CEREBROVASCULAR RESERVE

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• Background and concepts
• CVR evaluation and methods
• Implications and Applications
BACKGROUNDs

What is Cerebrovascular reserve (CVR)?

- CVR, or CVR capacity, is a general description of the range of cerebral perfusion variation from normal baseline

- Aspects and causes of the CVR change is a matter of point of view
  - Functional neuroscience (stimulation / task; local vs. network?)
  - Physiology/pharmacology (drugs: caffeine / CO2 / acetazolamide)
  - Vascular disease (aging / TBI / stroke / blood pressure / cardiac deficiency)

- CVR maintained via vascular autoregulation mechanism
  - Metabolism (CO2, Na+, K+, Ca2+, adenosine), blood pressure
  - Genes, life style, drug use …
BACKGROUNDS

- Why is CVR important?
  - Maintain the vital and normal functioning of the brain
  - Works as a protective mechanism
  - Can help diagnosis and/or prognosis
    - Stenosis / stroke / TBI / tumor / heart surgery…
  - Stabilizing or reinstating CVR can help improve treatment
BACKGROUNDs

• Cerebral circulation
  • The brain receives blood supply from 2x internal carotid arteries and 2x vertebral arteries
  • Oxygen and nutrients are perfused into tissues in capillary beds
  • Outgoing blood is drained to superior/inferior sagittal sinus, Sigmoid sinus etc. in the brain, and to internal Jugular veins in the neck
  • The CVR and clinical consequences of vascular disease in the cerebral circulation depend upon which vessels or combinations of vessels are involved.
EVALUATING CVR

- Transcranial Doppler (TCD) sonography
  - Basic idea: measuring the input blood flow
  - Easy and quick, low cost
  - Can only monitor blood flow in major arteries such as anterior, middle (80%), and posterior cerebral arteries
  - Relatively insensitive measuring blood flow (33~43% of CT)
  - Incomplete measures of blood flow in all major vessels/directions
  - Significant inter-subject difference, susceptible to cardiac motion / operator experience
EVALUATING CVR

- TCD test design
  - Experimentally induce functional activity, thus increasing the need for more blood supply
  
  - Use dynamic step blood pressure drop or static hypertensive challenge to evaluate cerebral autoregulation to blood flow
    - Autoregulation index (ARI) reflects relative changes in blood flow through the MCA caused by the change in distal cerebral vascular resistance per second, relative to the change in mean arterial blood pressure (MABP).

Njemanze, PC (2007)
EVALUATING CVR

- MR phase contrast flow quantification (PC FQ MRI) to replace TCD
  - MR velocity encoding using bipolar gradients
    \[
    \phi = \gamma GT (T + Td) \nu
    \]
    \[
    VENC = \frac{\pi}{\gamma GT (T + Td)}
    \]
  - Image phase is linearly proportional to velocity along G, normalized by VENC to \([-\pi, \pi)\)
  - VENC determines the maximal flow velocity without phase aliasing
    \[
    \frac{\nu}{VENC} = \frac{\phi}{\pi}
    \]
  - Use GRE sequence with VENC gradient, can be done 2D or 3D, high or low resolution

Markl M. J Comput Assist Tomogr 2004
EVALUATING CVR

- Examples of 2D PC FQ MRA
  - Normal
  - Narrowing in left IJV
  - Stenosis in both IJV
EVALUATING CVR

• MR Angiography (MRA)
  • TCD and PC FQ MRI only works on major vessels, do not reveal local blood supply/drainage
  • High resolution (<1mm³) MRA provides detailed information of local supplying vessels, as well as the fine geometry details of major arteries
  • Time-of-flight (TOF) MRA
    • Inflow blood is less T1 saturated than stationary tissues
    • Shortest TE and reasonably short TR
    • Best contrast with 2D (neck, leg), but high resolution with 3D (brain)
    • Reduced contrast with thick 3D slab (flow dependent), use multiple thin slabs
    • Can selectively image arteries or major veins, or both.
  • Contrast enhanced (CE) MRA
    • Utilize the T1 shortening effect of Gd contrast agent
    • Shortest TE and shortest TR, usually in 3D
    • Mixture of arteries and veins. Works on most body parts
    • Time resolved dynamic flow imaging
EVALUATING CVR

