Cerebral blood flow and metabolism – Lecture 1

For 3rd year Students of Medicine

Dr. Eszter Farkas

September 7, 2016
The aim of the course

An overview of cerebral circulation

• Important for normal vital functions;
• Disease states: disturbed cerebral circulation affects motor, intellectual and autonomic functions
• Detection of (ab)normal cerebral circulation;
• Diagnostic tools
Speakers

Prof. Ferenc Bari (Department of Medical Physics and Informatics)

Dr. Ferenc Domoki (Department of Physiology)

Dr. Eszter Farkas (Department of Medical Physics and Informatics)
# The structure of the course

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Content of the course

Is it too early (pathophysiology, pathology, internal medicine, radiology etc)?

Possibly, but

• you have basic knowledge (physiology, anatomy, biochemistry)
• you have motivation
• you can gain motivation
Content of the course

Is it too complex?
Possibly, but each part is exciting

Why take the course?

• Public health considerations (prevention, health education, rehabilitation etc)
• Basic science as well as applied science methods
• Just for some credit points? For some students, possibly – what can we do?
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http://www2.szote.u-szeged.hu/dmi/eng/
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Exam sample sheet
Formulas and tables
Biostatistical methods (manuscript - Dr. Krisztina Boda)

Faculty of Medicine - Cerebral blood flow and metabolism

Cerebral lecture 1 (Prof. Ferenc Bari)
Cerebral lecture 2 (Prof. Ferenc Bari)
Cerebral lecture 3 (Prof. Ferenc Bari)
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Cerebral lecture 11 (Dr. Eszter Farkas)
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Cerebral lecture 12 supplement (Prof. Ferenc Bari)
Cerebral lecture 13 (Dr. Eszter Farkas)

Cerebral blood flow supplement1

Handouts 2014/2015 (2nd semester)
Handouts 2014/2015 (1st semester)
Handouts 2013/2014 (2nd semester)
Handouts 2013/2014 (1st semester)
Visit CooSpace
Visit CooSpace

Additional study material (e.g. journal articles)
Visit CooSpace  Please, read them!

**STATE-OF-THE-ART PAPER**

**Stroke Prevention and Treatment**

James D. Marsh, MD,* Salah G. Keyrouz, MD†

*Little Rock, Arkansas

The decline in stroke incidence and mortality in the U.S. over the past 20 years is reaching a plateau, and the number of strokes may actually start to increase as the population ages. However, recent clinical trials have demonstrated that there are numerous opportunities to improve stroke prevention strategies and also opportunities to effectively intervene in and treat acute strokes. For patients with diabetes and those with prior strokes or transient ischemic attacks, it has become evident that aggressive low-density lipoprotein lowering with statin medications will decrease the risk for total and fatal strokes. Optimal anticoagulation and antiplatelet therapy for primary and secondary stroke prevention in atrial fibrillation is being carefully defined. With numerous novel factor Xa and direct thrombin inhibitor drugs completing phase III clinical trials, it is likely that additional oral anticoagulant drugs will be clinically available for stroke prevention soon. Additionally, a major clinical trial is nearing completion that may resolve the role of carotid stenting and carotid endarterectomy in primary and secondary stroke prevention. There are recent notable advances in the acute treatment of stroke. It is likely that the time window for thrombolysis for appropriate patients with strokes will be increased from 3 to 4.5 h, permitting the inclusion of more patients in this treatment approach. There is ongoing investigation of intra-arterial thrombolysis and of acute intra-arterial thrombus extraction for treatment of selected patients with strokes. Unlike the progress in treatment of ischemic strokes, treatment of hemorrhagic stroke is progressing more slowly. (J Am

DEPARTMENT OF MEDICAL PHYSICS AND INFORMATICS
University of Szeged, Faculty of Medicine, Faculty of Science and Informatics
Requirements and exam

- Attendance will be checked
- Teaching material: on the website and papers recommended
- Exam: MCQ, the last week of the semester
Blood supply to the brain: extracranial vessels

- common carotid → internal carotid
- vertebral → basilar

⇒ circle of Willis
Blood supply to the brain: Circle of Willis

Circle of communicating arteries at the base of the brain
Blood supply to the brain: intracranial vessels

Basilar A.
- ant-inf. Cerebellar A.
- int. Auditory A.
- Pontine Aa.
- sup. Cerebellar A.
  POSTERIOR CEREBRAL A.

