Brain Perfusion: Physiology and Role in Dementia

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OUTLINE

• Anatomy of brain vasculature
• Neurovascular coupling
• Variability in brain perfusion
• Measurement issues
• Dementias and the role of hypoperfusion
Vessels
Macrocirculation

- Carotids, internal
- Vertebrals, merging to basilar artery
Circle of Willis

- Basilar and internal carotids connected by communicating arteries.
- Give Rise to Posterior, Middle and Anterior cerebral arteries.
- Provides redundancy, although highly variable.
Cortical Vessels

- Large vessels on pial surface
- Arterioles penetrating into Gray Matter (GM)
- Fewer vessels in White Matter (WM)

Hirsch 2012, 952
Cortical Arterioles

- Pial arteries (1) give rise to arterioles
- 20-90 μm diameter
- Three zones, supplied by short (4), middle (3) and long (2) arterioles
- Transcortical arteries supply WM

De La Torre, 1998, 87
Cortical Arterioles

- Arterioles surrounded by bands of smooth muscle cells

De La Torre, 1998, 87
Capillaries

- Diameter 5-7 μm
- Pericytes (3)
- Volume: 1%
- Length: 370 mm / mm³
- Surface: 7 mm² / mm³
Capillary Density

- Nissl stain showing nuclei in 6 cortical layers, I-VI
- Corresponding vascular structure, note low density in WM
- Density(○) correlated with metabolic activity (☉)

Weber 2008, 2318
Dimensions and Velocities

A) Intravascular Pressure [mmHg] vs Diameter

B) Flow Velocity [cm/s] vs Diameter
Blood Brain Barrier

• Consists of
  - tight junctions between endothelial cells
  - thick basement membrane
  - astrocytic endfeet surrounding capillaries

• Restricts passage of larger molecules and hydrophilic substances.

• Water passes rapidly
Neurovascular Coupling
Lots of Energy Used

- Mainly for restoring ion-gradients
- Transmitter uptake and processing in astrocytes.
- High supply required!

Atwell 2010, 232
Basic Flow

- Main homeostatic mechanism:
  Autoregulation - flow is independent of arterial pressure (within limits).
  - May be dependent on Nitric Oxide/autonomic nerves
  - (eNOS) can be activated by flow-induced shear stress or by acetylcholine (ACh)

- Regulation in response to O$_2$, CO$_2$, pH
Basic Flow Regulation

- Extrinsic innervation from cervical ganglia (autonomic nervous system).
- Extrinsic innervation extends into Virchow-Robin spaces, but stays external to the brain.
- Intrinsic innervation from subcortical brain structures.
Basic Flow Regulation

- Extrinsic and intrinsic innervation
- Cholinergic drugs may enhance perfusion through intrinsic pathway

Hamel 2005, 1059
Neurovascular Coupling

• Metabolic feedback?
  - CO₂, low pH, low O₂, low glucose?
  - Not experimentally supported

• Feedforward
  - Signalling molecules from neurons and astrocytes elicit perfusion response.

• Glutamate (NMDAR) -> Ca^{++} -> nNOS -> Nitric Oxide (NO)
  - NO permissive, but not causative
Two Pathways: Neuronal & Glial

Atwell 2010, 232
Neuronal pathway

- Activation in nNOS producing vasodilating Nitric Oxide NO.
- NO is permissive, seems not direct mediator.
Astrocytic pathway, by glutamate stimulation

- Vasodilating prostaglandin (PGE2 and others).
- Vasoconstriction, due to 20-HETE.
- NO may act by inhibiting 20-HETE
Summary of Neurovascular Coupling

• Functional response is due to glutamate, causing increase in Ca^{++}

• Astrocyte pathway may be predominant, but neurons contribute NO (ensuring that astrocytic vasodilation prevails).

• Pathways interact, eg. NO both dilate and inhibit constriction.

• Redundancy secures robustness
Summary of Neurovascular Coupling

• Control of vascular tone:
  - arteriolar smooth muscle and
  - capillary pericytes

• Pericytes may be of importance in pathological conditions
  - e.g. prolonged hypoperfusion after stroke
What is the Purpose of Functional Hyperaemia?