- MR Angiography Examples

2D TOF

3D TOF

3D CE MRA

Time resolved CE MRA
EVALUATING CVR

- MR Angiography Examples
  - TOF vs. CE MRA in showing a class 4 coiled anterior communicating artery aneurysm remnant/recurrence

Kaufmann, AJNR, 2010
EVALUATING CVR

• Susceptibility Weighted Imaging (SWI), or MR venography (MRV)
  • Uses MR phase information to enhance image contrast based on high spatial frequency susceptibility differences
  • Sensitive to paramagnetic tissues (venous blood, iron deposition, microbleeds)
  • 3D high resolution, fully flow compensated, T2* GRE scan

\[ \Delta \phi(r) = -\gamma \Delta B(r) T E \]
EVALUATING CVR

- Quantitative Susceptibility Mapping (QSM), or Susceptibility weighted imaging and mapping (SWIM)
- Phase is directional, and SWI is non-quantitative
- Quantifies susceptibility underlying the image phase
- Susceptibility is highly correlated to blood oxygen saturation, iron/calcium deposition

\[
\Delta \phi(r) = -\gamma \Delta B(r) TE
\]

\[
\Delta B(r) = B_0 \cdot FT^{-1}\{g(k) \cdot FT[\chi(r)]\}
\]

\[
g(k) = \frac{1}{3} - \frac{k_z^2}{k_x^2 + k_y^2 + k_z^2}
\]

\[
g^{-1}(k) = \frac{3(k_x^2 + k_y^2 + k_z^2)}{k_x^2 + k_y^2 - 2k_z^2}
\]
EVALUATING CVR

- SWI and QSM examples
  - Venous oxygenation saturation pre- and post-caffeine intake
  - Results independent of blood flow
  - Can potentially convert to oxygen saturation map
EVALUATING CVR

- A 64 year old male suffered severe TBI after motor vehicle accident. MRI scan performed 36 days after injury.
- No vascular abnormality are seen on PWI or DWI on the left side.
- SWIM clearly shows reduced blood oxygen saturation in several veins on the left side.
EVALUATING CVR

- Vessel size imaging (VSI)
  - The microvasculature, which includes the smallest and intermediate vessels, cannot be imaged directly with current MRI techniques.
  - Obtaining info on mean vessel caliber can help draw a more comprehensive picture of brain histopathology and CVR.
  - Principle: $\Delta R2$ and $\Delta R2^*$ changes in the effective transverse relaxation rates depend on the size and architecture of the vascular compartment in that voxel.
  - Method: tracer bolus injection + double echo GE-/SE-EPI
  - Confounding factors: regional diffusion coefficient, water exchange and regional CBV.

Kiselev, MRM, 2005
EVALUATING CVR

- VSI example
  - 4 patients with different types of brain tumor
  - VSI is feasible to quantify the mean vessel caliber in normal and pathologic human brain tissues
  - Provides additional info about the micro- and meso-vasculature underlying different types of tumor
  - However, the precision and sensitivity of current VSI results on absolute quantification of the vessel caliber need further improvement

Kiselev, MRM, 2005
EVALUATING CVR

- Cerebral blood flow (CBF)
  - Blood supply to the brain in a given time, with unit of ml/min for whole brain or ml/min/100g for local tissue
  - Normal blood flow through the brain of the adult person averages 50-65 ml/min/100g of brain tissue; or 750 to 900 ml/min for the entire brain (10-15% of the resting cardiac output)
  - When CBF falls to less than 10-23ml/100g/min, physiological electrical function of the cell begins to fail- “ischemic penumbra”. Below 8 ml/100g/min, irreversible cell death- ionic membrane transport failure
  - Normal CBF is determined by a number of factors including cerebral perfusion pressure, blood viscosity, vessel size and elasticity
  - Perfused / local CBF is tightly coupled with the metabolism of the tissue and regulated by the brain's autoregulation mechanism, often used to represent CVR
EVALUATING CVR

