5th International Meeting on Cerebral Haemodynamic Regulation

13th - 14th July 2015
Chilworth Manor Hotel, Southampton

Organised by the Cerebral Autoregulation Research Network (CARNet)

Institute of Physics and Engineering in Medicine
www.ipem.ac.uk
CONTENTS

Final Programme

Poster list

Abstracts & PowerPoint Presentations

Exhibitors

Delegate List

Notes pages
The 5th International Meeting on Cerebral Haemodynamic Regulation (CARNet)
Monday 13th July 2015, Chilworth Manor Hotel, Southampton

FINAL PROGRAMME

08:50 – 09:00 Welcome
D M Simpson, University of Southampton, UK

Physiology 1

09:00 – 09:40 Neural control of the cerebral circulation
Invited Speaker: E Hamel, McGill University, Montreal, Canada

09:40 – 10:00 Cerebral blood flow changes in response to mild hypovolemia and positive pressure ventilation
M Skytioti, University of Oslo, Norway

10:00 – 10:20 Comparison between wavelet phaseshift and pressure reactivity index in determination of optimal cerebral perfusion pressure
X Liu, University of Cambridge, UK

10:20 – 10:40 Summary presentation of ‘Science Labs’
C Haubrich, University Hospital Aachen, Germany

10:40 – 11:10 Break & Exhibition & Set-up for posters

Measurement and Modelling 1

11:10 – 11:50 Individualised-patient modelling for in-silico interpretation and prediction of cerebral tissue physiology and pathophysiology
Invited Speaker: I Tachtsidis, University College London, UK

11:50 – 12:10 Assessment of dynamic cerebral autoregulation without blood pressure measurement
J L Jara, University of Santiago de Chile, Chile

12:10 – 12:30 The effect of random step-wise lower-body negative pressure on cardio and cerebrovascular measures
D Nikolic, University of Southampton, UK

12:30 – 12:50 Posters – 2 minute summary for posters

12:50 – 14:00 Lunch & Exhibition & Posters

Clinical 1

14:00 – 14:40 Lymphatic drainage of the brain and pathogenesis of Alzheimer’s disease
Invited Speaker: R Carare, University of Southampton, UK

14:40 – 15:00 Dynamic cerebral autoregulation is impaired in idiopathic Parkinson’s disease
V Haunton, University of Leicester, UK

15:00 – 15:20 Dynamic cerebral autoregulation impairment in stroke patients with coexistent large artery and small vessel disease
G Tian, Chinese University of Hong Kong, China

15:20 – 15:40 Posters – 2 minute summary for posters

15:40 – 16:10 Break & Exhibition & Posters

Measurement and Modelling 2

16:10 – 16:20 Consensus on TFA analysis – short presentation
J Claassen

16:20 – 16:40 Pseudorandom steps in lower body negative pressure can improve the repeatability in the assessment of cerebral autoregulation
D M Simpson, University of Southampton, UK

16:40 – 17:00 Contribution of identifiability techniques to cerebral autoregulation
A Mahdi, University of Oxford, UK

17:00 - 17:10 Posters – 2 minute summary for posters

17:10 – 17:30 Reproducibility of dynamic cerebral autoregulation measurement methods: a retrospective multicenter study
J W Elting, University Medical Centre Groningen, Netherlands

17:30 – 18:00 Break & Exhibition & Posters

18:00 – 19:00 CARNet AGM

19:00 – 19:30 Break

19:30 Dinner at Chilworth Manor
Clinical 2

09:00 – 09:40 The brain controls physical exercise, but is also challenged by it
Invited Speaker: J J van Lieshout, University of Amsterdam, The Netherlands

09:40 – 10:00 Cerebral autoregulation in different hypertensive disorders of pregnancy
T van Veen, University Medical Center Groningen, The Netherlands

10:00 – 10:20 Cerebrovascular autoregulation during and after surgical ligation of the ductus arteriosus using two surgical approaches in preterm infants
JW Elting, University Medical Center Groningen, The Netherlands

10:20 – 10:40 Is this autoregulation?
M Czosnyka, University of Cambridge, UK

10:40 – 11:10 Break & Exhibition & Posters

Measurement and Modelling 3

11:10 – 11:50 Managing an integrated database and large-scale collaboration: the pain and the pleasure
Invited Speaker: I Piper, South Glasgow University Hospital, Glasgow, UK

