Arrêt cardiaque
Nouveautés thérapeutiques : Epo et ciclosporine

Alain Cariou
Pôle Réanimations – Urgences : Hôpital Cochin
Université Paris Descartes – INSERM U970
ARRÊT CARDIAQUE :
1 VIE = 3 GESTES
Cardiac arrest management: hope and fears

Comparison of published VF OHCA survival percentages in various US cities before (white bars) and after (black bars) an EMS–based early defibrillation program was instituted.

New cases/yr in the US

- Persistent Vegetative State
- Minimally Conscious State
- Traumatic Brain Injury
- Cardiac Arrest Survivors

Thurman D et al. JAMA 1999
Outcome of cardiac arrest victims

- Pre-hospital period:
  - ≈ 30,000 SCA/yrs
  - 60% CPR
  - 15-20% ROSC...

- Post-resuscitation:
  - Post-cardiac arrest shock
  - Brain damages

- Long-term:
  - 3-5% survivors
  - 3% no or minor sequel

...and ICU admission
Immediate
Early
Intermediate
Recovery
Rehabilitation

ROSC
20 min
6-12 hours
72 hours
Discharge

Post-cardiac arrest disease
ILCOR Consensus Statement

Treatment targets

Persistent precipitating pathology
Systemic ischemia-reperfusion
Post-CA myocardial dysfunction
Post-anoxic brain injury
Spectre des conséquences neurologiques après arrêt cardiaque

- Conscience
- Coma
- Mort cérébrale
- EVE persistant
- EVE permanent
- ECM
- ECM permanent
- Conscience normale
- Séquelles majeures

ICU mortality after cardiac arrest: the relative contribution of shock and brain injury in a large cohort

Lemiale V, Dumas F, Mongardon N, Giovanetti O, Charpentier J, Chiche JD, Carli P, Mira JP, Nolan J, Cariou A.

![ICU mortality chart]

- Deaths to neurological injury
- Deaths related to post cardiac arrest shock
- Survivors
Time-course of brain injury caused by transient cardiac arrest

Stop cerebral circulation

No Flow

Depletion in neuronal O$_2$ stores

Loss of consciousness

4-6 minutes

Complete loss of in brain glucose and ATP stores

Neuronal membrane and pumps dysfunction:
- influx of calcium
- lactate acidosis
- glutamate release
- free fatty acids occurrence
- oxydative stress
- inflammatory response

Low Flow

Reperfusion

Reoxygenation-induced reactions

Free radical triggered injury & excito-toxicity:
- lipid peroxydation
- primary necrosis
- apoptosis

ROSC
The Big Chill

Lowering the body’s temperature improves the chances of surviving a cardiac arrest and other types of trauma; but as cold therapy expands, researchers are struggling to understand why and for whom it works.
Time-course of injury mechanisms after CA

- Ion homeostasis / neuroexcitotoxic cascade
- Mitochondrial injury - dysfunction
- Free radical production / reperfusion injury
- Coagulation activation / microthrombi
- Inflammatory response
- Permeability of the BBB / oedema / cellular mb permeability
- Apoptosis
- Cerebral thermopooling

First minutes
First hours
First days
First weeks
Neuroprotection after cardiac arrest: what’s new?

- Calcium channel antagonists
- NMDA receptor antagonists
- Dexanabinol
- Lubeluzole (Nitrous oxide modulator)
- CDP-choline
- Tirilizad (free radical scavenger)
- Anti-ICAM-1 antibody
- GM-1 ganglioside
- Clomethiazole
- Fosphenytoin
- Piracetam

Erythropoietin
Ciclosporine

?
Cell Death

Richard S. Hotchkiss, M.D., Andreas Strasser, Ph.D., Jonathan E. McDunn, Ph.D., and Paul E. Swanson, M.D.
Inhibition of mitochondrial permeability transition pore opening: translation to patients

Ludovic Gomez¹, Bo Li¹, Nathan Mewton², Ingrid Sanchez², Christophe Piot³,⁴, Meier Elbaz⁵,⁶, and Michel Ovize¹,²*
Effect of Cyclosporine on Reperfusion Injury in Acute Myocardial Infarction

Piot C et al. NEJM 2008
Myocardial Reperfusion Injury


- **Myocardial ischemia in absence of reperfusion**: Infarct size, 70%
- **Myocardial ischemia with reperfusion**: Reperfusion reduces infarct size by 40%. Part of the remaining 30% infarct is due to lethal reperfusion injury and is therefore preventable.
- **Myocardial ischemia with reperfusion and cardioprotection**: Preventing lethal reperfusion injury reduces infarct size by a further 25%, realizing the full benefits of reperfusion.
Inhibition of mitochondrial permeability transition to prevent the post-cardiac arrest syndrome: a pre-clinical study

Martin Cour¹,²,³, Joseph Loufouat¹, Mélanie Paillard¹, Lionel Augeul¹, Joëlle Goudable⁴, Michel Ovize¹,³, and Laurent Argaud¹,²,³*

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[Diagram and graphs illustrating the study's findings]
Brain injury: secondary injury cascade

Cyclosporine A in Cardiac Arrest (CYRUS)

This study is currently recruiting participants.