Carotidian system ~ ICA
- Hypophyseal A.
- Ophthalmic A.
- post. Communicating
  MIDDLE CEREBRAL A.
  ANTERIOR CEREBRAL A.
Microvessels

Blood vessels are responsible for 25-30% of total brain volume.

400 miles of microvessels (with 20 m² surface area) provide adequate cerebral perfusion at all times.

http://brainwaves.corante.com/Vasculature.gif
Microvessels

A lot more to come next time: Blood-brain barrier lecture
Physiology: some interesting facts

Brain weight: ~2% of body weight (1400-1500g)

The brain:
• Receives 15% of the cardiac output (700-750 ml)
• Consumes 20% of the oxygen used by the entire body

Has no metabolic reserve:
• 10 seconds of interruption of blood flow to the brain leads to unconsciousness
• 2-10 minutes interruption of blood flow may cause brain death
Physiology: some interesting facts

Continuous oxygen requirement: Neurons are predominantly aerobic

Few minutes of ischemia causes irreversible injury

- Oxygen extraction = 35%
- Oxygen supply is 3 times bigger than demand

Sensitive areas

**Adults:**
- Hippocampus,
- 3,5th & 6th layer of cortex,
- Purkinje cells
- Border zone (watershed areas)

**Infants:**
- Brain stem nuclei in infants.
Typical features of cerebral circulation

- The Monroe-Kelly hypothesis
- Autoregulation
- No sympathetic tone of blood vessels
- Blood-brain barrier
- The origin of interstitial fluid
The Monroe-Kelly hypothesis

Describes the pressure relationship between cranial compartments

- Closed cranium: fixed volume - incompressible
- Compartments:
  - Brain parenchyma: 88%
  - Cerebrospinal fluid (CSF): 7-8%
  - Blood: 4-5%
- State of volume equilibrium: any increase in volume of one of the cranial constituents must be compensated by a decrease in volume of another
- Maintainance of normal intracranial pressure (ICP) at any change in volume less than approximately 100–120 ml (buffers: CSF, venous blood)
- Pathophysiologic increase in any one of the components: at the expense of the other two, increased ICP
Cerebral perfusion pressure (CPP)

- Responsible for blood supply to the brain
- Cerebral perfusion pressure (CPP) = mean arterial pressure (MAP) – intracranial pressure (ICP)
- Normal value: 70-80 mmHg
- < 50 mmHg: insufficient blood supply (ischemia)
Cerebral blood flow

• Definition: the blood supply to the brain in a given time (ml/min, v. ml/min/100g)

• Adult:
  • 750 ml/min (15% of resting cardiac output)
  • 50 ml/min/100g

• Defining variables:  
  \[ \text{CBF} = \frac{\text{CPP}}{\text{CVR}} \]  
  \[ \text{CPP} = \text{MAP} - \text{ICP} \]

(CVR: cerebrovascular resistance)
# Cerebral blood flow regulation

## Categories:

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<th>Affected area:</th>
<th>Type:</th>
<th>Origin of stimulus:</th>
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<tr>
<td>• Global</td>
<td>• Myogenic</td>
<td>• Parenchyma</td>
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<tr>
<td>• Local</td>
<td>• Neurogenic</td>
<td>• Endothelium</td>
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<tr>
<td></td>
<td>• Metabolic Chemical</td>
<td>• Blood</td>
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Cerebral blood flow regulation

A lot more to come!
Cerebrovascular diseases

- Common denominator: ischemia
- What is ischemia?