11:50 – 12:10 Reduced dynamic cerebral vasomotor reactivity in patients with mild cognitive impairment
V Marmarelis, University of Southern California, Los Angeles, USA

12:10 – 12:30 Model-assisted assessment of effects of age and hypertension on cerebral blood flow velocity
G. Mader, North Carolina State University, USA

12:30 – 12:50 The time-dependent variability of arterial CO2 influences the nonstationary properties of dynamic CO2 reactivity estimates during resting conditions
G. Mitsis, McGill University, Montreal, Canada

12:50 – 14:00 Lunch & Exhibition & Posters

Physiology 2

14:00 – 14:40 Blood pressure trials in acute stroke: an exercise in futility? - what is the role of other haemodynamic parameters?
Invited Speaker: T Robinson, University of Leicester, UK

14:40 – 15:00 Comparison of cerebral tissue oxygenation with cerebral arterial flow velocity responses to spontaneous changes in blood CO2 and pressure in older adults
V Marmarelis, University of Southern California, Los Angeles, USA

15:00 – 15:20 Effects of ageing, and measurement method, on gross and cortical cerebral autoregulatory upper limits
E Thompson, University of Birmingham, UK

15:20 – 15:40 Aging is associated with maintained cerebral autoregulation despite impaired cerebrovascular dilatory response to carbon dioxide
J Serrador, Rutgers Biomedical Health Sciences, Newark, NJ, USA

15:40 – 16:10 Break & Posters

Clinical 3

16:10 – 16:30 Acute stages of sport concussion: heart rate variability and blood pressure suppression during postural hemodynamic drives
J P Neary, University of Regina, Canada

16:30 – 16:50 Autoregulation-based optimal cerebral perfusion pressure in a prospective traumatic brain injury cohort
J Donnelly, University of Cambridge, UK

16:50 – 17:10 Relationship between cerebrovascular pressure reactivity and intracranial hypertension in traumatic brain injury
M Czosnyka, University of Cambridge, UK

17:10 – 17:30 Association of the outcome of traumatic brain injury patients with cerebrovascular autoregulation impairment events
V Petkus, Kaunas University of Technology, Lithuania

17:30 – 17:45 Break & remove posters

17:45 – 18:45 Tutorial / Clinic
J Serrador, Rutgers Biomedical Health Sciences, Newark, NJ, USA

19:15 Dinner
The 5th International Meeting on Cerebral Haemodynamic Regulation (CARNet)
Wednesday 15th July 2015, Chilworth Manor Hotel, Southampton
FINAL PROGRAMME

09:00 – 10:30  Bootstrap project
                J W Elting

10:30 – 10:50  Break

10:50 – 12:20  Science Labs
                C Haubrich


- Improved orthostatic tolerance - better cerebral blood flow regulation Andrea Maier MD, Christina Haubrich, Aachen, Germany.

- Can cerebral haemodynamic and autoregulation indices be used to determine disease phenotype in idiopathic Parkinson’s disease? Victoria Haunton, Leicester, UK.


- MRI measurements of cerebral autoregulation – proof of principle Daan de Jong, Nijmegen, the Netherlands.

- The effect of an extensive exercise program on mild cognitive impairment (MCI) and the role of cerebral perfusion regulation. Marit Sanders, Jurgen Claassen, Nijmegen, the Netherlands.

12:20 – 13:30  Lunch

13:30 – 14:30  Consensus on data analysis
                J Claassen

14:30 – 14:50  Break

14:50 – 15:50  Collaborative CARNet projects (TBC)
Physiology
1. Static and dynamic cerebral autoregulation – are we measuring the same thing?
   D. L. K. de Jong, Radboud University, Nijmegen, The Netherlands
2. Multimodal measurements of blood pressure and cerebral hemodynamic responses to hypercapnia in the MRI
   T. Myllylä, University of Oulu, Oulu, Finland
3. Are hormonal changes throughout the menstrual cycle associated with changes in cerebral autoregulation?
   M. Favre, Rutgers Biomedical Health Sciences, Newark, NJ, USA
4. Cerebrovascular responsiveness to carbon dioxide in atrial fibrillation
   I.D. Braz, University of Birmingham, UK
5. Influence of carbon dioxide on dynamic cerebral autoregulation during head-down tilt
   T. Kurazumi, Nihon University, Japan
6. Dopamine infusions improves cerebral autoregulation in newborn piglets
   V. Eriksen, Copenhagen University Hospital, Denmark