Verified May 2012 by Hospices Civils de Lyon

Sponsor:
Hospices Civils de Lyon

Information provided by (Responsible Party):
Hospices Civils de Lyon

ClinicalTrials.gov Identifier:
NCT01595958

First received: April 30, 2012
Last updated: May 9, 2012
Last verified: May 2012

Purpose

The investigators hypothesised that cyclosporine A administration at the onset of cardiopulmonary resuscitation, by inhibiting the mitochondrial permeability transition pore, could prevent the post cardiac arrest syndrome and improve outcomes.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
</tr>
</thead>
</table>
| Non Shockable Out of Hospital Cardiac Arrest | Drug: Cyclosporine A  
Procedure: cardio-pulmonary resuscitation | Phase 3 |

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Parallel Assignment
Masking: Single Blind (Outcomes Assessor)
Primary Purpose: Treatment

Official Title: Cyclosporine A in Non-shockable Out-of-hospital Cardiac Arrest ResUScitation
# Neuroprotection after cardiac arrest: what’s new?

- Calcium channel antagonists
- NMDA receptor antagonists
- Dexanabinol
- Lubeluzole (Nitrous oxide modulator)
- CDP-choline
- Tirilizad (free radical scavenger)
- Anti-ICAM-1 antibody
- GM-1 ganglioside
- Clomethiazole
- Fosphenytoin
- Piracetam

Erythropoietin
Ciclosporine

?
« A humoral factor regulates the red blood cell production (...) »

Paul Carnot
(1869-1957)

« Sur l’activité hémopoïétique du sérum au cours de la régénération du sang »

C R Acad Sci Paris 1906; 143: 432-435
Potential mechanisms of Epo cytoprotection

- Antiapoptotic
- Antioxidant
- Glutamate-inhibitor
- Anti-inflammatory
- Neurotrophic
- Stem cell–modulatory
- Angiogenic

Clinical effects?
Intravenous Erythropoietin in Patients With ST-Segment Elevation Myocardial Infarction
REVEAL: A Randomized Controlled Trial

Infarct size (cardiac magnetic resonance)

Najjar SS et al. JAMA 2011
Cardioprotective effects of erythropoietin on postresuscitation myocardial dysfunction in appropriate therapeutic windows

Chien-Hua Huang, MD, PhD; Chiung-Yuan Hsu, MD; Min-Shan Tsai, MD; Tzung-Dau Wang, MD, PhD; Wei-Tien Chang, MD, PhD; Wen-Jone Chen, MD, PhD

Crit Care Med 2008 Vol. 36, No. 11 (Suppl.)
Epo and the Epo-receptor (Epo-R) are expressed constitutively in neurons.

Hypoxia–ischemia affects erythropoietin and erythropoietin receptor expression pattern in the neonatal rat brain.

Hypoxia–ischemia only marginally affected EPO expression.

In contrast, EPOR was dramatically upregulated within 24 h after hypoxia–ischemia.

Spandou et al. Brain Res 2004
# Erythropoietin and the hypoxic brain

<table>
<thead>
<tr>
<th>Cell types</th>
<th>EPO Rodents</th>
<th>EPO Humans</th>
<th>EPO receptor Rodents</th>
<th>EPO receptor Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In vitro</td>
<td>In vivo</td>
<td>In vitro</td>
<td>In vivo</td>
</tr>
<tr>
<td>Neurones</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Astrocytes</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Microglial cells</td>
<td>NA</td>
<td>NA</td>
<td>-</td>
<td>NA</td>
</tr>
<tr>
<td>Oligodendrocytes</td>
<td>+</td>
<td>NA</td>
<td>-</td>
<td>NA</td>
</tr>
<tr>
<td>Endothelial cells</td>
<td>-</td>
<td>?</td>
<td>NA</td>
<td>?</td>
</tr>
</tbody>
</table>

Erythropoietin crosses the blood–brain barrier to protect against experimental brain injury

Michael L. Brines*†, Pietro Ghezzi*†, Sonja Keenan*, Davide Agnello†, Nihal C. de Lanerolle§, Carla Cerami*, Loretta M. Itri†, and Anthony Cerami*

Systemic administration of rhEpo attenuates injury after blunt trauma or cerebral artery occlusion

Brines et al. PNAS 2000
Erythropoietin administration protects retinal neurons from acute ischemia-reperfusion injury

Anna K. Junk*, Antonios Mammis*, Sean I. Savitz†, Manjeet Singh*, Steven Roth†, Samit Malhotra*, Pearl S. Rosenbaum*, Anthony Cerami*, Michael Brines†, and Daniel M. Rosenbaum*,**