- CBF coupling with metabolism
  - Carbon dioxide increases cerebral blood flow by combining first with water in the body fluids to form carbonic acid, with subsequent dissociation of this acid to form hydrogen ions.
  - The hydrogen ions cause vasodilation of the cerebral vessels. The dilation being almost directly proportional to the increase in hydrogen ion concentration up to a blood flow limit of about twice normal.
  - Any other substance that increases the acidity of the brain tissue, and therefore increases hydrogen ion concentration, will likewise increase cerebral blood flow.
  - Such substances include lactic acid, pyruvic acid, and any other acidic material formed during the course of tissue metabolism.
EVALUATING CVR

- CBF regulated by caffeine
EVALUATING CVR

- CBF regulated by CO2/O2 challenge (hypercapnia / hypocapnia)
  - CO2 is a potent vasodilator
    - increased CO2 --> vasodilation / increased CBF / decreased BP
    - decreased CO2 --> vasoconstriction / decreased CBF / increased BP
  - Inhale 5% CO2 + 95% O2 or 100% O2 via a mask / Breath holding
  - PET, ASL or T2* BOLD imaging
  - Induce CBF/CBV changes without neuronal activity, i.e. decoupled
  - Temporarily modifying the CBF baseline in a controllable manner
    - Test the baseline variation
    - Test the autoregulation under different baseline levels

![Graph showing CBF changes with Arterial Pco2](image)
EVALUATING CVR

- Measuring CBF using Positron Emission Tomography (PET)
  - PET detects pairs of gamma rays emitted indirectly by a positron-emitting radionuclide (H$_2$O$_{15}$ or O$_2^{15}$), which is introduced into the body via IV or inhalation.
  - 3D images of tracer concentration within the body are then constructed by computer tomography methods

- Pros
  - Precise imaging of CBF, CBV and CMRO2 (OEF)
  - High temporal resolution

- Cons
  - Complexity and radiation exposure
  - Half-life of O$^{15}$ is 122.24s
  - Limited spatial resolution
EVALUATING CVR

Example of PET CBF

- 42-year-old woman 16 h after injury with left hemisphere subdural hematoma evacuated

- Reduced CBF and increased OEF in hematoma region after evacuation

- Damaged blood vessels and extravasation of blood is a frequent consequence of trauma. Hemorrhages resulting from the injury may play a role in post-traumatic ischemic insults as this often leads to focal regions of vessel spasm, which can substantially lower regional blood flow, increasing vulnerability towards the incidence of post-traumatic ischemic events

(Yi, NeuroChem Int. 2006)
EVALUATING CVR

- Dynamic susceptibility contrast (DSC) PWI - Exogenous
  - Uses the T2 shortening effect of Gadolinium (Gd) based contrast agents (there is also T1 shortening effect)
  - DSC PWI MR protocol:
    - $T2^*$ or T2 weighted single shot EPI ($TR<=2s$, $\sim3\times3\times3mm^3$ voxels)
    - IV injection of contrast agent ($0.1mmol/kg$ b.w., 2-6ml/s)
EVALUATING CVR

• DSC PWI
  • Can quantify rCBF, rCBV, MTT, TTP, tissue similarity maps (TSM)
  • Requires precise knowledge of tracer kinetics, i.e. concentration–time curves C(t), or Arterial Input Function (AIF)

\[
C(t) = CBF \cdot R(t) \otimes AIF(t)
\]

(R = tracer residual function, 0<=R<=1)

\[
CBF_{est} = \max [CBF \cdot R(t)]
\]

\[
CBV = \frac{k_H \int_0^\infty dtC(t)}{\rho \int_0^\infty dtAIF(t)}
\]

\[
MTT = \int_0^\infty dtR(t) = \frac{CBV}{CBF}
\]
EVALUATING CVR

- DSC PWI considerations
  - Imaging protocols
    - T2 or T2* / TE / TR / partial volume / nonlinear $\Delta R2^*$ / SNR
    - Tracer dose and injection speed / bolus dispersion
  - Physiological effects
    - AIF (global vs. local; bolus recirculation)
    - Hematocrit (red blood cell volume fraction)
    - Tracer exchange between plasma and extravascular/extracellular space
  - Data processing
    - High frequency component loss due to long TR
    - Deconvolution of AIF
EVALUATING CVR