Measurement and Modelling
7. Measuring blood pressure oscillations in the MRI
   D. L. K. de Jong, Radboud University, Nijmegen, The Netherlands
8. Neurovascular Coupling and the BOLD signal
   T. David, University of Canterbury, New Zealand
9. Prospective comparative clinical study of non-invasive cerebrovascular autoregulation monitor
   V. Petkus, Kaunas University of Technology, Lithuania
10. A new index of dynamic cerebral autoregulation applied to the sit-to-stand maneuver
    M. Chacon, University of Santiago de Chile, Chile
11. Time varying estimates of dynamic cerebral autoregulation at rest
    R. Panerai, University of Leicester, UK
12. Can critical closing pressure replace EtCO2 as a determinant of CBFV in multivariate models?
    F.A. Bello Robles, Universidad de Santiago de Chile, Chile, CITIAPS
13. Controlling for heart rate variability improves the estimation of cerebral autoregulation and vasomotor reactivity in older adults and MCI patients
    V. Marmarelis, University of Southern California, Los Angeles, USA

Clinical
    J.M.D. van den Brule, Radboud University Nijmegen Medical Centre, the Netherlands
15. The relationship between BP variability, white matter lesions and frailty in Alzheimer's disease patients
    G. van Spijker, Radboud University Nijmegen Medical Centre, the Netherlands
16. Acute stages of sport concussion: heart rate variability and blood pressure suppression during postural hemodynamic drives
    J P Neary, University of Regina, Canada
17. Dynamic cerebral autoregulation in patients with hypertension
    R. Nogueira, University of São Paulo School of Medicine, São Paulo, Brazil
18. Cerebral Hemodynamics in thrombolysis for acute ischemic stroke: a systematic review and meta-analysis
    R. Nogueira, University of São Paulo School of Medicine, São Paulo, Brazil
19. Cerebral autoregulation in acute stroke: the influence of the NIH scale
    A Salinet, University of São Paulo, Brazil
Please note the following presentations are the versions received by IPEM by our printing deadline. Presenters may make subsequent changes to their presentations prior to the meeting. IPEM cannot guarantee the accuracy of the content.
Invited talk: Neural control of the cerebral circulation

Edith Hamel, PhD

Laboratory of Cerebrovascular Research, Montreal Neurological Institute, McGill University, Montréal, QC, Canada H3A 2B4

**Background:** The brain relies on a moment-to-moment supply of blood to replenish nutrients such as oxygen and glucose, which uses increase during neuronal activity. The cerebral circulation is thus under a tight control such that active neurons during a given task are preferentially perfused. This spatial and temporal correlation between changes in neurophysiology and hemodynamics under physiological conditions forms the basis of brain imaging techniques (fMRI, PET, SPECT) that use vascular signals as proxy for changes in neuronal activity, a phenomenon known as neurovascular coupling (NVC). Hence, changes in the activity of the neuronal networks that process incoming information drive the hemodynamic responses. In the cerebral cortex, the identity of the interneurons that shape the changes in the activity of neuronal networks varies depending on the afferent input activated. Moreover, how NVC responses are affected in conditions that deviate from baseline physiology remains unclear.

**Aims:** (1) Identify neuronal networks being selectively recruited by different afferent inputs (whisker or basal forebrain (BF) stimulation) and transducing neuronal signals into vasomotor responses, leading to increases in local cerebral blood flow (CBF). (2) Provide evidence for a role of astrocytes in these neurovascular interactions. (3) Interrogate how modulation of cortical activity by subcortical pathways can alter the coupling between changes in neuronal activity and brain hemodynamics.