An inadequate blood supply to an organ or part of the body ⇒ shortage of oxygen and glucose needed for cellular metabolism
Clinical Categories of Inadequacy

1. Global Ischemia
   - Hypotension, hypoxemia, anemia
   - Hypoxemic encephalopathy

2. Focal Ischemia
   - Obstruction to blood supply to focal area
   - Thrombosis, embolism or hemorrhage
Global ischemia

Etiology:
- Impaired blood supply - Lung & Heart disorders
- Impaired O$_2$ carrying – Anemia/Blood disorders

Morphology:
- Laminar necrosis, damage in: Hippocampus, Purkinje cells
- Border zone infarcts – “Watershed”
- Sickle shaped band of necrosis on cortex.

Clinical Features:
- Mild transient confusion state
- Severe irreversible brain death; flat EEG, vegetative state, coma
Global ischemia

Mild cognitive impairment

Dementia

- Alzheimer’s Disease, cerebral amyloid angiopathy
- CADASIL (Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy): mutations of the Notch 3 gene on chromosome 19
- Cerebral microhemorrhage - results from rupture of small blood vessels
- Multi-infarct dementia - multiple strokes (disruption of blood flow to the brain)
Alzheimer’s disease

An upcoming lecture dedicated to the topic!
Focal ischemia

Cessation of blood circulation, oxygen and nutrients in a particular region of brain

~ Stroke
Definition of stroke

Cerebro-vascular disorder caused by insufficient cerebral circulation, and resulting in sudden neurological deficits.
Incidence

• **Hemorrhage**: bleeding, within the skull
  
  Incidence 20% - mortality 80%
  
  • Intracerebral or subarachnoid
  
  • Aneurysm (hypertension/congenital), arteriovenous malformation

• **Infarction**: tissue death (necrosis) due to a local lack of oxygen caused by obstruction of the tissue's blood supply.
  
  Incidence 80% - mortality 40%
  
  • 50% - Thrombotic – atherosclerosis
    
    • Large-vessel 30% (carotid, middle cerebral)
    
    • Small vessel 20% (lacunar stroke)
  
  • 30% Embolic (heart disease/atherosclerosis)
    
    • Young, rapid, extensive
Infarction (ischemic stroke)

Zones of tissue damage

Penumbra: Viable but non-functional cells

Core (umbra): Infarcted area – non-viable cells
Residual blood flow

Collateral circulation helps to maintain some CBF to post obstruction area

• Core ~ CBF < 10 ml/100gm/min
  Early irreversible membrane rupture & cell death

• Penumbra ~ CBF < 20 ml/100gm/min
  Rapid energy depletion & loss of neuronal activity (electrically silent)
Infarct maturation

Reduced blood supply $\Rightarrow$ hypoxia/anoxia
Altered metabolism $\Rightarrow$ Na/K pump block
Glutamate receptor activation $\Rightarrow$ Ca influx

1-6 min – ischemic injury
>6 min – cell death
Duration of ischemia $\Rightarrow$ infarct maturation

- Animal models & human studies (MRI, PET) of acute ischemia shows:
  - $< 2$ hrs reversible neuronal deficit
  - $> 6$ hrs irreversible neuronal deficit

Clinical studies & current therapies aim for *reperfusion within 2 to 6 hrs* (*therapeutic window*)
Stages of infarct maturation

• Immediate – 6 hours; no change (both macro & micro)

• Acute stage – 2 days; edema, loss of grey/white matter border, inflammation, red neurons, neutrophils

• Intermediate stage – 2 weeks; demarcation, soft friable tissue, cysts; macrophages, liquifactive necrosis

• Late) stage – after 4 weeks; fluid filled cysts with dark grey margin (gliosis), removal of tissue by macrophages
Stroke

An upcoming lecture dedicated to the topic!