Neurological prognosis after cardiac resuscitation

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2-AG: 2-Arachidonoyl Glycerol

ADL: Activity of Daily Living

AMPA: Amino-3-(5-Methyl-3-oxo-1,2-oxazol-4-yl) Propionic Acid

APACHE: Acute Physiology and Chronic Health Evaluation

ARDS: Acute Respiratory Distress Syndrome

BBB: Blood-Brain Barrier

BDNF: Brain-Derived Neurotrophic Factor

BE: Base Excess

BMR: Basal Metabolic Rate

BNP: Brain Natriuretic Peptide

CA: Cardiac Arrest

CA-ROSC: Cardiac Arrest to Return Of Spontaneous Circulation

CBF: Cerebral Blood Flow

CI: Confidence Interval

CKBB: Creatine Kinase BB

$CMRO_2$: Cerebral Metabolic Rate for oxygen

CNS: Central Nervous System

CPA: Cardiopulmonary Arrest

CPC: Cerebral Performance Category

CPP: Cerebral Perfusion Pressure

CPR: Cardiopulmonary Resuscitation

CT: Computed Tomographic

CVR: Cerebrovascular Resistance

DAR: Duration of Arrest

DDAVP: 1-Desamino-8-D-Arginine Vasopressin

DI: Diabetes Insipidus

DWI: Diffusion-Weighted Imaging

EEG: Electroencephalogram

ELAM: Endothelial Leukocyte Adhesion Molecules

eNOS: Endothelial NOS

EP: Evoked Potential

Epo: Erythropoietin

Epo-R: Erythropoietin Receptor

$ETCO_2$: End-Tidal carbon dioxide

FGF: Fibroblastic Growth Factors

FLAIR: Fluid Attenuated Inversion Recovery

FPR: False Positive Rate

GABA: G-Aminobutyric Acid

GCS: Glasgow Coma Scale

GDNF: Glial-Derived Growth Factor

GFs: Growth Factors

GM: Grey Matter

GOS: Glasgow Outcome Score

GP-CPC: Glasgow-Pittsburgh Cerebral Performance Categories

HSPs: Heat Shock Proteins

ICAM: Intracellular Adhesion Molecules

ICE: Interleukins Converting Enzyme.

ICP: Intracranial Pressure

ICU: Intensive Care Unit

IGF-I: Insulin-like Growth Factor-I

IMM: Inner Mitochondrial Membrane

IPL: Inter-Peak Latency

JVP: Jugular Venous Pressure

MAP: Mean Arterial Pressure

MBS: Man in a Barrel Syndrome

MRI: Magnetic Resonance Imaging

MSE: Neuron-Specific Enolase

mtPTP: mitochondrial Permeability Transition Pore

NFL: Neurofilament protein

NGF: Nerve Growth Factor

NMDA: N-Methyl-D-Aspartate

NNOS: Neuronal NOS

NO: Nitric Oxide

NOS: NO Synthase

NSE: Neuron-Specific Enolase

OHCA: Out-of-Hospital Cardiac Arrest

PBI: Post-cardiac arrest Brain Injury

$PbrO_2$: Partial pressure brain tissue oxygen tension

PCI: Percutaneous Coronary Intervention

PET: Positron Emission Tomography

PKC: Protien Kinase C

PROPAC: Prognosis in Post-Anoxic Coma study group

PVS: Permenant Vegetative State

QEEG: Quantitative EEG

ROS: Reactive Oxygen Species

ROSC: Restoration Of Spontaneous Circulation

rSO_2: Regional cerebral oxygen Saturation

S-100B: S-100 calcium binding protein B

SE: Sulcal Effacement

SEP: Sensory evoked potentials

SIRS: Systemic Inflammatory Response Syndrome

$SjVO_2$: O_2 jugular venous Saturation

SSEP: Somatosensory Evoked Potential

SSRI: Serotonin-Specific Reuptake Inhibtors

TBI: Traumatic Brain Injury

TGF: Transforming Growth Factor

WM: White Matter

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Introduction

Cardiac arrest (CA) is the leading cause of death in Europe and the USA affecting about 750.000 people annually. The rate of restoration of spontaneous circulation (ROSC) has risen in the past decades due to considerable efforts to establish and improve of rescue chains comprising both layman and professional emergency services **(Becker et al., 2008)**. The trade-off of improved ROSC may be an increasing number of patient suffering from various degrees of brain damage after successful resuscitation **(Puttgen et al., 2009)**.

