Review

Post cardiac arrest syndrome

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\textbf{A R T I C L E  I N F O}

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\textbf{A B S T R A C T}

Background: Resuscitation from cardiac arrest with global ischemia restores spontaneous circulation in some patients; however, survival depends on many factors associated with post cardiac arrest syndrome. During the last ten years, the understanding and control of these factors have improved the prognosis in a subgroup of patients.

Objective: To describe the pathophysiology and current management of the post cardiac arrest syndrome (PCAS).

Methodology: Narrative review of the literature using Medline via PubMed and Clinical Trials, using the terms MeSH cardiac arrest – Cardiopulmonary Resuscitation and (no term MeSH) Post cardiac arrest syndrome.

Results: Clinical trials have established a set of management protocols and guidelines based on therapeutic objectives with survival rates exceeding 50% of the cardiac arrest victims.

Conclusions: The management of this syndrome has actually strengthened the last link in the survival chain by standardizing the evaluation and selection of cardiac arrest victims via a therapeutic hypothermia protocol and early percutaneous coronary intervention.

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\textbf{Síndrome posparo cardíaco}

\textbf{R E S U M E N}

Antecedentes: La reanimación en el paro cardíaco con isquemia global logra restablecer la circulación espontánea en algunos pacientes; sin embargo, la sobrevida depende de muchos factores que explican el síndrome posparo cardíaco. El entendimiento y el control de estos factores durante la última década han logrado mejorar el pronóstico en un subgrupo de pacientes.

Objetivo: Describir la fisiopatología y el manejo actual del síndrome posparo cardíaco.

Metodología: Revisión narrativa de la literatura a través de las bases electrónicas de Medline vía PubMed y Ensayos Clínicos usando los términos MeSH Cardiac arrest – Cardiopulmonary Resuscitation y (el término no MeSH) Post cardiac arrest syndrome.

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Resultados: Los estudios clínicos han establecido una serie de protocolos y guías de manejo basadas en objetivos terapéuticos con tasas de sobrevida que superan el 50% de las víctimas de paro cardíaco. 

Conclusiones: Actualmente el manejo de este síndrome ha fortalecido el último eslabón de la cadena de supervivencia al estandarizar la evaluación y la selección de víctimas de paro cardíaco con un protocolo de hipotermia terapéutica e intervención coronaria percutánea precoz.

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Introduction

In 1972 the Russian pathophysiologist Vladimir Negovsky described the syndrome as “a post-resuscitation disease”. However, since it involves a series of uncontrolled events, the International Liaison Committee on Resuscitation (ILCOR) adopted the term post cardiac arrest syndrome.

The incidence rate due to all cardiac causes is 460,000 deaths/year. Prospective trials refer to 350,000 coronary disease-related deaths/year; this is 1–2/1000 people for the American population. There are survival reports of patients with extra-hospital cardiac arrest of 23.8% at the time of admission and of 7.6% at the time of discharge.

Biological death depends on the cardiac arrest mechanism, on the underlying disease and on the delay in starting the resuscitation maneuvers (CPR). A poor neurological prognosis after 4–6 min of an unattended arrest is irreversible, and hence resuscitation must be a constant mission.

When the arrest mechanism is an asystole or a pulseless electrical activity (PEA), the progression to neurological injury is faster and leads to a worse prognosis.

Mild therapeutic hypothermia (32–34 °C) is the gold standard in post-arrest care.

A narrative review of the literature using Medline via PubMed and Clinical Trials using the terms MeSH cardiac arrest – Cardiopulmonary Resuscitation and no term MeSH Post cardiac arrest syndrome was carried out.

Clinical evolution

Once the patient recovers spontaneous cardiac circulation, a cascade of events develops, mainly characterized by anoxic brain injury, post cardiac arrest myocardial dysfunction, “ischemic/reperfusion” systemic response, and the typical pathology of the triggering cause of the cardiac arrest. The clinical evolution shall be dependent on clinical conditions such as the patient’s co-morbidities, the duration of the ischemic lesion and the cause that triggered the cardiac arrest.

Pathophysiology

Oxygen deficiency and generalized acidosis develop during cardiac arrest. If the victim is resuscitated using CPR/defibrillation maneuvers, with resumption of spontaneous circulation, PCSS develops, which is characterized by a systemic inflammatory response of the immune system and of coagulation. Cell damage seems to affect the enzyme calpain and peroxidation caused by oxygen free radicals that begin to develop during the phase of global ischemia and perpetuates during reperfusion.