**Methods:** Rats were used in these studies. Whisker or BF stimulation was used to increase CBF measured using laser Doppler flowmetry under control conditions or following pharmacological blockade of specific neuronal receptors or astroglial pathways. Additionally, whisker stimulation was performed under acute sub-threshold acetylcholine (ACh) enhancing conditions that do not directly increase CBF or, alternatively, under conditions of chronically depleted ACh (lesion of the BF with the selective cholinotoxin saporin). Cortical electrical activity was recorded (EEG, or local field potentials, LFPs), CBF was measured and brains perfused for identification of the neuronal networks recruited by the different stimulation conditions.

**Results:** Cortical glutamate-releasing excitatory pyramidal cells including those that constitutively co-express cyclooxygenase-2 (COX-2) and GABA-releasing inhibitory interneurons that contain vasoactive intestinal polypeptide (VIP) or somatostatin (SOM) were recruited during whisker or BF stimulation. A role for glutamate and GABA could be demonstrated, as well as their additive effect on the CBF responses. Both glutamate- and GABA-releasing neurons interacted with astrocytes to induce the NVC responses. CBF and neurophysiological responses to whisker stimulation were potentiated under enhanced ACh tone, and remained tightly correlated. In contrast, under deprived ACh tone, neuronal and vascular responses were both reduced, but the tight correlations between electrophysiology and hemodynamics were abolished.

**Conclusions:** Changes in the activity of both excitatory and inhibitory neurons contribute to the neurophysiological response computed to signal changes in the neurovascular unit leading to increased CBF. Further, our results reveal a mismatch in the coupling between sensory-evoked neuronal activity and hemodynamic signals in an ACh-deprived brain, a condition that mimics Alzheimer’s disease, raising caution in interpreting activity-induced hemodynamic responses in pathological conditions.

**Acknowledgements:** Supported by the Canadian Institute of Health Research (CIHR) and the Heart and Stroke Foundation of Québec and Canada.
CEREBRAL BLOOD FLOW CHANGES IN RESPONSE TO MILD HYPOVOLEMIA AND POSITIVE PRESSURE VENTILATION

Maria Skyttoi, Signe Søvik, Maja Elstad
Division of Physiology, Institute of Basic Medical Sciences, University of Oslo, Norway
Akershus University Hospital, Oslo, Norway

Background: Cerebral blood flow is related among other factors to mean arterial blood pressure (MAP), arterial pressure of carbon dioxide (CO₂), cardiac stroke volume and cardiac output (CO) [1-3]. Positive pressure ventilation (PPV) with low positive end expiratory pressure does not affect CO [4], but it may reduce cerebral blood flow through an increase in cerebral venous outflow resistance [5]. The purpose of the current study was to investigate the changes in internal carotid artery (ICA) blood flow in relation to changes in CO in simulated hypovolemia during spontaneous breathing and PPV.

Methods: Blood velocity in ICA and aorta measured by Doppler ultrasound was recorded during normovolemia and simulated central hypovolemia (Lower body negative pressure chamber) with or without pressure-regulated volume control ventilation (PPV) in 9 healthy volunteers. Heart rate (electrocardiogram), MAP (Finometer), respiratory frequency and end-tidal CO₂ (ETCO₂) were also recorded. Beat by beat cardiac stroke volume, CO, ICA blood beat volume and ICA blood flow were calculated from the velocity, diameter, angle of the beam in relation to ICA or aorta. Medians and 95% confidence intervals (CI) were calculated by Hodges-Lehmann’s estimate and Wilcoxon signed rank test for paired samples was used to test the difference between conditions.

Results: The preliminary results (median, 95% CI) show that ICA blood flow was preserved from baseline (289, 202-324ml/min) to mild hypovolemia (240, 213-330ml/min) under spontaneous breathing, but significantly decreased following PPV under hypovolemia (220, 157-259ml/min, p=0.0039). On the contrary, CO and MAP during hypovolemia did not change significantly from spontaneous breathing (CO: 3.6, 2.2-4.0L/min, MAP: 80, 72.9-85mmHg) to PPV (CO: 3.4, 2.4-3.6L/min, MAP: 79.4, 70.7-82.4mmHg). Another finding was that there was no difference in ICA blood flow between PPV-normovolemia (243, 157-280ml/min) and spontaneous breathing-hypovolemia. ETCO₂ did not differ significantly between spontaneous breathing (4.9, 4.3-4.5 kPa) and PPV (4.4, 4-4.7kPa) during normovolemia, but it decreased during combined hypovolemia and PPV (4.0, 3.5-4.5 kPa).