Contrôles Ischémie Ischémie
ILM GCL IPL INL OPL ONL OLM
Epo pré Epo pré

Junk et al. PNAS 2002
<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>Animal</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurones</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral ischemia</td>
<td>Rat, mouse, gerbil</td>
<td>Neuronal survival increased, learning ability improved; ischemic tolerance developed</td>
</tr>
<tr>
<td>Retinal ischemia</td>
<td>Rat, mouse</td>
<td>Photoreceptor and retinal ganglion cell apoptosis decreased</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>Rat</td>
<td>Motor neuronal apoptosis and inflammation decreased; neuronal function improved</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>Rabbit</td>
<td>Neuronal function and blood flow Improved</td>
</tr>
<tr>
<td>Peripheral nerve injury</td>
<td>Rat</td>
<td>Spinal neuronal apoptosis decreased; neuronal myelin repair fostered</td>
</tr>
<tr>
<td>Oxidative stress injury</td>
<td>Rat</td>
<td>DNA fragmentation, PS exposure, free radical production, and caspase activity decreased</td>
</tr>
<tr>
<td>Glutamate toxicity</td>
<td>Rat</td>
<td>Glutamate release decreased; neuronal survival increased</td>
</tr>
<tr>
<td>Development and maturation</td>
<td>Mouse</td>
<td>Apoptosis decreased; neuronal progenitor stem cell number increased</td>
</tr>
<tr>
<td><strong>Microglia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral inflammation</td>
<td>Rat</td>
<td>Cellular inflammation decreased; cytokine release diminished</td>
</tr>
<tr>
<td><strong>Vascular cells</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxidative stress injury</td>
<td>Rat</td>
<td>DNA fragmentation, PS exposure, free radical production, and caspase activity decreased; EC survival increased</td>
</tr>
</tbody>
</table>
EPO: Different actions

- antiapoptotic
- antioxidant
- glutamate-inhibitor
- anti-inflammatory
- neurotrophic
- stem cell–modulatory
- angiogenic

Question: ?
Epo : perspectives thérapeutiques en neuroprotection

- Souffrance cérébrale néo-natale
- Traumatisme
  - Médullaire
  - Cérébral
- Hémorragie méningée
- Pathologies neuro-dégénératives
- Ischémie-reperfusion
  - Focale : accident ischémique
  - Globale : arrêt cardiaque réanimé
Recombinant Human Erythropoietin in the Treatment of Acute Ischemic Stroke

Hannelore Ehrenreich, MD, DVM; Karin Weissenborn, MD; Hilmar Prange, MD; Dietmar Schneider, MD; Christian Weimar, MD; Katja Wartenberg, MD; Peter D. Schelling, MD; Matthias Bohn, PhD; Harald Becker, MD; Martin Wegrzyn, BS; Peter Jähnig, MBA; Manfred Herrmann, MD; Michael Knauth, MD; Mathias Bähr, MD; Wolfgang Heide, MD; Armin Wagner, MD; Stefan Schwab, MD; Heinz Reichmann, MD; Günther Schwendemann, MD; Reinhard Dengler, MD; Andreas Kastrup, MD; Claudia Bartels, PhD; for the EPO Stroke Trial Group

**A**
Barthel Index score Day 90

- EPO
  - 95-100: 37.9
  - 55-90: 16.4
  - 0-50: 45.7
- Placebo
  - 95-100: 39.1
  - 55-90: 19.2
  - 0-50: 41.7

p = 0.58

**B**
Modified Rankin Scale score Day 90

- EPO
  - 0: 9.4
  - 1: 16.4
  - 2: 14.1
  - 3: 12.1
  - 4: 18.4
  - 5 or death: 29.7
- Placebo
  - 0: 9.8
  - 1: 21.1
  - 2: 10.2
  - 3: 13.2
  - 4: 19.9
  - 5 or death: 26.9

p = 0.53
“In OHCA patients treated by Epo and hypothermia, we observed a high survival rate with no or minor cerebral sequels but we observed potential hematological side effects. Future efficacy studies of Epo in OHCA patients should pay a particular attention to these events.”

Epo-ACR 02

<table>
<thead>
<tr>
<th></th>
<th>Epo-treated (n=18)</th>
<th>Controls (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPC 1, n (%)</td>
<td>10 (55)</td>
<td>15 (37.5)</td>
</tr>
<tr>
<td>CPC 2, 3 or 4, n (%)</td>
<td>0</td>
<td>4 (10)</td>
</tr>
<tr>
<td>CPC 5 (%)</td>
<td>8 (45)</td>
<td>21 (52.5)</td>
</tr>
</tbody>
</table>
Essai Epo-ACR-02 : **Dessin**

Durée de participation d’un patient : **60 jours**

**Diagramme :**

1. **Groupe contrôle**
   - Inclusion Randomisation
   - Traitement standard

2. **Groupe interventionnel**
   - Epo 40.000 UI x 5 + Tt standard
   - À 12h d’intervalle

3. **Évaluation par médecin indépendant**
   - Score CPC
   - Evaluation à J48, J7, J28, J60

**Période d’inclusion** → **Période de traitement** → **Période d’évaluation**
Essai Epo-ACR-02 :
Calendrier & état d’avancement

Inclusions théoriques cumulées
Inclusions réelles cumulées

426