Several clinical outcome scores, electrophysiological techniques, and imaging methods have attempted to predict the presence, degree and course of neurological outcome after CA **(Wijdicks et al., 2006)**. This has been complemented by neural tissue derived biomarkers such as neuron-specific enolase (NSE) and S-100B **(Shinozaki al., 2009)**.

Brain protection therapy for patients with out-of-hospital cardiac arrest (OHCA) has greatly improved in recent years due to the development of emergency post-cardiac arrest interventions e.g. mild therapeutic hypothermia, early percutaneous coronary intervention and extracorporeal cardiopulmonary resuscitation (CPR) .**(Nagao et al., 2000).**

However, the indications for these costly interventions have not yet been established mainly because of difficulty in prognosticating neurological outcomes at hospital discharge on hospital arrival **(Booth et al., 2004)**.

Aim of the work

The aim of the work is to spot light on predictors and prognosis of neurological outcome after cardiac arrest and how to improve the outcome.

Pathophysiology of brain injury after cardiac arrest

The human brain has about 10,000,000,000 neurons, each of which makes about 1000 synaptic contacts with other neurons. To maintain physiologic function of the neuronal network, the brain requires much energy **(Mitani et al., 1991)**.

When the duration of ischemia is sufficiently long, acute necrosis occurs in glia and endothelial cells as well as neurons, and there is no room to apply therapies for degenerated neurons **(Mitani et al., 1991)**.

Brain injury is common due to cardiac arrest or profound hypotention. Brain injury can occur as consequence of reduction in either cerebral blood flow (CBF) or oxygen supply or both**. (Nolan et al., 2008).**

Physiology of Cerebral Blood Flow:

Normal blood flow through the brain of the adult person averages 50 to 65 ml /100 g of brain tissue/min. For the entire brain, this amounts to 750 to 900 ml/min, or 15% of the resting cardiac output. The lack of CBF has immediate impact on the brain's metabolic condition. **(Guyton and John, 2006)**. (table 1)

Table (1): Brain metabolic conditions and relationship to CBF**(Forster et al., 1999)**

CBF (mL per 100g tissue/min)	**Brain metabolic condition**
45–65	Resting brain (normal)
75–80	Normal grey matter CBF
20–30	Normal white matter CBF
25	EEG suppression (flat line)
10 or less	Disrupted cell metabolism, membrane transport, cell death

CBF is calculated by cerebral perfusion pressure (CPP), divided by cerebrovascular resistance (CVR). CPP is calculated by mean arterial pressure (MAP) minus intracranial pressure (ICP) or jugular venous pressure (JVP). When ICP (or JVP) equals zero, CPP is directly related to the MAP. Fluctuations in CPP (60-140 mmHg) are compensated for at the cerebral arteriolar level (CVR) to provide constant CBF, termed cerebral autoregulation**.** Cardiac arrest causes the MAP (and thus CPP and CBF) to approach zero. **(Forster et al., 1999)**.

Autoregulation of cerebral blood flow when the arterial pressure changes:

Cerebral blood flow is "autoregulated" extremely well between arterial pressure limits of 60 and 140 mmHg. That is, mean arterial pressure can be decreased acutely to as low as 60 mmHg or increased to as high as 140 mmHg without significant change in cerebral blood flow. In people who have hypertension, autoregulation of cerebral blood flow occurs even when the mean arterial pressure rises to as high as 160 to 180 mmHg **(Guyton and John, 2006)**.