Discussion: Cerebral blood flow declined during hypovolemia and PPV, whereas no change was observed in CO and MAP. The decrease in cerebral blood flow decrease could be attributed to the increase of cerebral venous outflow resistance due to PPV and the mild hypocapnia. The slight change in ETCO₂ justifies the assumption that the diameter of ICA did not change[6].

Conclusion: ICA blood flow reduced significantly during PPV combined with simulated hypovolemia compared to hypovolemia alone. Mechanical ventilation may represent a challenge for cerebral blood flow regulation during hypovolemia, which is clinically relevant for hemodynamically compromised patients.

Key references
Cerebral blood flow changes in response to mild hypovolemia and positive pressure ventilation
M Skytioti, University of Oslo, Norway

Background

- Positive pressure ventilation (PPV)
- Hypovolemia

Regulation of cerebral blood flow

- Arterial pressure of carbon dioxide (PaCO₂)
- Mean ArTERIAL blood pressure (MAP)
- Cardiac output (CO)

Effects of MAP, PCO₂, CO on CBF

Mean cerebral blood flow Fluctuation (cm/s)

MAP fluctuation (mmHg)

Purpose

Cerebral blood flow changes in response to hypovolemia combined with positive pressure ventilation

- Spontaneous breathing – PPV
- Normovolemia – Simulated hypovolemia

Methods

- Subjects
  - Medical students
    - n=9
    - Age: 22 (19-30)

- Positive Pressure Ventilation
  - Training of the subjects
  - Mild positive pressure (max.: 14 cmH₂O)
  - Low degree of Positive End Expiratory Pressure (1.4 cmH₂O)

- Lower Body Negative Pressure
  - Simulated hypovolemia
  - Negative pressure: -30mmHg

Methods – Study protocol

Lower body negative pressure (LBNP)

Spontaneous breathing

Positive pressure ventilation

5 min

LBNP

5 min

Spontaneous breathing

Positive pressure ventilation

5 min

5 min

Spontaneous breathing

Positive pressure ventilation
Cerebral blood flow changes in response to mild hypovoleemia and positive pressure ventilation
M Skytioti, University of Oslo, Norway

Measurements

- Internal carotid artery (ICA) blood velocity (doppler u/s)
- Aorta blood velocity (doppler u/s)
- Diameters of ICA and aortic ring
- Respiratory frequency
- ECG - Heart rate
- Mean arterial pressure - Finometer
- End tidal CO$_2$ - capnography
- LBNP

Recordings

- Left cardiac stroke volume
- Cardiac output
- ICA blood beat volume
- ICA blood flow

Calculations

- Left cardiac stroke volume
- Cardiac output
- ICA blood beat volume
- ICA blood flow

Statistical analysis

- Non-parametric statistics
- Level of significance p=0.01 (Bonferroni correction)

Recordings

- MAP changes

<table>
<thead>
<tr>
<th>Condition</th>
<th>MAP (mmHg)</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normovolemia</td>
<td>74.3</td>
<td>74</td>
</tr>
<tr>
<td>Hypovolemia</td>
<td>79.4</td>
<td>80</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>CO (L/min)</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normovolemia</td>
<td>4.9</td>
<td>4.9</td>
</tr>
<tr>
<td>Hypovolemia</td>
<td>3.6</td>
<td>3.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>EtCO$_2$ (kPa)</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normovolemia</td>
<td>4.9</td>
<td>4.8</td>
</tr>
<tr>
<td>Hypovolemia</td>
<td>4.5</td>
<td>4.4</td>
</tr>
</tbody>
</table>

*p* difference from baseline

**p**=0.008
Cerebral blood flow changes in response to mild hypovolemia and positive pressure ventilation
M Skytioti, University of Oslo, Norway

ICA blood flow changes

<table>
<thead>
<tr>
<th></th>
<th>Normovolemia</th>
<th>Hypovolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood flow (ml/min)</td>
<td>269</td>
<td>243</td>
</tr>
<tr>
<td>Median</td>
<td>217</td>
<td>240</td>
</tr>
</tbody>
</table>

