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PREDICTORS OF NEUROLOGICAL DISORDERS AFTER CARDIPULMONARY RESUSCITATION

Essay

Submitted for partial fulfillment of master degree
Of intensive Care
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2013

Acknowledgment

*First of all, all gratitude is due to **GOD** almighty for blessing this work until it has reached its end, as a part of this generous help, throughout my life.*

*Really I can hardly find the words to express my gratitude to **Prof. Dr. Bahaa Al- Din Ewes Hassan** professor of anesthesia and intensive care, faculty of medicine, Ain Shams University, for his supervision, continous help, encouragement throughout this work and tremendous effort he done in the meticulous revision of the whole work it is a great honor to work under his guidance and supervision.*

*I would like also to express my sincere appreciation and gratitude to **Dr. Fady Adib Abd El Malek** lecturer of Anethesia and Intensive care, Faculty of medicine, Ain Shams University, for his continous directions and support throughout the whole work.*

Lastly but not least, I dedicate this work to my family and my husband, whom without their sincere emotional support, pushing me forward this work would not have ever been completed.

Walaa Hazem Abd Al Hakam

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List of Abbreviations

ABC	ATP Binding Cassette
ACS	Acute Coronary Syndrome
ADC	Apparent Diffusion Coefficient
APACHE	Acute Physiology and Chronic Health Evaluation
ARDS	Acute Respiratory Distress Syndrome
ATP	Adenosine Triphosphate
BBB	Blood Brain Barrier
BCL- 2	B-cell lymphoma-2
BCRP	breast cancer resistance protein
CA	Cardiac Arrest
Ca	Calcium
CAD	Coronary Artery Disease
CNS	Central Nervous System
CoA	Coenzyme A
CPP	Cerebral Perfusion Pressure
CPR	Cardiopulmonary Resuscitation
CSF	Cerebrospinal fluid
CSVS	Cerebrospinal Venous System
CT	Computed Tomography
CVO	Circum Ventricular Organs
Da	Dalton (It is the standard unit indicating Mass)
DO_2	Oxygen Delivery
DWI	Diffusion Weighted Imaging
ECMO	Extra Corporeal Membrane Oxygenation
EEG	Electroencephalography
$ETCO_2$	End Tidal Carbon dioxide
FIO_2	Fractional Inspired Oxygen
FPR	False Positive Rate
HACA	Hypothermia After Cardiac Arrest
ICU	Intensive Care Unit
IEL	Internal Elastic Lamina
ISF	Interstitial fluid
K	Potassium
LDL	low-density lipoprotein
MAP	Mean Arterial Pressure

List of Abbreviations (Cont.)

MDR	Multidrug resistance
MR Spectroscopy	Magnetic Resonance Spectroscopy
MRI	Magnetic Resonance Imaging
Na	Sodium
NADH	Nicotinamide Adenine Dinucleotide H (reduced form)
NIRS	Near Infrared Spectroscopy
NRCPR	National Registry of Cardiopulmonary Resuscitation
OHCA	Out-of-hospital cardiac arrest
PDHC	Pyruvate Dehydrogenase Complex
P-gp	P-glycoprotein
PO_2	Pressure of O_2
ROIs	Regions Of Interests
ROSC	Return of spontaneous Circulation
$ScvO_2$	Central Venous Oxygen Saturation
SPECT	Single Photon Emission Computed Tomography
SSEP	Somatosensory Evoked Potential
SSS	Superior Sagittal Sinus
TCA	Tricarboxylic Acid
VVS	Vertebral Venous System

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Introduction

Patients successfully resuscitated from cardiac arrest are at high risk of increased mortality and their long term outcome is often complicated by developing severe neurological disorders up to a persistent vegetative state. Today cardiac arrest is the third leading cause of coma, second only to trauma and drug overdose **(Berek K and Mayr M, 2004)**

Brain damage is one of the major causes of morbidity and mortality after cardiac arrest and cardiopulmonary resuscitation in hospitalized patients. **(Peberdy MA et al., 2010)**

Reperfusion following the return of spontaneous circulation after complete whole-body ischemia is an unnatural pathophysiological state created by successful cardiopulmonary resuscitation. Systemic ischemia/ reperfusion response induces generalized tissue damage with a release of reactive oxygen species and endothelial-leukocyte interaction, resulting in a systemic inflammatory response, endothelial activation and injury and coagulation abnormalities. This so-called post-cardiac arrest syndrome shares many features with severe sepsis and may complicate the clinical course of resuscitated patients at the intensive care unit **(Adrie C et al., 2002)**