- DSC PWI – tissue similarity map (TSM)  (Haacke et al, MRI, 2013)
  - Estimate the perfusion similarity in terms of the whole signal time curve, including tracer 2\textsuperscript{nd} pass
  - Estimate rCBV without the need for AIF
EVALUATING CVR

- DSC PWI example

<table>
<thead>
<tr>
<th>rCBF</th>
<th>rCBV</th>
<th>MTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td>(b)</td>
<td>(e)</td>
</tr>
<tr>
<td>GE-EPI</td>
<td>SE-EPI</td>
<td>GE-EPI</td>
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<tr>
<td>(c)</td>
<td>(d)</td>
<td>(f)</td>
</tr>
<tr>
<td>GE-EPI</td>
<td>SE-EPI</td>
<td>TSM-vessel</td>
</tr>
<tr>
<td>(a)</td>
<td>(b)</td>
<td>(e)</td>
</tr>
<tr>
<td>TSM-vessel</td>
<td>TSM-rCBV</td>
<td>TSM- standard error</td>
</tr>
</tbody>
</table>
EVALUATING CVR

- Arterial spin labeling (ASL) – Endogenous
  - Uses magnetically labeled arterial blood water protons as tracer for CBF

1. Tag inflowing arterial blood by magnetic inversion
2. Acquire the tag image
3. Repeat experiment without tag
4. Acquire the control image

(http://www.umich.edu/~fmri/asl.html)
EVALUATING CVR

• Continuous vs. Pulsed ASL
  • cASL: continuously tags blood as it passes through a thin tagging plane
  • pASL: tags blood in a large slab proximal to imaging slice
EVALUATING CVR

- ASL properties
  - ASL provides a non-invasive means of measuring CBF.
  - Low intrinsic SNR due to subtraction, only 1 – 5% of mean MR signal intensity, need repeating the tag-control acquisition many times to enhance SNR.
  - Arterial transit time is critical for correctly quantifying CBF.
  - Relaxation Effects: different relaxation rates for blood and tissue, time of water exchange.
  - Bolus Width in PASL: ASL signal equation
    \[ \Delta M = CBF \cdot A_{eff} \]
    (\( A_{eff} \) is the effective area of the tagged arterial bolus)
EVALUATING CVR

- Continuous vs. Pulsed ASL
  - Inherent SNR for CASL is higher, but SNR/time is roughly the same.
  - Temporal resolution for PASL slightly better (2 s TR vs. 3 s TR).
  - PASL amenable to use of a presaturation pulse for simultaneous CBF/BOLD
  - CASL may be better for lower slices when using a head coil for transmit.
  - Both have non-quantitative variants that are useful for mapping.
  - CASL has higher SAR requirements.
EVALUATING CVR

- Emerging ASL techniques
  - Territorial ASL allows labeling and visualization of perfusion in territories of individual arteries, labeling only blood flowing through an artery of interest.
  - ASL at multiple inversion times avoids effect of arterial transit time. Long scan time often rendering it impractical especially in patients.
  - ASL perfusion can also be used as fMRI contrast to localize task activation as BOLD contrast.

Hartkamp, NMR Biomed, 2012
EVALUATING CVR

- ASL example studies
  - Occipital hyper-perfusion corresponding to visual cortex activation

- CBF in TBI rat model

B: control
C-G: TBI rat model at different time after TBI insult

Hayward: JCBFM, 2011
EVALUATING CVR

• Blood oxygenation level dependent (BOLD) effects
  • Best and most complicated reflection of CVR, by the many affecting factors and experimental designs
• Induced by neuronal activities, active or passive
• Modulated by blood oxygenation (PaO2/SaO2), CBF and CBV (~5%)
• Detected by susceptibility related T2* imaging, CBF imaging or CBV imaging (<5% image signal changes)
EVALUATING CVR