*Significant difference from baseline, p<0.004

Preliminary Results

<table>
<thead>
<tr>
<th></th>
<th>PPV</th>
<th>Hypovolemia</th>
<th>PPV + hypovolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood flow (ml/min)</td>
<td>269</td>
<td>243</td>
<td>217</td>
</tr>
<tr>
<td>Median</td>
<td>240</td>
<td>240</td>
<td>240</td>
</tr>
</tbody>
</table>

Discussion

PPV
- No change in CO
- No change in MAP
- ↓ ETCO₂

Hypovolemia
- ↓ CO
- ↓ ETCO₂
- ↑ MAP

- Slight decrease in ETCO₂ → ICA diameter constant (Sato et al, 2012)

Conclusion

Significant reduction in cerebral blood flow during hypovolemia and positive pressure ventilation.

Positive pressure ventilation may represent a risk for cerebral perfusion in hemodynamically compromised patients.

Acknowledgments

“Neuroprotection and Cardiovascular control”
Group leader: Marianne Thoresen
University of Oslo

Thank you
Comparison between wavelet phaseshift and pressure reactivity index in determination of optimal cerebral perfusion pressure

Xiuyun L, Marek C, Joseph D, Georgios V, Manuel C, Danilo C, Cristine C, Peter S

Division of Neurosurgery, Department of Clinical Neurosciences, Addenbrooke’s Hospital, University of Cambridge, Cambridge, UK

Background
The latest Brain Trauma Foundation guidelines for the management of traumatic brain injury (TBI) mention the need for the development of efficient methods to determine the optimal cerebral perfusion pressure (CPP) based on quantitative indices of pressure autoregulation. We investigated the relationship between the wavelet based phase-shift between slow waves of arterial blood pressure (ABP) and intracranial pressure (ICP). We hypothesized it reflects the state of cerebral vasoractivity and compared it to the pressure reactivity index (PRx) [1-8].

Methods
A retrospective analysis of prospectively collected data from 287 TBI patients (admitted to the NCCU, Addenbrooke’s Hospital between 1992 to 2013) with continuous ABP and ICP monitoring was conducted. Outcome was assessed at 6 months. CWT analysis was performed (using complex Morlet wavelet) and a phase shift between ABP and ICP calculated in the frequency range of 0.01-0.07 Hz (very low frequency, VLF) and 0.07–0.2 Hz (low frequency, LF) from 300s windows. PRx was calculated as a short term moving Pearson correlation coefficient between 30 samples of consecutive 10 second averages of ICP and ABP. Subsequently phase-shift and PRx values were averaged within corresponding CPP bins of 5 mmHg. An automated curve fitting method was applied to determine the optimal CPP (at the minimum value for PRx or maximum value for phase shift). A time trend of CPPopt was created using a moving 4-hr window, updated every minute. The difference between median CPP and CPPopt (determined by wavelet method) was calculated for each patient.

Results

Fig. 1 shows the relationship between the phase shift and PRx with CPP. Phase-shift_VLF and PRx both showed an extremum at CPP of 75 mmHg, while phase-shift_LF remained inconclusive.

Fig. 2 shows that both wavelet phase-shift and PRx can distinguish the favorable and unfavorable...
(GOS 1-3), as well as fatal and non-fatal outcome. In favorable group, as well as in the non-fatal group, PRx is significantly lower and the phase shift is higher (p<0.001), compared to the unfavorable and fatal outcome groups respectively.

Fig.2 Wavelet phase shift vs. outcome (A,B, D,E); PRx vs outcome (C,F).

Fig.3 demonstrates that for this TBI cohort, using wavelet method to determine the CPPopt, the patients outcome was associated significantly with the difference between CPP and CPPopt. Mortality was associated with relative “hypoperfusion” (CPP < CPPopt), severe disability with “hyperperfusion” (CPP > CPPopt), and favorable outcome was associated with smaller deviations of CPP from the individualized CPPopt.

Fig.3 The relationship between outcome and distance of CPP from CPPopt, determined by the wavelet method.( A) Mortality increases steadily when median CPP decreases below the threshold of optimal CPP; (B) Severe Disability increases while the CPP increases above CPPopt.