Post cardiac arrest care has significant potential to reduce early mortality caused by hemodynamic instability and later morbidity and mortality from multiorgan failure and brain injury **(Neumar RW et al., 2008)**

However, many patients will remain permanently unresponsive, or remain permanently unable to perform independent activities. Early assessment of brain damage and prediction of cerebral outcome after cardiac arrest has a major ethical and socioeconomic implication & may affect post arrest treatment strategies. The main determinant used by clinicians to

prognosticate for patients with brain dysfunction has been the clinical neurological examination Including Glasgow Coma Scale brain stem reflexes and vestibular reflexes, as well as assessing for seizure or myoclonic activity, EEG, Evoked Potentials and neuroimaging studies may also play a role in predicting the outcome. **(Teasdale G et al., 1974)**

Several biochemical markers of hypoxic brain damage have been explored as early predictors of poor outcome in comatose cardiac arrest survivors; neuron-specific enolase, and S-100 have been found to be the most promising. **(Fogel W et al., 1997)**

Aim of The Work

This essay aims to discuss the pathophysiology of ischemic brain injury and the various clinical, electrophysiological, biomarkers and neuroimaging modalities that may early predict the neurological outcome after cardiac arrest, cardiopulmonary resuscitation and return of spontaneous circulation.

Anatomy of the cerebral circulation

The Arteries

The brain is one of the most highly perfused organs in the body. It is therefore not surprising that the arterial blood supply to the human brain consists of two pairs of large arteries, the right and left internal carotid and the right and left vertebral arteries (Figure 1). **(Jones EG, 1970)**

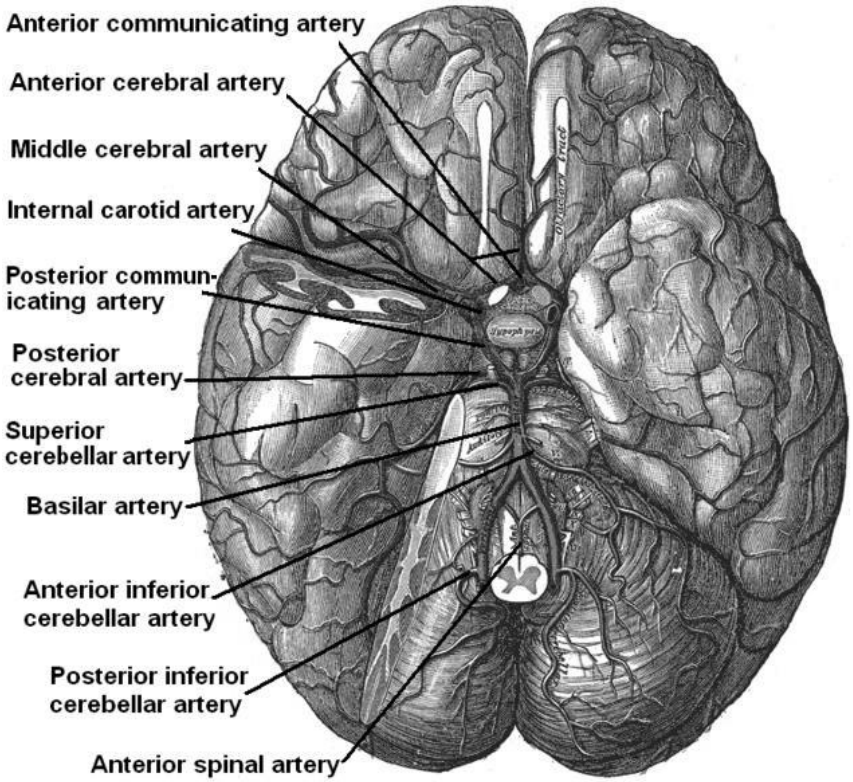

Figure 1: The arteries of the base of the brain (Gray's Anatomy, 2008)

The internal carotid arteries principally supply the cerebrum, whereas the two vertebral arteries join distally to form the basilar artery. Branches of the vertebral and basilar arteries supply blood for the cerebellum and brain stem. Proximally, the basilar artery joins the two internal carotid arteries and other

communicating arteries to form a complete anastomotic ring at the base of the brain known as the circle of Willis, named after Sir Thomas Willis who described the arterial circle (circulus arteriosus cerebri). **(Cipolla MJ et al., 2004)**

