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REVIEW ARTICLE

Care of Patient Resuscitated from Cardiac Arrest*

Abordagem do Paciente Reanimado, Pós-Parada Cardiorrespiratória

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SUMMARY

BACKGROUND AND OBJECTIVES: Out-of-hospital cardiac arrest is a major cause of death with survival rates as low as 5% to 35%. A large number of patients who survive resuscitation will face significant neurological damage, as a result of the ischemia that occurs both during cardiac arrest and reperfusion. However understanding of the mechanisms responsible for brain damage has not resulted in prognostic improvement. Therapeutic hypothermia after resuscitation may be a valid option associated to reduction of neurological damage. The purpose of this study was to review scientific evidence related to a therapy for patients resuscitated from cardiac arrest.

CONTENTS: Description and analysis of the main risk factors associated with neurological damage after resuscitation from cardiac arrest as well as prognostic criteria was carried out. A non-systematic search was conducted in the PubMed data base for papers on a therapeutic approach for patients resuscitated from cardiac arrest. Bibliographic references of reviewed papers were also analyzed. Practical rules were drafted for such an approach.

CONCLUSIONS: Patients resuscitated from cardiac arrest face a high level of risk of neurological damage. Therapeutic hypothermia and control of physiological parameters to optimise brain perfusion, may improve prognosis.

Key Words: Cardiac arrest, Hypothermia, Postanoxic brain damage

RESUMO

JUSTIFICATIVA E OBJETIVOS: A parada cardiorrespiratória (PCR) ocorrida em ambulatório tem elevada mortalidade, sendo a sobrevida entre 5% e 35%. Dos pacientes que são reanimados uma percentagem elevada fica com déficits neurológicos, resultantes das lesões ocorridas, tanto no período de ausência de circulação ou durante a reperfusão. No entanto a compreensão dos mecanismos da lesão cerebral não tem traduzido na melhoria do prognóstico. A hipotermia terapêutica após a reanimação parece ser uma opção válida associada à diminuição destas seqüelas neurológicas. O objetivo deste estudo foi rever a evidência científica relativa à abordagem do paciente reanimado após PCR.

CONTEÚDO: Descrição e abordagem dos principais fatores de risco associados à lesão neurológica após PCR, bem como dos seus critérios de prognóstico. Feita pesquisa não sistemática na base de dados PubMed dos artigos referentes à abordagem terapêutica dos pacientes reanimados de parada cardíaca. As referências bibliográficas dos artigos de revisão foram igualmente analisadas. Elaboradas normas práticas para essa abordagem.

CONCLUSÕES: Os pacientes que sobrevivem à PCR têm elevado risco de ficar com lesões neurológicas graves. A hipotermia terapêutica e o controle das variáveis fisiológicas, com otimização da perfusão cerebral, podem melhorar o seu prognóstico.

Unitermos: Encefalopatia pós-anóxica, Hipotermia, Parada cardiorrespiratória

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INTRODUCTION

Cardiac arrest (CA), notwithstanding the underlying causes has high morbidity and mortality rates. Survival is less than 40% if it takes place in-hospital and lower than 10% if it takes place out-of-hospital, a percentage that has remained unchanged during the last years[1]. Many of the patients who survive remain with neurological damage[2].

During CA, absence of circulation causes brain hypoperfusion, especially of the sub-cortical areas and of the threshold territories between cerebral arteries that, due to lower perfusion, are more subject to ischemia (hemodynamic infarctions). Areas with former ischemic injury are especially affected.

After cardiac resuscitation, reperfusion also contributes to ischemia and cerebral edema[3], activating biochemical cascades responsible for migration of intracellular calcium, production as well as local release of free oxygen radicals and excitatory amino acids, (notably glutamate), mechanisms that contribute for apoptosis. Likewise local production of lactate and thrombosis of the micro-circulation increase the risk of ischemia[3]. These phenomena last for about 48-72 hours after recovery of the cardiac rhythm and of circulation[4].

Identification of these physiopathological processes has contributed to the development of treatments that, with the possible exception of hypothermia, have not shown to be beneficial (Table 1).