The main cause of extra-hospital cardiac arrest in the adult is acute myocardial infarction. There are many other pathologies leading to multisystem failure and subsequent cardiac arrest in the hospitalized patient.

Treatment

According to the ILCOR document, the PCAS classification follows physiological criteria in five phases:

1. Immediate care: the initial 20 min following the patient’s spontaneous recovery of circulation.
2. Early phase: from 20 min to 6–12 h, when critical protective and therapeutic measures are required for a successful outcome.
3. Intermediate phase: from 6–12 h to 72 h a close surveillance and ICU treatment are required consistent with the therapeutic objectives.
4. Recovery phase: comprises the patient’s condition after the initial 72 h when there is a clearer diagnosis and a more predictable result.
5. Rehabilitation phase: focuses on the patient’s complete recovery. Any electrolytic abnormalities shall be corrected during phases 1 and 2, in addition to providing inotropic support and optimized oxygenation.

Goal-targeted therapy

Ventilation support

1. Normocapnia (PaCO₂ between 40 and 45 mmHg). However, arterial gasometry should be properly interpreted in patients undergoing therapeutic hypothermia. When a patient reaches a central body temperature of close to 33 °C, the actual PaCO₂ may be up to 7 mmHg below the value in the arterial gases machine. Hyperventilation has been associated with a drop in coronary perfusion and venous return, in addition to cerebral vasconstriction.
2. Normoxia. Both, hypoxia and hyperoxia (PaO₂ > 300 mmHg) may result in secondary neurological injury. Using an inspired oxygen fraction to maintain the arterial saturation between 95% and 99% or a PaO₂ > 100 mmHg is
considered very reasonable. However, other authors have not achieved similar results.

**Hemodynamic support**
Systemic perfusion and in particular cerebral perfusion have prognostic implications. Cardiac arrest patients experience a loss of cerebral self-regulation. Based on positron emission tomography studies, the suggestion is to maintain a mean pressure between 80 and 100 mmHg because this is the range in which perfusion matches the cerebral metabolic activity. During the first 48–72 h following the cardiac arrest, vasopressors and inotropic agents are usually needed. Transthoracic echocardiography may assist in accomplishing this goal. Apparently there is no difference in terms of the clinical prognosis regardless of the vasopressor (norepinephrine versus dopamine). Monitoring the mixed venous saturation may help in the interpretation of pharmacological interventions such as the introduction of inotropic agents.

Hypothermia has shown huge benefits since 2002; however, the procedure is not standardized in every country. There is an Italian study in ICUs indicating that only 16% used the therapeutic hypothermia protocol.

**Hypothermia Management Scheme**

1. The induction phase (body temperature between 32 °C and 34 °C). It should be started early to prevent neuroexcitotoxicity. It has been shown that the benefit of hypothermia will not be achieved if it is introduced after 6 h of the spontaneous return of circulation. Both PRINCE (Pre-ROSC Intranasal Cooling Effectiveness) and Nagao trials showed that initiating hypothermia before the patient recovers spontaneous cardiac circulation during CPR improves the neurological results and protects the myocardium from reperfusion injuries. Therapeutic hypothermia may not last less than 6 h and it should be continued for 12–24 h.

Some recommend starting a rapid saline solution infusion at 4 °C to accomplish these goals. The rate at which the body temperature drops is close to 1 °C in 15 min, when administering 1 liter of cold saline solution. This method is thought to be comparable to or even better than the use of intravascular catheters. The infusion of 30 ml/kg of saline solution at 4 °C lowers the body temperature at a rate of over 2 °C/h. Chills are one of the side effects of cooling down because of the rise in metabolic oxygen consumption; the recommendation to prevent chills includes administering magnesium sulfate (5 g/5 h), sedation and proper analgesia, in addition to the occasional administration of muscle relaxants. A very common intravenous sedation regime is titrating with a continuous infusion of Propofol (up to 50 μg/kg/min) and Fentanyl. Hypothermia between 32 °C and 34 °C results in a drop in cardiac output (between 25% and 40%) at the expense of a heart rate decrease. Arrhythmias occur at much lower temperatures than these ranges or as a result of electrolyte imbalances. The most destabilizing factors during this phase are hypovolemia and electrolyte imbalances (hypokalemia and hypomagnesemia). Increased diuresis results in a hydro-electrolytic imbalance, hemoconcentration and a rise in blood viscosity.