**Conclusion**

Wavelet phase shift is a new index of cerebral autoregulation assessment. It can distinguish the patients’ outcome. Wavelet phaseshift between ABP and ICP in very low frequency range can be applied in determination of CPPopt. Patients with a median CPP close to CPPopt were more likely to have a favorable outcome than those in whom median CPP was widely different from CPPopt.


Assessment of dynamic cerebral autoregulation without blood pressure measurement

Jara JL, 1Chacón M, 2Panerai RB
1Departamento de Ingeniería Informática, Universidad de Santiago de Chile, Chile.
2Department of Cardiovascular Sciences, University of Leicester, UK.

**Background.** Horsfield et al. [2] assessed the efficiency of Dynamic Cerebral Autoregulation (dCA) in different regions of the brain from magnetic resonance (MR) images by fitting templates to the MR signal scanned during an unknown transient drop in arterial blood pressure (ABP) provoked by thigh-cuff manoeuvres (THCM). The MR time-series exhibited a decrease and subsequent recovery, similar to the cerebral blood flow velocity (CBFV) responses observed in the main cerebral arteries using transcranial Doppler [3]. Recently, Chacón et al. [1] proposed a novel dCA index, namely the model-free dynamic AutoRegulation Index (mfARI), which yielded slightly higher and less fluctuating values than the classic ARI proposed by Tiecks et al. [4]. Calculating an mfARI value involves three parameters, of which two are gauged by examining exclusively the autoregulatory response signal, as the MR approach does, whilst the other requires knowing the ABP signal. This study aims at comparing mfARI values obtained using the two response-only and all three parameters to assess its potential application with MR images.

**Methods.** This study uses the same data of [1], which correspond to the mean ABP and CBFV signals of 16 healthy subjects. 91 theoretical CBFV responses were generated with the traditional dCA model defined in [4] for ARI values equally-spaced in the range 0-9. The three mfARI parameters were gauged from these theoretical responses and mfARI values were calculated using a linear regression between the generating ARI values and the set of three parameters. Similarly, a new dCA index, named no-pressure AutoRegulation Index (npARI), could be obtained utilising the set of two response-only parameters. Subject mean values were calculated and compared with a confidence level of 95%.

**Results.** The regression models obtained were successful in both cases with adjusted R² of 0.998 using three parameters and 0.991 using the two response-only parameters respectively. The Anderson-Darling test found no deviation from normality for both subject mean mfARI values (A=0.300, p=.592) and subject mean npARI values (A=0.198, p=.864). No significant difference between the subject means could be determined with a Paired Student’s T test (t(82)=0.63, p=.531, Cohen’s d=0.07). However, the overall mean npARI (5.72±1.05) was slightly higher than the overall mean mfARI (5.54±0.95).

**Discussion.** It is rather surprising than the relationship between the recoveries of ABP and CBFV could have so little effect in the overall mean value. One possible explanation is that only healthy individuals were considered and thus the drop and recovery of ABP produced by the THCM is similar for all of them. Although individual differences could deserve a more detailed analysis, mfARI and npARI values are quite similar in the population studied. Unlike the index for MR images, npARI values closely correspond to classic ARI values, as guaranteed by the goodness-of-fit- of the regression model utilised, facilitating their comparison with previous studies in the literature.

**Conclusion.** The proposed npARI, an adaptation of the novel mfARI, can be used with MR images to assess dCA in different regions of the brain, at least for healthy subjects.

**Key references.**
Assessment of dynamic cerebral autoregulation without blood pressure measurement
J L Jara, University of Santiago de Chile, Chile

Motivation

- TCD has a poor spatial resolution
- MR images could provide it
  - Saeed et al. showed mean MR signal is similar to TCD
  - Horsfield et al. proposed a method to assess dCA at voxel level
    - They found indications that dCA might not be uniform across the brain

Assessment of dCA without ABP

- They found indications that dCA might not be uniform across the brain

Motivation

- MR dCA maps were obtained fitting templates
  - Similar to traditional ARI
  - Based on autoregulatory response only
    - Unknown blood pressure drop
    - But MRARI is in scale [0, 1.5]
    - Making comparisons difficult

