Annales Françaises d'Anesthésie et de Réanimation 33 (2014) 98–101

Anarlf meeting

Neurological consequences of cardiac arrest: Where do we stand?☆,☆☆

Conséquences neurologiques post-arrêt cardiaque : où en sommes-nous ?

G. Geri [a,d,f], N. Mongardon [c,e], F. Daviaud [a,d], J.-P. Empana [d,f], F. Dumas [b,d,f], A. Cariou [a,*,d,f]

[a] *Medical Intensive Care Unit, Cochin Hospital, Assistance publique des Hôpitaux de Paris, 27, rue du Faubourg-Saint-Jacques, 75014 Paris, France*
[b] *Emergency Department, Cochin Hospital, Assistance publique des Hôpitaux de Paris, 27, rue du Faubourg-Saint-Jacques, 75014 Paris, France*
[c] *Department of Anesthesiology and Surgical Intensive Care, Henri-Mondor Hospital, Assistance publique des Hôpitaux de Paris, 51, avenue du Maréchal-de-Lattre-de-Tassigny, 94000 Créteil, France*
[d] *Faculté de médecine, université Paris Descartes & Sorbonne Paris Cité, 15, rue de l'École-de-Médecine, 75006 Paris, France*
[e] *Faculté de médecine, université Paris Est, 8, avenue du Général-Sarrail, 94000 Créteil, France*
[f] *Paris Cardiovascular Research Center, European Georges-Pompidou Hospital, INSERM U970, 56, rue Leblanc, 75015 Paris, France*

ARTICLE INFO

Keywords:
Cardiac arrest
Prognostication
Therapeutic hypothermia
Cardio-pulmonary resuscitation

ABSTRACT

With increasing public education in basic life support and with the widespread use of automated defibrillators, post-cardiac arrest comatose patients represent a growing part of ICU admissions. However the prognosis remains very poor and only a very low proportion of these resuscitated patients will recover and will leave the hospital without major neurological impairments. Neurological dysfunction predominantly includes disorders of consciousness, and may also include other manifestations such as seizures, myoclonus status epilepticus and other forms of movement disorders including post-anoxic myoclonus. In the most severe cases, coma may be irreversible or evolve towards a minimally conscious state, a vegetative state or even brain death. These severe conditions represent by far the leading cause of mortality and disability in such patients. Currently, early use of mild therapeutic hypothermia is the only treatment that demonstrated its ability to decrease neurological consequences and to improve the prognosis. Prognostication outcome is still mainly based on a rigorous clinical evaluation coupled with neuro-physiological investigations, but brain functional imaging could become a valuable tool in the near future. Clinical research focusing on survivors should be strongly encouraged in order to assess the mid- and long-terms outcome of survivors and to evaluate the impact of new treatments or strategies.

Mots clés :
Arrêt cardiaque
Évaluation pronostique
Hypothermie thérapeutique
Réanimation cardiopulmonaire

RÉSUMÉ

La prise en charge de patients réanimés avec succès d'un arrêt cardiaque extrahospitalier représente une part d'activité de plus en plus importante en réanimation, grâce notamment aux progrès réalisés en matière d'éducation du grand publique pour la réanimation cardiopulmonaire et la diffusion des défibrillateurs semi-automatiques. Cependant, le pronostic reste sombre et seulement une faible proportion de ces patients réanimés avec succès sortiront de l'hôpital sans séquelle neurologique majeure et retrouveront leur état neurologique antérieur. Les séquelles neurologiques sont dominées par les troubles de la conscience, mais peuvent également se présenter sous la forme de crises convulsives, d'état de mal épileptique et d'autres formes de mouvements anormaux comme les myoclonies post-anoxiques. Dans les cas les plus sévères, le coma est irréversible ou évolue vers un état pauci-relationnel, un état végétatif ou la mort encéphalique. Ces séquelles lourdes représentent la principale cause de mortalité et de handicap chez ces patients. Actuellement, l'hypothermie thérapeutique est le seul traitement ayant démontré son efficacité pour la diminution des séquelles neurologiques et l'amélioration du pronostic. Prédire l'évolution neurologique est toujours actuellement basée sur une évaluation neurologique clinique rigoureuse, associée aux explorations neurophysiologiques, mais

☆ French NeuroAnesthesia and Intensive Care society Meeting, Paris, November 2013, 21st and 22nd: "The acutely brain-injured patient: consciousness and neuroethic".
☆☆ This article is published under the responsibility of the Scientific Committee of the "35e Journée de l'Association des neuro-anesthésistes réanimateurs de langue françaises" de la SFAR. The editorial board of the *Annales françaises d'anesthésie et de réanimation* was not involved in the conception and validation of its content.

* Corresponding author.
E-mail address: alain.cariou@cch.aphp.fr (A. Cariou).

0750-7658/$ – see front matter
http://dx.doi.org/10.1016/j.annfar.2013.11.003

l'imagerie fonctionnelle cérébrale pourrait devenir un outil pertinent à l'avenir. Les études s'intéressant particulièrement aux survivants doivent être soutenues afin d'évaluer le devenir à moyen et long termes de ces patients et l'impact des nouvelles stratégies thérapeutiques.