2. The maintenance phase should be free of any temperature variations beyond 0.2–0.5 degrees centigrade of the temperature achieved. Be very careful with the metabolic requirements of the patient since these are reduced in up to 50% and monitor coagulation, although different trials do not show a significant risk of bleeding. Hypothermia extends the half-life of all drugs. The administration of muscle relaxants may suppress chills and hence prevent rises in body temperature. However, muscle relaxants may mask seizures (that are present in up to 44% of the cases). The therapeutic approach includes the use of multiple anti-convulsive agents as is the case in status epilepticus (valproic acid, phenytoin, midazolam, phenobarbital and propofol) because seizures tend to be refractory.

3. The premise during the warm-up phase is to slowly recover the temperature at a rate of 0.2–0.3 degrees centigrade. It is recommended to start warming-up after 12–24 h of introducing the hypothermia until the temperature is normalized. It is usual to experience hyperkalemia, cerebral edema, and seizures during this phase; likewise, ruling out any risk of infection is a priority since one of the effects of hypothermia is the inhibition of the immune response. The use of antibiotic prophylaxis is only indicated for high-risk patients or in prolonged hypothermia (over 48 h). The level of coagulopathy is considered to be mild when compared against that of cardiac arrest victims who are maintained at a normal temperature. Increased infection rates have been described associated with therapeutic hypothermia for 24 h; however, it has not been associated with higher mortality. There can also be bradycardia, prolongation of the QTc segment, hyperglycemia, diuresis with subsequent hypokalemia, hypomagnesemia and hypofosfatemia.

**Hypothermia protection**
During the first phase, when the patient recovers spontaneous circulation, hypothermia reduces the metabolic consumption of oxygen and glucose.

During the second phase, hypothermia reduces the occurrence of excitative amino acids, particularly glutamate; these amino acids are responsible for the activation of the cytotoxic cascade, the formation of reactive oxygen species (ROS) and nitric oxide.

During the third phase, hypothermia preserves the integrity of cell membranes interfering with the action of calpain and thus preventing the occurrence of cerebral edema, neuronal death and blood brain barrier injury.

The benefits of therapeutic hypothermia have been very well explained in a recent meta-analysis. Patients treated with therapeutic hypothermia exhibited improved neurological function (RR 1.55; 95 CI 1.22–1.96) and had a higher probability of survival at discharge (RR 1.35; 95 CI 1.10–1.65) compared to patients not treated with hypothermia.
The international agencies (AHA – ERC) have accepted and promoted the indication of hypothermia for managing the post cardiac arrest syndrome, not only in defibrillator-acceptable patients, but also in cases of worse AESP prognosis and asystole in which the most important prognostic factor is the initiation of therapy.\textsuperscript{16,29}

**Indications for therapeutic hypothermia\textsuperscript{46,45}**

- Return to spontaneous cardiac circulation following cardiac arrest (any type of rhythm)
- Coma
- Over 18 years old

**Absolute contraindications**

- Non-compressible active bleeding
- Do not resuscitate medical order (DNR)

The hypothermia protocol must be interrupted in the presence of sepsis or pneumonia, refractory hemodynamic instability and severe refractory arrhythmia.

Hypothermia in patients with a FV cardiac arrest has an NNT of 6 (confidence interval of 4–13). Despite the consistency of the trials in terms of the rhythm of presentation of the arrest, cooling method used, time to reach therapeutic hypothermia and duration thereof, no follow-up studies have been made beyond one year to establish the final neurological involvement.\textsuperscript{46}

Hypothermia should not be delayed, even when the patient requires transluminal percutaneous coronary angioplasty.\textsuperscript{47}

The best site to monitor the central temperature is through the pulmonary artery catheter or the central venous line; however, other sites are recommended such as the esophagus and the bladder, because they are easy to place and have minimal effects.\textsuperscript{43,46} The bladder temperature may be misinterpreted in the presence of oliguria.

### Recommendation for neurological follow-up of the patient

The brain is the key organ in resuscitation, hence the high importance given to therapeutic hypothermia.\textsuperscript{55} There is an interesting article on the "self-fulfilling prophecy"\textsuperscript{56} that states that no negative prior judgments should be made in a patient who has overcome the arrest, regardless of the cause because by not doing what should be done, the patient will not survive, giving the false impression that what is appropriate is not to start any medical intervention under these circumstances. However, there is always room for uncertainty in every prognosis.\textsuperscript{56}

The prognosis after the clinical and paraclinical exams at different points in the evolution must have a 72-h (3 days) period of observation before any decision is made.\textsuperscript{57} The American Academy of Neurology suggests that in the absence of brain death, findings of the clinical examination such as absence of corneal or pupillary reflexes, of motor response or extended absence of motor response, lead to a high rate or poor prognosis and consequently low false positives.\textsuperscript{58}