Regulation of cerebral blood flow:

As in most other vascular areas of the body, cerebral blood flow is highly related to metabolism of the tissue. At least three metabolic factors have potent effects in controlling cerebral blood flow:

1. Carbon dioxide concentration.

2. Hydrogen ion concentration.

3. Oxygen concentration.

(Guyton and John, 2006)

Oxygen deficiency as a regulator of cerebral blood flow:

O_2 consumption by the human brain (cerebral metabolic rate for O_2, $CMRO_2$) averages about 3.5 mL/100 g of brain/min (49 mL/min for the whole brain) in an adult. This figure represents approximately 20% of the total body resting O_2 consumption. The brain is extremely sensitive to hypoxia and occlusion of its blood supply produces unconsciousness in as short a period as 10 sec. The vegetative structures in the brain stem are more resistant to hypoxia than the cerebral cortex, and patients may recover from accidents such as cardiac arrest and other conditions causing fairly prolonged hypoxia with normal vegetative functions but severe, permanent intellectual deficiencies. The basal ganglia use O_2 at a very high rate, and intellectual deficits can be produced by chronic hypoxia. The thalamus and the inferior colliculus are also very susceptible to hypoxic damage. **(Bajetto et al., 2001)**

If blood flow to the brain ever becomes insufficient to supply this needed amount of oxygen, the oxygen deficiency mechanism for causing vasodilation immediately causes vasodilation, returning the brain blood flow and transport of oxygen to the cerebral tissues to near normal. **(Guyton and John, 2006)**.

Experiments have shown that a decrease in cerebral tissue P_{O_2} below about 30 mmHg (normal value is 35 to 40 mmHg) immediately begins to increase cerebral blood flow. This is because brain function becomes deranged at not much lower values of P_{O_2}, especially so at P_{O_2} levels below 20 mmHg. Even coma can result at these low levels. Thus, the oxygen mechanism for local regulation of cerebral blood flow is a very important protective response against diminished cerebral neuronal activity and, therefore, against derangement of mental capability **(Guyton and John, 2006)**.

Oxygen delivery depends on several variables including cardiac output, oxygen content of the blood, and concentration of haemoglobin and oxygen saturation of haemoglobin. When oxygen delivery drops below the metabolic demands of the tissue, ischaemia occurs **(Morris et al., 2005)**.

Pathophysiology of brain injury

Ischaemia and hypoxia cause pathologically and clinically distinct patterns of brain injury.

- Ischaemia (hypoxic–ischemic encephalopathy) describes a reduction in blood supply leading to decreased oxygen delivery, there is also limited or no removal of damaging cellular metabolites (eg, lactate, H+, glutamate) which contributes to severe brain injury.

- The neuronal pathophysiology of pure hypoxia (hypoxic encephalopathy) is different than that of cerebral hypoperfusion. Gas exchange is deficient with rising $PaCO_2$ and declining PaO_2 levels. Cerebral autoregulation adapts to rising $PaCO_2$ levels by vasodilatation, causing CBF to increase. Glucose and other nutrients are supplied and metabolic waste products are removed by systemic circulation. Isolated oxygen depletion eventually leads to depressed cellular energy metabolism, affecting synaptic activity and depletes neuronal gamma-aminobutyric acid within the CNS leading to seizures and myoclonus. Overall, the prognosis for isolated cerebral hypoxia, even prolonged cerebral hypoxia, may be better than cardiac arrest. **(Greer et al., 2006)**.

Hypoxic-ischemia encephalopathy:

Cerebral ischemia results from impaired (CBF) and leads to deprivation of both oxygen and glucose. Under resting but awake conditions, the metabolism of the brain accounts for about 15% of the total metabolism in the body, even though the mass of the brain is only 2% of the total body mass. Therefore, under resting conditions, brain metabolism per unit mass of tissue is about 7.5 times the average metabolism in non–nervous system tissues. **(Guyton and John, 2006)**.

Cells at the center of the ischemic focus, the ischemic core, are especially vulnerable and may die within minutes of ischemic onset. **(Kaufmann et al., 1999)**.