Table 1 – Care of Patients in the First 48 hours after Cardiac Arrest

Blood pressure	Mean BP from 80 to 120 mmHg (PVC 8-12 mmHg). Aggressively avoid periods of hypotension
Diuresis	Urinary output > 1 mL/kg/h.
Glycemia	< 200 mg/dL (insulin in perfusion in selected cases).
Intracranial pressure	Headrest inclined (30º) keeping the head aligned with the trunk. Reduce coughing effort and aspiration of bronchial secretions.
Temperature	Aggressively combat against fever in the first 72h. Consider therapeutic hypothermia in the first 24h.
Ventilation	Normoventilation: avoid alcalosis; $PaCO_2$ > 35 mmHg; $SaO_2 \geq 92\%$. Avoid high PEEP (> 8 cmH_2O).
Sedation	As needed: propofol (0.5-2 mg/kg/h) + alfentanil (5-15 µg/kg/h) +/- midazolam (0.01-0.1 mg/kg/h).
Electrolites	Dose every 6 hours. Potassium > 4 mEq/L and magnesium > 2.5 mEq/L.
Nutrition	Continued enteral nutrition at 20 mL/h (or enteral glucose). Avoid parenteral nutrition.

OVERALL MEASURES

Treatment of post-cardiac arrest aims to preserve organic functions (especially the brain), avoiding perfusion pressure on various vascular territories. This strategy complements the diagnostic and therapeutic approach to the cause of CA and potential complications, particularly eventual fibrinolisys, coronary intervention or conversion of cardiac dysrhythmias.

The initial approach must include an electrocardiogram (to identify the cause of CA and of intercurrent dysrhythmia), chest X-ray (for exclusion of iatrogenies associated with resuscitation maneuvers such as pneumothorax and rib fractures) and blood gas analysis (with dosing of electrolytes and lactic acid).

Blood Pressure

In the healthy individual, cerebral perfusion pressure (CPP) is independent from systemic blood pressure (SBP). This is the function of brain self-regulation with adjustment of its vascular tonus to the systemic pressure variations. This capacity is altered by lack of circulation[5].

After CA there is a period of brain hyperthermia that lasts about 15-30 minutes followed by vasodilation and consequent decrease of CPP. Under these conditions any decrease of BP may cause hypoperfusion and diffuse cerebral ischemia[5].

Indeed, in the absence of central self-regulation the CPP is equal to the difference between systemic BP and intracranial pressure (ICP), the latter normally ranging between 5 and 20 mmHg. Because the required CPP is 60 mmHg[6,7], the mean BP must be above 80 mmHg (especially in the first 72 hours after cardiac arrest), to maintain an adequate brain perfusion. This is assured by early administration of volume and vasopressor amines, as well as by conversion of dysrhythmias to avoid prolonged periods of hypotension[8].

After CA, another common hemodynamic phenomenon is myocardial depression[9], even when there is no acute or chronic coronary disease. This disease is a consequence of cardiac hypoperfusion and of resuscitation maneuvers (above all that of electric cardioversion), normally reverting in 24 hours. Dobutamine and combined insulin, glucose and potassium therapy[10] may contribute to minimize this phenomenon.

It is not clear that arterial hypotension, even when severe, contributes to brain injury[6] Nevertheless, since it is associated to injury of systemic vessels, it seems prudent to avoid a mean BP of over 120 mmHg.

Intracranial Pressure

After a cardiac arrest, even a temporary increase of ICP may contribute to brain injury. ICP increases with obstruction of blood drainage along the internal jugular veins and catheterization of these veins must be avoided or cervical rotation maintained. Ideally, the head must remain aligned with the trunk and the headrest inclined at a 30º.

Because sedoanalgesics decrease sympathetic response and because neuromuscular blockers reduce the coughing reflex and the respiratory effort, they may minimize elevation of thoracic pressure related to aspiration of bronchial secretion, with the alveolar recruitment maneuvers[11] and with high PEEP (above 8 cmH_2O).

In this framework of cardiac arrest, invasive monitoring of ICP does not seem clinically advisable, as the clearly pathological values (above 20 mmHg) which as such would have a therapeutic indication) reveal diffuse cytotoxic brain edema, with irreversible dysfunction, whose treatment is pointless[12].

Blood Glucose

Glycemia indices are often high in patients admitted at the ICU. This alteration is multifactorial, probably related to endocrine response to stress[13]. After CA hypoglycemia, at in-hospital admission as well as during the first 24 hours, worsens independently of prognosis[8,14]. It remains unclear if this alteration contributes to the neurological injury or if it is in itself an indicator of severity. Nevertheless, experimentally, increase of glycemia eases accumulation of lactate in the brain tissues during hypoxia[13] and this alteration may contribute to brain injury.