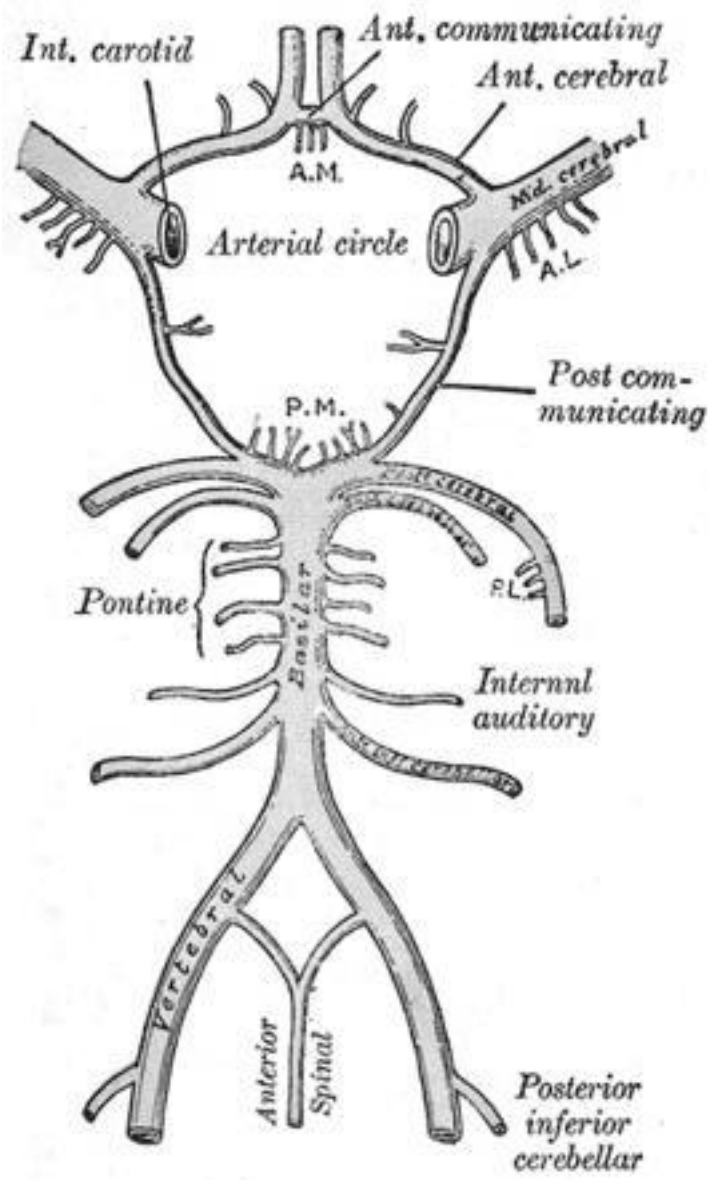

Figure 2: The arterial circulation at the base of the brain and circle of Willis (Gray's Anatomy, 2008)

The circle of Willis gives rise to three pairs of main arteries, the anterior, middle, and posterior cerebral arteries, which divide into progressively smaller arteries and arterioles that run along the surface until they penetrate the brain tissue to supply blood to the corresponding regions of the cerebral cortex (Figure 2). **(Abbott NJ, 2000)**

Cerebral Vascular Architecture

The pial vessels are intracranial vessels on the surface of the brain within the pia–arachnoid (also known as the leptomeninges) or glia limitans (the outmost layer of the cortex comprised of astrocytic end-feet). **(Jones EG, 1970)**

Pial vessels are surrounded by cerebrospinal fluid (CSF) and give rise to smaller arteries that eventually penetrate into the brain tissue. Penetrating arterioles lie within the Virchow–Robin space and are structurally between pial and parenchymal arterioles. **(Cohen Z et al., 1996)**

The Virchow–Robin space is a continuation of the subarachnoid space and varies considerably in depth by species. The penetrating arteries become parenchymal arterioles once they penetrate into the brain tissue and become almost completely surrounded by astrocytic end-feet. **(Rennels M and Nelson E, 1975)**

Pial arteries on the brain surface have perivascular nerves that give rise to penetrating arteries within the Virchow–Robin space. As penetrating arterioles become parenchymal arterioles within the brain neuropil, they become associated with neurons. **(Cohen Z et al., 1996)**