• Two Compartment Model (IV/EV) for BOLD signal
  • T2* effect (susceptibility change in venous blood)
  • T2 effect (↑10% Hbr02 ➔ ↑40ms venous blood T2 at 1.5T)
  • Diffusion effect (EV dynamic averaging)

• MRI sequences:
  GE-EPI, SE-EPI, TSE, SPIRAL, etc

(fMRIB Brief Intro to fMRI)
GE-EPI (T2*W)

neural activity $\Rightarrow$ ↑ blood flow $\Rightarrow$ ↑ oxyhemoglobin $\Rightarrow$ ↑ T2* $\Rightarrow$ ↑ MR signal

(Handbook of MRI pulse sequences, M.A. Berstein)
EVALUATING CVR

- BOLD signal characteristics
  - Impulse Hemodynamic Response Function (HRF)
  - Detected BOLD signal
EVALUATING CVR

- Basic BOLD experimental design
  - Block design – a & b
  - Event related design - c
  - Mixed design - d & e
  - Resting state fMRI

- ‘Control’ condition is very important since the baseline BOLD signal is unknown
  - Intra subject (condition) control
  - Inter subject (group) control

Birn, Neuroimage, 2004
EVALUATING CVR

- Basic BOLD activation calculation
  - General Linear Model (GLM) in two steps
    - Does an analysis of variance separately at each voxel (univariate)
    - Makes t statistic from the results of this analysis, for each voxel

$Y = X \cdot \beta + \varepsilon$

**Observed data:**
- $Y$ is the detected BOLD signal at various time points at a single voxel

**Design matrix:**
- Several components which explain the observed data, i.e. the BOLD time series for the voxel
- Equals experimental design convolute with HRF

**Parameters:**
- Define the contribution of each component of the design matrix to the value of $Y$
- Estimated so as to minimise the error, $\varepsilon$, i.e. least sums of squares

**Error:**
- Difference between the observed data, $Y$, and that predicted by the model, $X\beta$. 
EVALUATING CVR

- BOLD fMRI examples
  - Patients display compromised activation and connectivity patterns during the finger-thumb opposition task
  - Possible explanation: TBI-induced damage may extend beyond obvious lesion sites to affect remote brain networks due to damage to the integrity of CVR, which may imply functional reorganization of motor networks following TBI.

M. Kasahara, Neurology, 2010
EVALUATING CVR

- Other BOLD fMRI methods
  - ASL (CBF fMRI)
  - VASO (Vascular Space Occupancy, CBV fMRI)
  - SSFP (steady state free precession, frequency fMRI)
  - Others (Diffusion fMRI/ T2W / )

Scheffler, NMR Biomed, 2001
CONCLUSION

• CVR is a general definition of the range of cerebral perfusion variation from normal baseline
  • Assessed as blood flow, CBF/CBV, blood pressure, oxygen saturation, BOLD
  • Evaluated via TCD, PET, MRI, Optical infrared Spectroscopy, etc
  • Reflects cerebral vascular/perfusion response under various normal or diseased conditions

• Challenge
  • Further understand the working principle of CVR and autoregulation
  • Improving accuracy and specificity of the evaluating methods
  • Joint analysis of multi-modal data
THANK YOU
Methods to calculate CBF

- Kety-Schmidt’s Arteriovenous Difference
- Positron Emission Tomography (PET)
- Single Photon Emission Computed Tomography (SPECT)
- Magnetic Resonance Imaging (MRI)
- Cerebral Optical Infrared Spectroscopy
- Transcranial Doppler
- Thermal Diffusion
- Radioactive Tracer Washout
BACKGROUNDS

• CEREBRAL CIRCULATION

  • The Circle of Willis is a grouping of arteries near the base of the brain which is called the *Arterial Circle of Willis*. It is origin of six large vessels supplying the cerebral cortex.

  • Blood in one carotid artery distributed almost completely to the cerebral hemisphere on that side. Normally no crossing over occurs probably because the pressure is equal on both sides.