In a clinical trial carried out in a single center, in an ICU with surgical patients[15] control of capillary glycemia with a cut off level of 110 mg/dL, reduced mortality as well as incidence of neuropathy. This result however was not reproduced in other studies.

Although control of capillary glycemia seems to be associated to a better prognosis of the critical patients (especially if not diabetic)[15], the ideal cut off level remains unclear. There seems to be sufficient evidence to recommend maintaining glycemia below 200 mg/dL, (ideally at a lower level)[13]. The recommended value also depends upon experience in the ICU and its monitoring capacity, because aggressive use of insulin to maintain low levels of glycemia is associated with a higher risk of hypoglycemia and neuroglycopenia that may, themselves worsen neurological injury.

In general, glucose solutions (especially in the first 24 hours after admission) should be avoided as well as parenteral nutrition, considering the possibility of low doses of enteral nutrition in hemodynamically stable patients.

Temperature

Cerebral temperature normally is about 0.5º C above systemic temperature. In the injured brain this difference is significantly higher and may reach up to 3º C. In acute cerebral ischemia there is also a regional increase of temperature, asymmetric to the rest of the brain mass[16].

Animal studies have shown that increment of cerebral temperature is accompanied by neurological deterioration and that its controlled decrease reduces these injuries.

Indeed in mice submitted to asphyxia (where spontaneous hypothermia is noted), forced rewarming increases mortality and histological injuries in the various brain areas during the first 72 hours[17]. In dogs submitted to experimental ventricular fibrillation (20 minutes period of absence of circulation), induction of hypothermia reduces the observed neurological deficits, as well as encephalic histological alterations[18].

On the other hand, also in the experimental ischemic BVA, cerebral cooling decreased the volume of the infracted region[16].

After CA, increase of the systemic temperature can be noted and consequent cerebral hyperthermia. Upon admission or in the first 24 hours, such an event worsens prognosis, although it remains unclear if this change is an indicator of severity of neurological disease or the determinant of clinical worsening[16,19].

Thus, in the presence of acute brain injury, diffuse or not, after CA or after any other etiology, fever must be aggressively avoided[20] in the first 72 hours of evolution.

Recently two studies, an European and an Australian, showed independently that therapeutic hypothermia after CA that occurred in an out-of-hospital facility significantly reduced neurological damage and one of the studies found a significant decrease in mortality[3,21].

In the multicentric European study, 55% of patients submitted to hypothermia had a significant neurologic functional recovery, contrary to the control group in which only 39% recovered (Risk Reduction (RR) – 1.4 with number of treated patients to achieve an additional recovery of 6 (NNT number needed to treat)). This benefit continued at 6 months, and a statistically significant decrease of mortality was noted (41% *versus*

55%) p = 0.012, RR of 0.74 and NNT of 7[21].
In the Australian study there was also a more frequent neurological recovery in the group of patients submitted to hypothermia (49% *versus* 26%, RR de 1.85 with NNT of 4)[3].
In both studies inclusion criteria were very restricted. In the first, about 90% of the evaluated patients were excluded; therefore it remained doubtful if the benefit of this therapeutic strategy was not overestimated.
Therapeutic hypothermia consists of reducing the central temperature to 32º C - 33º C, to interrupt the physiopathological cascade responsible for the neurological reperfusion injury. It must be maintained for 12 hours and seemingly it is beneficial to prolong up to 24 hours. It must be considered for all patients in whom there is indication for active treatment. This is regardless of the heart rate at the moment of the CA (IIa indication of the ILCOR for CA post ventricular fibrillation occurred in out-of-hospital environment and indication IIb for CA at any rhythm, and any place) whenever there is no contraindication[22] (Table 2).

Table 2 – Contraindication for Therapeutic Hypothermia

Time of sustained hypotension (Systolic BP < 80 mmHg or mean AP < 45 mmHg) over 30 min after resuscitation
Time of medically non-assisted CA more than 10 minutes.
Resuscitation during more than 45 min.
Time after CA longer than 12h
CA secondary to trauma
Primary coagulopahy (but no oral anticoagulation)
CA acknowledged as secondary to aortic dissection, intracranial hemorrhage or massive hemorrhage
Terminal disease or indication of no resuscitation