- Response intact during total CBF block
- Not necessary for CMRO$_2$ increase

Leithner, 2010, 311
Measurement of Brain Perfusion
Flow and Perfusion

- **Flow:** transport of blood in a vessel,
  - Units: ml/min.
  - Eg. Velocity sensitive phase mapping

- **Perfusion:** delivery of blood to a tissue element
  - Units ml/hg/min.
  - Intravascular tracers
  - Diffusible tracers
Measuring Perfusion

- The Perfusion Daemon: Measures flow at one level of the vascular tree
- Large vessel flow ✓
- Micro-spheres ✓
- Diffusible tracers (✓)
- Intravascular tracers %
**Criteria for Absolute Mapping**

- Across subjects: correlation with physiological parameters
- Within subjects: adequate response to challenge (diamox or CO2).
Absolute vs Normalised Maps

- Normalisation can lead to strange results...
- Trivial but instructive example: ventricular size

![Absolute](image1.png)  ![Normalised](image2.png)

Absolute  Normalised
Criteria for Clinical Utility

- Ability to predict outcome
  - at patient or tissue level
- Ability to influence therapeutic decisions
## QUALITY OF EVIDENCE RATING

<table>
<thead>
<tr>
<th>Class</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| Class I | • Prospective study  
• Broad selection of patients and controls  
• Blinded observers and clinicians  
• vs ‘gold standard’ test of diagnosis or outcome. |
| Class II| • Prospective, broad selection  
• Retrospective, broad selection of diagnosed pts vs. controls  
• Blinded observers and clinicians |
| Class III| • Retrospective, narrow selection of pts and controls.  
• Blinded observers and clinicians |
| Class IV| • Unblinded observers or clinicians  
• Cases series without controls |

Recommendation grading A-D, based on no. of Class I, II or III studies

Lachaw 2003, p. 1084
Variability
Variability

- Large variability across healthy subjects

<table>
<thead>
<tr>
<th>Method</th>
<th>Mean±SD (ml/100g/min)</th>
<th>CV</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kety-Schmidt</td>
<td>46 ±10</td>
<td>22%</td>
<td>Madsen 1993</td>
</tr>
<tr>
<td>Intra-art. $^{133}$Xe</td>
<td>50 ± 8</td>
<td>16%</td>
<td>Høedt-Rasmussen 1967</td>
</tr>
<tr>
<td>$^{133}$Xe-SPECT</td>
<td>56 ± 7</td>
<td>13%</td>
<td>Shirahata 1985</td>
</tr>
<tr>
<td>$\text{H}_2^{15}$O PET</td>
<td>37 ±7</td>
<td>19%</td>
<td>Coles 2006</td>
</tr>
<tr>
<td>MR ASL (δ²)</td>
<td>53 ±10</td>
<td>19%</td>
<td>Parkes 2004</td>
</tr>
<tr>
<td>MR PCM</td>
<td>51 ± 9</td>
<td>18%</td>
<td>Vernooij 2008</td>
</tr>
</tbody>
</table>

- Low vs high 16% fractile: 50% difference
- Low vs high 2.5% fractile: 100% difference
**Variance components**

Linear mixed model

\[ y_{ji} = \mu + \beta_1 x_1 \ldots + \beta_h x_h + \zeta_i + \varepsilon_{ji} \]

True between
Subject specific error

True within
Random error

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Monday, 30 September 2013
Variance components

<table>
<thead>
<tr>
<th></th>
<th>PCM n=17</th>
<th>DCE n=16</th>
<th>ASL n=16</th>
<th>PET n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD</td>
<td>65 ± 12</td>
<td>41 ± 11</td>
<td>37 ± 6</td>
<td>42 ± 8</td>
</tr>
<tr>
<td>CV</td>
<td>18%</td>
<td>26%</td>
<td>17%</td>
<td>19%</td>
</tr>
<tr>
<td>CV&lt;sub&gt;b&lt;/sub&gt;</td>
<td>17%</td>
<td>18%</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>CV&lt;sub&gt;w&lt;/sub&gt;</td>
<td>7%</td>
<td>14%</td>
<td>5%</td>
<td>12%</td>
</tr>
</tbody>
</table>

- Distinguish between and within subject variability (CV<sub>b</sub> and CV<sub>w</sub>)
- CV<sub>w</sub> contains both measurement noise and true biological variance
Sources of Variability