1. Scope of the problem

Sudden cardiac death remains a major public health issue, as highlighted by epidemiological data showing that nearly 40,000 people are supported for out-of-hospital cardiac arrest (CA) in France each year. Even more problematic, only a very low proportion of resuscitated patients will recover and will leave the hospital without major neurological impairments [1–6]. Across the different studies focusing on early prognostic factors, a common finding is that the frequency and intensity of post-CA complications depend mainly on the quality and duration of cardio-pulmonary resuscitation (CPR). Nevertheless, with increasing public education in basic life support and with the widespread use of automated defibrillators, post-CA comatose patients have now become more and more frequent among ICU population. After traumatic brain injury and drug overdose, CA is considered to be the third cause of coma in Western countries, a fact that is associated with a multitude of medical, ethical, and economic questions. In parallel, experimental and clinical research has focused on a better comprehension of the mechanisms responsible for post-CA brain damages, as well as on the development of several neuroprotective strategies able to improve outcome of these patients.

2. Pathophysiology of brain damages

Contrary to traumatic or focal ischemic causes of coma, CA provokes a global ischemic insult to the brain. The extent of cerebral damage is largely influenced by the duration of interrupted cerebral blood flow. Accordingly, minimizing both the arrest time (“no-flow”) and CPR time (“low-flow”) are key issues. Schematically, cerebral oxygen stores and consciousness are lost within 20 seconds of the onset of CA, while glucose and adenosine triphosphate (ATP) stores are lost within 5 minutes. Cerebral ischemia then triggers a complex cascade of pathways, which lead to neuronal death and clinically translates in post-CA coma [7]. Of importance, it is now well demonstrated that brain injury continues even after restoration of cerebral perfusion and oxygenation, in a process known as “reperfusion injury”. The injurious mechanisms involved in this process are partially modulated by brain temperature, as hyperthermia may worsen the anoxic insult [8]. Finally, even after the restoration of adequate blood supply and cellular energy stores, a global hypoperfusion state is commonly observed, called the “no reflow phenomenon”, which results from the combination of increased blood viscosity, microvascular alterations and altered cerebral flow regulation [9]. This hypoperfusion, potentially associated with other secondary injuries, such as alterations in blood glucose concentrations, abnormal carbon dioxide levels, seizures and hyperthermia, may further lead to secondary brain injury and may worsen initial brain damages.

3. Clinical consequences of post-CA brain damages

CA and subsequent brain damages may result in heterogeneous neurological signs and symptoms, reflecting the different susceptibility of cerebral areas to anoxia. These differences could be related either to the poor circulation, to the higher energy requirement and glutamate release of cerebral cells or to the lower expression of some proteins, such as heat-shock proteins, which confer a relative tolerance to ischemia, in certain vulnerable brain regions [10,11]. Nevertheless, neurological dysfunction in post-CA patients predominantly includes disorders of consciousness, which ranges from mild confusion (difficult concentrating, poor judgment or euphoria) and delirium to coma [10], depending on the injury on subcortical and brainstem functions. Symptoms observed in the first hours and days may also include other manifestations of neurological dysfunction, such as seizures, myoclonus status epilepticus and other forms of movement disorders including post-anoxic myoclonus. In the most severe cases, coma may be irreversible or evolve towards a minimally conscious state, a vegetative state or even brain death. These severe conditions represent the leading cause of mortality and disability in such patients. In a recent French cohort, while 66% of patients died after ICU admission – a rate that is consistent with studies from other Western countries [1–5] –, brain damages accounted for around two thirds of fatalities. In survivors, long-term symptoms may be very various and include memory and cognitive impairment, late-onset seizures and cerebral palsy.

4. Prevention of post-CA brain damages

In the recent years, the evidence of further cerebral damage occurring during the reperfusion phase encouraged intense research aiming to limit the worsening of the neurological lesions occurring during the post-CA period. This culminated 10 years ago with the demonstration that post-CA cooling was an effective treatment in these patients.

4.1. Therapeutic hypothermia

Many experimental data previously showed that mild hypothermia can exert neuroprotective effects through multiple mechanisms of action, i.e. decrease of cerebral metabolism, reduction of apoptosis and mitochondrial dysfunction, reduction of the cerebral excitatory cascade, decrease of local inflammatory response, reduction of free oxygen radicals production, and decrease of vascular and membrane permeability. These convergent experimental effects were confirmed by two landmark clinical studies published in 2002 [12,13]. In both trials, the implementation of mild hypothermia permitted to achieve a survival rate without major sequel in around 40–50% of a highly “selected” population (out-of-hospital CA with an initial rhythm of ventricular fibrillation in front of a bystander). Their publication was decisive and led to a rapid change in international recommendations on the management of patients surviving after CA. It is now strongly recommended to routinely induce moderate hypothermia (32 to 34 °C) for 12 to 24 hours in any comatose adult successfully resuscitated after out-of-hospital CA caused by ventricular fibrillation/tachycardia [14]. If numerous clinical studies further confirmed the benefit of this treatment in shockable patients, the level of evidence remains weaker in patients presenting an initial non-shockable rhythm [15]. In these patients, some recent data suggest a lack of neurological benefit [16]. Considering that the risk-benefit ratio is sufficiently favorable, guidelines recommend discussing its use on a case-by-case basis.