Cooling can be internal or external, that is to say, with infusion of iced solution, ice packs, ventilators, thermal blankets or plaques as well as appropriate intravascular catheters[19,23]. Extracorporeal circulation can also be used with external cooling of the blood.
To increase tolerance to cold and reduce production of heat (by tremors and shivers) sedoanalgesia may be used, magnesium sulphate in perfusion[24] and neuromuscular blockers, preferably administered in an intermittent form.
Cooling must be early and aggressive to rapidly decrease central temperature avoiding periods of hyperthermia, and later can be slower (about 1º C/h). Rewarming must always be slow and passive (not above 0.5º C/h) to prevent worsening of the injury and brain edema associated to hypothermia rebound, frequent in such circumstances[17].
Infection, heart rate instability (especially bradydysrhythmias), coagulation, pressure sores and cold burns as well as hyperglycemia and hypomagnesemia are potential complications of hypothermia[19] (Table 3).

Table 3 – Therapeutic Hypothermia

Overall procedures	Nasogastric intubation. Central temperature catheter (vesicular, pharynx, Swan-Ganz or tympanic). Tracheal intubation Paracetamol 1 g (enteral). Prevent hypotension
Infusion of solutions	Polyelectrolytic at 4º C – 30 mL/kg at 100 mL/min (if needed use pressure cuff). Interrupt if temperature < 34º C.
Curarization	Preferably intermittent – if trembling or refractory to cooling (< 1º C/h) i.e.: vecuronium 0.1 mg/kg (or 0.8-1.2 µg/kg/min).
Magnesium sulphate	*Bolus* 4-6 g followed by perfusion of 1-3 g/h until reaching target temperature. Afterwards adjust perfusion to maintain serum levels between 2 and 4 mg/dL.
Complementary measures	Wrap hand and feet in dry towels. Apply ice in the axillas, groins and eventually wet sheets on the body. Ventilators with cold air. Turn off heating in the humidification circuit of ventilation. Compensate diuresis with infusion of more iced solution until target temperature is reached. If after 90 min temperature is of less than 1.5º C, consider beginning extracorporeal circulation (continuous venous hemofiltering) with external cool Ingredients of the blood circulation lines.
Rewarming	Slow, for a minimum of 8h with a steady passive speed not surpassing 0.5ºC/h. Aggressively avoid temperature over 37.5º C. Interrupt sedation (and curarization) when temperature ≥ 36º C.

Indicated for patients with cardiocirculatory recovery maintained during at least 5 min with the Glasgow coma score ≤ 9 or abnormal agitation (attributed to neurological function). In cardiac arrest in the presence of physicians consider the possibility of waiting for 60 min to evaluate eventual early neurological recovery.

Ventilation

Mechanical ventilation after CA must be adjusted to the patient's clinical condition and to his gas exchange for prevention of hypoxemia and maintenance of normocapnia.
Hypoxemia may worsen prognosis especially due to a higher risk of a second episode of CA[20]. Therefore, PaO_2 must remain above 65 mmHg and the SaO_2 higher than 92%. Because hypothermia increases oxygen affinity to hemoglobin during this procedure, a higher minimum saturation is required.
Hypocarpia ($PaCO_2$ lower than 32 mmHg) and respi-

ratory alkalosis must be avoided as they can trigger brain vasoconstriction and consequent decrease of global perfusion and diffuse ischemia[25,26]. Indeed, paradoxically hyperventilation sometimes used to reduce cerebral edema may induce worsening of the clinical condition.

PHARMACOLOGICAL SUPPORT

Sedation

Post CA sedation facilitates patient adjustment to the ventilatory prostheses and/or realization of therapeutic maneuvers, especially hypothermia. Benzodiazepinics or propofol may be used, preferentially according to sedation scales, to avoid a cumulative effect[27]. Utilization of short life drugs allows for neurological intermittent evaluation.

Opioids are elected for control of the automatic respiratory stimuli, normally sustained after a CA, which interferes with mechanical ventilation and contributes to hypercapnia and alkalosis, often found in patients with central neurological injuries. Further, they are more effective for prevention of muscle tremor associated with hypothermia.

There is no evidence that maintenance of this sedoanalgesia for a pre-established period of time influences neurological preservation, therefore it should be interrupted, if not needed.

Electrolytes

Electrolytic disorders are common after CA, due to lack of circulation and of resuscitation maneuvers, including administration of solutions and adrenalin[28].

Decrease of the potassium concentrations, also aggravated by intracellular migration of this cation during hypothermia, is associated to increased dysrhythmias and its concentration should remain at 4 and 4.5 mEq/L.