- Xe-SPECT data

<table>
<thead>
<tr>
<th></th>
<th>Model A without Hct (n=430 obs in 152 subjects)</th>
<th>Model B with Hct (n=277 obs in 77 subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>95% Conf. Interval</td>
</tr>
<tr>
<td>$P_{ET}CO_2$ (kPa)</td>
<td>9.91%</td>
<td>6.24%–13.72%</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>-14.1%</td>
<td>-17.95%–-10.15%</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Intercept (ml/100g/min)*</td>
<td>52.82</td>
<td>50.69–55.03</td>
</tr>
</tbody>
</table>

Henriksen 2013, 787
## Sources of Variability

- **Carotid flow**

<table>
<thead>
<tr>
<th>Source</th>
<th>Coef.</th>
<th>95% conf. interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>-1.01</td>
<td>-1.95 - 0.08</td>
<td>0.035</td>
</tr>
<tr>
<td>$P_{ET}CO_2$ (kPa)</td>
<td>6.88</td>
<td>1.97 - 11.79</td>
<td>0.008</td>
</tr>
<tr>
<td>Age (year)</td>
<td>-0.243</td>
<td>-0.740 - 0.255</td>
<td>0.329</td>
</tr>
<tr>
<td>Male gender</td>
<td>-5.44</td>
<td>-11.72 - 0.83</td>
<td>0.087</td>
</tr>
<tr>
<td>LDL:HDL ratio</td>
<td>1.93</td>
<td>-1.27 - 5.15</td>
<td>0.229</td>
</tr>
<tr>
<td>IMT</td>
<td>4.25</td>
<td>-36.82 - 45.33</td>
<td>0.834</td>
</tr>
<tr>
<td>Caffeine (µmol/L)</td>
<td>-0.295</td>
<td>-0.494 - -0.097</td>
<td>0.005</td>
</tr>
<tr>
<td>Homocysteine (µmol/L)</td>
<td>-2.00</td>
<td>-3.86 - -0.13</td>
<td>0.036</td>
</tr>
<tr>
<td>Arg:ADMA (per 100)</td>
<td>-2.22</td>
<td>-11.99 - 7.54</td>
<td>0.647</td>
</tr>
</tbody>
</table>

- **Equal effect sizes, total $r^2$~0.50**
GLOBAL VARIABILITY

- Physiological
  - Age
  - (Gender)
  - Haemoglobin / Haematocrit
  - Carbon dioxide

- Risk factors
  - Homocysteine

- Pharmacological
  - Caffeine
Caffeine

- Adenosine receptor antagonist
- Adenosine raises perfusion,
- Adenosine is an inhibitory neurotransmitter?
- Blocking adenosine receptors decreases response to activation (Ko 1990)
Impairment of Brain Perfusion
Perfusion Imaging
Acute Ischemia - Stroke

• Clinical questions
  - Bleeding? (CT),
  - Transitory Ischemic Attack? (Clinics)
  - Reversibility? - needs perfusion imaging.

• Salvageable tissue
  - 10-20 ml/hg/min (need quantitative CBF)
  - With MRI: Diffusion / Perfusion mismatch
Perfusion Imaging

Chronic Ischemia

- Vascular occlusion (carotid stenosis / occlusion)
-Transient ischemic attacks in patient with vascular disease (eg previous infarct)
-Perfusion may be normal, due to vasodilation
-Exhausted vasodilation may increase sensitivity to decreased perfusion pressure (absence of autoregulation)
Vascular Occlusion, Challenge Tests

• Diamox given to increase perfusion
  - alternatives: CO₂, Breath-hold or Cued Deep Breathing tests
• Healthy tissue: flow will increase
• Compromised tissue: perfusion unchanged or decreased ("vascular steal")

• Quantitative CBF is needed to
  - detect global increase
  - distinguish small increase from decrease.
Chronic Ischemia, Challenge Tests

- Flow may be altered in other conditions than stroke or arterial occlusion/stenosis
Hypertension, Hypercholesterol, Diabetes, Cardio-vascular disease, Carotid disease, Stroke, Chronic Brain Hypoperfusion, Vascular Dementia, Alzheimer, de la Torre, 2010, 218
Vascular Dementia

- NINDS-AIREN criteria
- Dementia: memory deficit + other cognitive domains
- Cerebrovascular disease
- Temporal relationship between the two, stepwise progression
Vascular Dementia

