggested to have neuroprotective properties as well. A small clinical study using Epo in OHCA patients failed however to show significant survival benefit [47].

5) In a different way will applying stopping rules for pre-hospital termination of resuscitation in OHCA will affect outcome of patients surviving to the ED or the ICU. In a recent retrospective validation study, Sasson *et al.* found that BLS and ALS termination-of-resuscitation rules performed well in identifying OHCA patients who have little or no chance of survival [48]. Strict BLS and ALS stopping rules were defined. For BLS: *Event not witnessed by emergency medical services personnel; No automated external defibrillator used or manual shock applied in out-of-hospital setting; No return of spontaneous circulation in out-of-hospital setting.* Additional for ALS: *Arrest not witnessed by bystander; No bystander-administered cardiopulmonary resuscitation.* A patient must meet all of the criteria included in either rule to warrant termination of resuscitation in the out-of-hospital setting. Pre-hospital selection of post cardiac arrest patients who will invariably die will increase the likelihood of survival for the remaining cohort, and probably change the attitude of

the treating physicians towards these patients, theoretically resulting in more aggressive treatment and better outcome [48].

## **Conclusion**

After cardiac arrest, immediate restoration of the circulation is of the utmost importance. Good quality basic life support (BLS) and early defibrillation are crucial steps in this phase of CPR. After resumption of spontaneous circulation (ROSC), considerable improvement of outcome of the post-cardiac arrest patient can be achieved by actively treating many complications of the ischemia-reperfusion phenomena known as the post-resuscitation syndrome. The most important treatment modality of these is induced mild hypothermia. Other important treatment modalities include early coronary reperfusion, controlled ventilation to achieve normal arterial blood  $pO_2$  and  $pCO_2$ , hemodynamic optimization, judicious use of sedatives and analgesics and prevention of shivering to reduce oxygen consumption, control of electrolytes and glucose, prevention and treatment of seizures, prevention of complications as infections and the use of validated predictors for prognosis.

Presently, there is accumulating evidence to support the view that a standardized protocol should be used to optimize the treatment of the post-cardiac arrest patient admitted to the ICU.

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## **Table 1**

### **Proposal for a model for standardized post-cardiac arrest treatment**

After return of spontaneous circulation: control hemodynamics and oxygenation

Diagnose and treat the cause of arrest; reperfusion (PCI; thrombolysis) after STEMI

Therapeutic hypothermia (32-34 °C in comatose patients for 24 h) should be initiated as quickly as possible. Try to reach temperatures below 34°C and then achieve target temperature as rapidly as possible. Initially 2 – 3L of ice-cold (4 °C) Ringer's Lactate or 0.9% NaCl i.v. and as soon as possible start endovascular or surface cooling for maintenance, striving for minimal fluctuations of temperature.

Blood pressure: MAP > 75 mmHg

Cardiac output during hypothermia may be 20-30%. Use SvO<sub>2</sub> to monitor oxygen balance; SvO<sub>2</sub> > 70%

Use volume, inotropes and/or vasopressors to reach these goals

Consider IABP in cardiogenic shock

Heart rate: 60 - 100/min Use volume, sedation, beta-blocker (normally not indicated when using therapeutic hypothermia because of relative bradycardia)

Temperature 32-34 °C for 24 h

SpO<sub>2</sub> 95 - 98 Using controlled ventilation; not support ventilation; tidal volumes of 6ml/kg/ IBW

pCO<sub>2</sub> 5 - 6 kPa (avoid hyperventilation/hypocapnia)

Blood glucose 4.4-6.1 mmol/l actrapid-infusion (insulin resistance; avoid hypoglycemia/hypokalemia)

Electrolytes: Aim for normal values

Hemoglobin 5.5 – 6.0 mmol/l (9—10 g/dl) Transfusion if necessary

Diuresis >0.5 ml/kg/h Use volume, inotropes, and/or vasopressors. Start renal replacement therapy early in acute kidney failure.

pH > 7.20, BE > -10 Use when indicated, sodium bicarbonate or start CVVH

Seizures: Prevent/treat seizures using sedation, and/or specific anticonvulsive medication

EEG when indicated

Sedation and analgesia: Morphine or fentanyl and midazolam

Treat shivering with magnesium, meperidine (pethidine); paralysis only when necessary. Use strategies to prevent complications, such as (ventilator associated) pneumonia, wound infections, and bedsores.

Use of other evidenced based critical care strategies as thrombo-prophylaxis and early enteral feeding

Monitoring:

Continuous ECG

Arterial catheter

O<sub>2</sub>-saturation

ScvO<sub>2</sub> or SvO<sub>2</sub>

Cardiac output

Central venous line with central venous pressure

Core temperature

Arterial blood gases (pH, BE, pCO<sub>2</sub>, pO<sub>2</sub>; lactate)

Blood glucose and electrolytes

Echocardiography, chest X-ray

EEG and SEP

After 24 h of cooling, patients should be slowly rewarmed in a controlled fashion (0.2 - 0.5 °C /h). Sedation may be stopped after the body temperature has reached 36.0 °C.

Use only established predictors of death and/or unfavorable outcome in patients remaining unconscious after cardiac arrest. The indicators of poor outcome after CPR are absent pupillary light response or corneal reflexes, and extensor or no motor response to pain after 3 days of observation; and bilateral absent cortical responses on somatosensory evoked potential studies recorded 3 days after CPR.

Treatment protocol based on Sunde et al. [4], Polderman [19] and Arawwawala and Brett [49]