Similarly, hypomagnesiemia worsens neurological prognosis[29]. Its infusion facilitates therapeutic hypothermia[24] and decreases incidence of dysrhythmias.

Anticoagulation

Utilization of thrombolytic therapy during a refractory CA increases the number of patients with sustained hemodynamic recovery[30].

This, together with evidence of the pro-thrombotic conditions after resuscitations infers that anticoagulation may have therapeutic benefits as it reduces risk of thrombus. Indeed, after cardiac resuscitation there is a greater pro-thrombotic activity and overall decrease of anticoagulant factors (antithrombine II, protein C and S). These alterations are pronounced in patients who die in the first two days[31].

Anticoagulation may contribute to decrease the risk of another CA, more so after myocardial infraction or pulmonary embolism[20].

However, this theoretical benefit was not documented in *in vivo* clinical studies.

Anticonvulsants

After CA, convulsions and myoclonias are frequent and found in about 30% of the patients. They do not have a significant prognostic worsening when the event is isolated. On the contrary, the state of epileptic illness alone worsens neurological injury and must be aggressively managed (phenyltoin, phenobarbital and sedatives)[32] with eventual continued electroencephalic monitoring. Levatiracetam and sodium valproate do not have a significant action on the stage of the illness, but can be used as chronic maintenance therapy after clinical stabilization.

This stage of epileptic illness may take place without motor manifestation (non-convulsive stage of disease) however, in view of an unknown cause of persistent coma; an ECG must be made[33].

Conversely, the stage of myoclonic disease describes extensive brain injury, usually irreversible[34-36]. The therapeutic approach includes sodium valproate and clonazepan, although these drugs to not seem to influence clinical evolution.

This is different from the Lance Adams syndrome where there are generalized myoclonies, together with preservation of vigility and level of consciousness. Use of pyracetam may improve such manifestations.

Evaluation of the Prognosis

Early assessment of the neurological prognosis is fundamental for stratification of the therapeutic intervention, especially to identify patients that do not benefit from intensive care.

Form the clinical point of view, in the non-sedated patient, absence of papillary reflex and response to pain on the 3rd day of evolution after CA, is an independent factor of poor prognosis, with a specificity of over 95%[35].

In addition, bilateral absence of early response (N_2O) in SSEP of the median nerves has a very high specificity for unfavorable evolution which is understood as absence of recovery of the level of consciousness. Al-

though the auditory evoked potentials do not increase this specificity, they are useful to confirm the integrity of the conduction paths of the cerebral trunk (essential for assessment of SSEP)[37].

The pattern of burst-suppression at ECG, although less specific, also portrays very severe brain injury[34]. Its prognostic usefulness increases with time after CA, that is why this exam must not be performed before the 3rd day[38].

Enolase (Neuron-Specific Enolase) dosed in blood or in cephalorachidian fluid correlates to cerebral injury and to the prognosis. However, thresholds for clinical assessment are not yet defined[39,40].

Final Considerations

Therapeutic interventions intended to preserver life and organic functions after CA improve prognosis, but at the same time increase the survival of patients with neurological injuries and a cognitive commitment with severe sequels.

The option to implement extraordinary measures for life support in these circumstances therefore has social implications and must be discussed in view of the legislation in force, of the sensibility of society and of the medical community, as well as that of the families involved. This will help to decide which therapeutic options are to be carried out or omitted, especially in extreme cases.

CONCLUSION

Cardiac arrest is a dramatic event with a high mortality. In patients that survive, the period of absence of circulation and the reperfusion injuries may lead to severe neurological damage.

Although there are no efficient pharmacological therapies for such a situation, minimizing risk factors (hypotension, hyper or hypoglycemia, hypoxemia or hypocapnia, hyperthermia, electrolytic disorder), optimizing of CA and therapeutic hypothermia may improve prognosis.

Acronyms

CA - Cardiac arrest
CPP – Cerebral perfusion pressure
BP – Blood pressure
ICP – Intracranial pressure
PEEP – Positive end expiratory pressure
ICU - Intensive care unit
BVA - Brain vascular accident
ILCOR – *International Liaison Committee on Resuscitation*
PaO_2 – Partial arterial pressure of oxygen
SaO_2 – Hemoglobin arterial saturation
$PaCO_2$ – Carbon dioxide arterial pressure
EEG – Electroencephalogram
SSEP - Somatosensitive evoked potentials

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