- Extensive white matter changes
- Lacunar infarcts
- Enlarged vascular spaces (Virchow-Robin)
Chronic Brain Hypoperfusion

- Brain perfusion declines with age
- Risk factors & susceptibility genes may accelerate structural and metabolic decline, de la Torre, 2010, 218
- leading to neuronal energy crisis
- Subclinically impaired cognition, potentially leading to dementia.
- However, direct verification lacking..
Alzheimer’s Disease

• Most common form of dementia
• Histology:
  - plaques consisting of beta Amyloid (Aβ)
  - neurofibrillary tangles (intracellular tau-protein)
• Aβ is a normally occurring peptide, with unclear function
• Familial form has genetic defects in Aβ precursor -> “Amyloid Hypothesis”
Alzheimer’s Disease
Clinical Criteria

Probable AD: A plus one or more supportive features B, C, D, or E

Core diagnostic criteria
A. Presence of an early and significant episodic memory impairment that includes the following features:
   1. Gradual and progressive change in memory function reported by patients or informants over more than 6 months
   2. Objective evidence of significantly impaired episodic memory on testing: this generally consists of recall deficit that does not improve significantly or does not normalise with cueing or recognition testing and after effective encoding of information has been previously controlled
   3. The episodic memory impairment can be isolated or associated with other cognitive changes at the onset of AD or as AD advances

Supportive features
B. Presence of medial temporal lobe atrophy
   • Volume loss of hippocampi, entorhinal cortex, amygdala evidenced on MRI with qualitative ratings using visual scoring (referenced to well characterised population with age norms) or quantitative volumetry of regions of interest (referenced to well characterised population with age norms)
C. Abnormal cerebrospinal fluid biomarker
   • Low amyloid β₄₂ concentration, increased total tau concentrations, or increased phospho-tau concentrations, or combinations of the three
   • Other well validated markers to be discovered in the future
D. Specific pattern on functional neuroimaging with PET
   • Reduced glucose metabolism in bilateral temporal parietal regions
   • Other well validated ligands, including those that foreseeably will emerge such as Pittsburgh compound B or FDDNP
E. Proven AD autosomal dominant mutation within the immediate family

Dubois, 2007, 734
Alzheimer’s Disease Imaging

• Grey matter atrophy
  - Medial temporal / Hippocampal
  - possible early cases: precuneus and occipital.
• Reduced perfusion/metabolism in precuneus and temporal parietal lobes
• Small vessel disease: White matter hyperintensity, lacunes, microbleeds.
• Amyloid deposition (low specificity)
**Hippocampal Atrophy**

- Medial temporal lobe
- Yearly decline 2.5 times higher in AD patients than controls

Bastos Leite, 2004, 369
Perfusion in AD

Decreases in
- Inf. Parietal
- Sup. Frontal
- Precuneus

Johnson, 2005, 851
Alzheimer’s Disease
Myelin Hypothesis

- Low correlation between Aβ and severity / atrophy
- Aβ as a byproduct of myelin metabolism, axonal transport.
- Gene APOE4 is a risk gene for sporadic Alzheimer.
- Myelin has high turn-over, mediated by ApoE, transporting degraded membrane lipids for recycling (all cholesterol is produced locally by astrocytes)

Bartzokis, 2011, 1341
Alzheimer’s Disease
Myelin Hypothesis

- High risk gene: ApoE4 is the evolutionary older, but less efficient genotype.
- Low risk gene: ApoE2 and 3 are uniquely human.

Bartzokis, 2011, 1341
Age, TBI, toxins, iron, Hypoperfusion

Myelin breakdown

Remyelination

Axonal transport stops, (due to phospho-tau)

APOE4 (low clearance)
Iron, Free Radicals, Cortisol

Axonal transport resumes

APOE2/3 (high clearance)

Axonal Loss
Release of Aβ

Neuronal tissue loss
Cognitive dysfunction

Bartzokis, 2011, 1341
Conclusions

- Perfusion imaging established use in a few clinical situations:
  - stroke (normalised)
  - vascular occlusion (absolute)
  - dementia (normalised)
- Perfusion deficits closely associated with most neurodegenerative diseases
- Role of baseline perfusion or vascular reactivity should be established.