There are several important structural and functional differences between pial arteries on the surface of the brain and smaller parenchymal arterioles. First, pial arteries receive perivascular innervation from the peripheral nervous system also

known as "extrinsic" innervation, whereas parenchymal arterioles are "intrinsically" innervated from within the brain neuropil. While parenchymal arterioles have only one layer of circumferentially oriented smooth muscle, they possess greater basal tone and are unresponsive to at least some neurotransmitters that can have large effects on upstream vessels (e.g., serotonin, norepinephrine) **(Cipolla MJ et al., 2004)**

Lastly, pial vessel architecture forms an effective collateral network such that occlusion of one vessel does not appreciably decrease cerebral blood flow. However, penetrating and parenchymal arterioles are long and largely unbranched such that occlusion of an individual arteriole results in significant reductions in flow and damage (infarction) to the surrounding local tissue. **(Nishimura N et al., 2007)**

Despite differences in vessel architecture, all vessels in the brain have endothelium that is highly specialized and has barrier properties that are in some ways more similar to epithelium than endothelium in the periphery. Because of these unique barrier properties that tightly regulate exchange of nutrients, solutes, and water between the brain and the blood, the cerebral endothelium is known as the blood brain barrier (BBB). **(Roggendorf W and Cervos-Navarro J, 1977)**

The Veins

The cerebral venous system is a freely communicating and interconnected system comprised of dural sinuses and cerebral veins. Venous outflow from the cerebral hemispheres consists of two groups of valveless veins, which allow for drainage: the superficial cortical veins and the deep or central veins. The superficial cortical veins are located in the pia matter on the surface of the cortex and drain the cerebral cortex and subcortical white matter. **(Schaller B, 2004)**

The deep or central veins consist of subependymal veins, internal cerebral veins, basal vein, and the great vein of Galen (Figure 3). These veins drain the brain's interior, including the deep white and gray matter surrounding the lateral and third ventricles or the basal cistern and anastomose with the cortical veins, emptying into the superior sagittal sinus (SSS). Venous outflow from the SSS and deep veins is directed via a confluence of sinuses toward the sigmoid sinuses and jugular veins. **(Kiliç T and Akakin A, 2008)**

The cerebellum is drained primarily by two sets of veins, the inferior cerebellar veins and the occipital sinuses. The brain stem is drained by the veins terminating in the inferior and transverse petrosal sinuses. **(Nishimura N et al., 2007)**

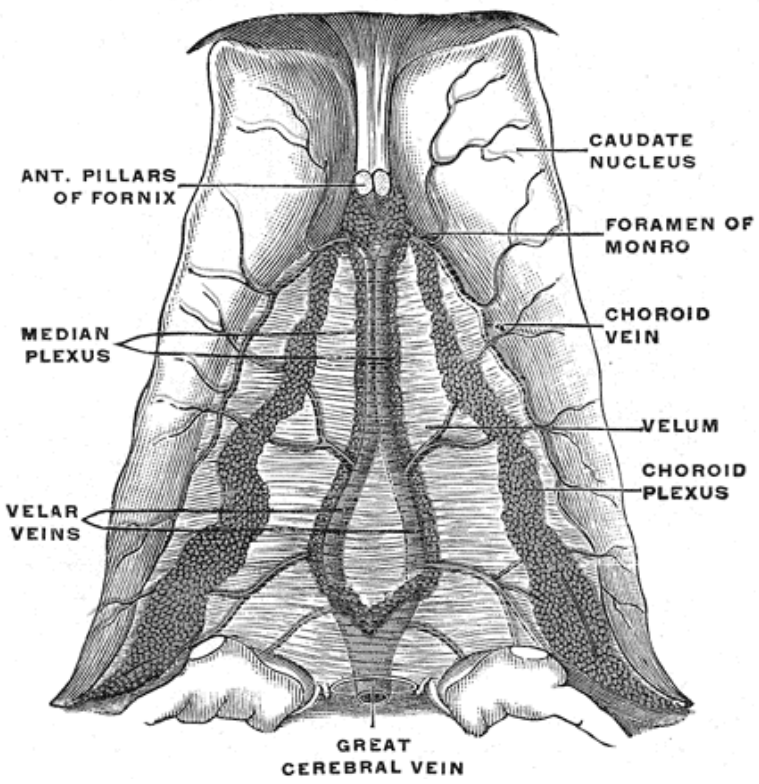

Figure 3: Deep or central cerebral veins (Gray's Anatomy, 2008)