Efforts have been made to identify serum markers for predicting the development of multiple organ failure in PCAS patients. Soluble Ang1 factor stabilizes the endothelium Ang2 levels, and a higher proportion of Ang2/Ang1 is predictive of multiple organ failure and poor prognosis.\textsuperscript{59}

High procalcitonin levels are shown to be associated with PCAS and adverse neurological prognosis rather than to early infection in patients with anoxic encephalopathy.\textsuperscript{50} Among the clinical factors themselves, a research comparing two hospitals in distant geographical regions showed that the pre- and intra-cardiac arrest conditions determine the severity of the PCAS.\textsuperscript{51}

**Prognostic factors\textsuperscript{13}**

- Patient history: old age – diabetes – sepsis – CVA
- Cardiac arrest and resuscitation conditions: time elapsed since the cardiac arrest and the start of CPR – CPR quality – asystole as arrest rhythm – implementation of a protocol for managing the PCAS\textsuperscript{52}
- Later evolution in accordance with the neurological examination, neurophysiological exams, neuroimaging, biochemical markers and intracranial Doppler.

The two scales used to establish the degree of disability and the quality of life are the Glasgow prognostic scale\textsuperscript{13} and the Glasgow-Pittsburgh\textsuperscript{13} scale for categorizing brain performance.

When should you do percutaneous coronary intervention (PCI) and thrombolysis

Ask about any history of coronary heart disease, prior chest pain symptoms and initial arrest rhythm (if the QRS tracing in the ECG is widened, it is most likely of coronary etiology); however, the literature has not found a positive predictive value for coronary obstruction of these two parameters.\textsuperscript{59}

Thrombolysis is only recommended in isolated cases of pulmonary embolism and acute myocardial infarction with ST elevation (IAMST) and a 3-h therapeutic window or in the case of IAMST, with no other option for invasive coronary intervention.\textsuperscript{50}

In cardiac arrest patients with no evident extra cardiac cause or who present ST elevation in the ECG or sudden left branch blockade, an early angiographic exploration is recommended, followed by percutaneous coronary intervention.\textsuperscript{50}

In a report written by Spaulding et al.,\textsuperscript{51} 49% of all cardiac arrest survivors who underwent routine coronary angiography showed a severe coronary obstruction.

Further randomized clinical trials are needed showing the positive impact of emergency percutaneous coronary intervention in this syndrome. As of now, the studies reporting benefits with the use of PCI-associated therapeutic hypothermia exhibit various biases and undetermined confounding factors.\textsuperscript{52}

The similarity of the cardiohemic involvement of PCAS\textsuperscript{13} to septic shock has led to the search of alternative aggressive management options with quite successful results such as circulatory support with extracorporeal oxygenation\textsuperscript{53} and renal replacement therapy with high volume hemofiltration.\textsuperscript{54}

In refractory cardiac arrest patients, the alternative to use venous-arterial extracorporeal membrane oxygenation and PCI has been suggested.\textsuperscript{52}
What is currently being done?

A large international prospective trial was completed coordinated from Sweden\(^2\) – the TTM trial (Target Temperature Management, identified as NCT01020916), whose results were published late in 2013. The purpose of the trial was to establish the level of evidence of hypothermia for the management of PCAS with optimal control to avoid hyperthermia in both groups; \(n = 939\) adult patients. Comparison: controlled hypothermia (\(33^\circ\)C) versus patients maintained with a temperature of \(36^\circ\)C. Period of time during which the patients were evaluated: up to 180 days. The results obtained are controversial with regard to the optimal threshold of hypothermia. The conclusion of the trial was based on a strict temperature control (below \(36^\circ\)C) to prevent hyperthermia, which is considered a determining factor for poor prognosis.\(^4\)

Emphasis was also placed on the establishment of standardized protocols, even for each subgroup of patients who may benefit from individualized treatment.\(^5\)

The recommendation is to optimize the perfusion of vital organs in addition to the brain, since the prevalence of multiple extra-cerebral organ failure impacts mortality, particularly the involvement of the cardiovascular (depends on the fine vasopressor support) and respiratory system (by providing improved oxygenation). An independent association has been identified between these two organs and their involvement has been linked to a higher hospital mortality in PCAS.\(^6\)

Conclusion

PCAS is an entity that has been recognized for the last 40 years; however, the treatment for PCAS has only been established in an organized manner in the last decade.

The pathophysiology includes a serious involvement of the brain and leads to myocardial dysfunction and systemic inflammation. Failure to intervene early on results in irreversible brain injury, vegetative state and death.

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Authors.

Conflicts of interest

The authors have no conflicts of interest to declare.

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