Previous work

- Chacón et al. proposed model-free ARI (mfARI)
  - Based on general approximations (rather than equations)

Assessment of dCA without ABP

Aim

- Evaluate a two-parameter version of mfARI
  - Using only the CBFV response parameters: $\Delta t$ and $K_s$
  - It could be adapted for MR images
  - No-pressure AutoRegulation Index: npARI

Method

- npARI parameters
  - 91 theoretical CBFV responses were generated
    - Using dCA model defined by Tiecks et al.
    - ARI values 0.0, 0.1, 0.2, 0.3, ..., 8.9, 9.0
    - mfARI parameters were gauged from these theoretical responses
    - $\phi$ parameter was discarded
Assessment of dynamic cerebral autoregulation without blood pressure measurement
J L Jara, University of Santiago de Chile, Chile

Method

- Estimation of npARI
  - A linear regression model was obtained between ARI values and pairs of npARI parameters
- Subjects
  - 16 healthy individuals
  - Three thigh-cuff manoeuvres
- Comparisons
  - Subject-mean mfARI and npARI values
  - Compared with 95% confidence level

Results

- Regression model
  - Adjusted R² of 0.991 using the npARI parameters
    - 0.998 using all three mfARI parameters
- Subject mean values
  - No deviation from normality was found in both indices
    - Anderson-Darling test: mfARI p=0.592, npARI p=0.864
  - Overall mean npARI: 5.72 ± 1.05
    - Slightly higher than overall mean mfARI: 5.54 ± 0.95
  - No significant difference between indices
    - Paired Student’s T test: p=0.531, Cohen’s d=0.07

Discussion

- mfARI and npARI values were quite similar on the population studied
  - The relationship ABP/CBFV had little effect on the index values
    - Suggests the drop and recovery of ABP were similar
    - Perhaps only healthy individuals were considered
- npARI values closely correspond to classic ARI values
  - Unlike the index for MR images
  - Guaranteed by the goodness-of-fit of the regression model
  - Comparison with previous studies will be easier

Conclusion

- npARI can be used with MR images to assess dCA
  - In different regions of the brain
  - At least for healthy subjects

Key references

THE EFFECT OF RANDOM STEP-WISE LOWER BODY NEGATIVE PRESSURE ON CARDIO AND CEREBROVASCULAR MEASURES

1Nikolic D, 2Birch, AA, 3Panerai RB, 1Simpson DM
1Institute of Sound and Vibration Research, University of Southampton, UK
2Department of Medical Physics and Bioengineering, University Southampton Hospital, UK
3Department of Cardiovascular Sciences, University of Leicester, UK
email: D.Nikolic@soton.ac.uk

Background. One of the issues in the measurement of dynamic cerebral autoregulation (CA) from spontaneous fluctuations in arterial blood pressure (ABP) is the low variability, which is associated with reduced repeatability. Therefore, pseudorandom step-wise lower-body negative pressure (LBNP) was introduced with aim to provoke a small increase in blood pressure variability. We report on the dynamic changes in ABP, cerebral blood flow velocity (CBFV), end-tidal CO₂ (etCO₂) and heart-rate (HR) thus introduced.

Methods. Thirty approximately 5 minutes long recordings were acquired during two sessions between 2 and 25 days apart, from 15 healthy subjects (aged 32±10 years, 7 female, height 171.3±8.0 cm, weight 72.9±15.2 kg), in supine rest. In each recording, a total of 20 LBNP periods of 5, 10 and 20 s duration (changing approximately from –20 to –100 mmHg) were applied at random intervals. ABP was recorded with a Finometer, CBFV with transcranial Doppler ultrasound in the middle cerebral artery, heart-rate using an ECG and end-tidal CO₂ from a capnograph. For each subject, 5 minutes of baseline data (no LBNP) were also acquired.

Results. No significant change in autoregulation (mean phase in the range 0.07-0.20 Hz, p>0.4, Wilcoxon) was noted, though there was a drop in etCO₂ (5.00 to 4.68%, p<5·10⁻⁵) between the average values calculated for the 5 minute baseline and LBNP epochs. Moreover, HR over the whole recording decreased significantly during the random LBNP application (p<10⁻²). The step-wise LBNP introduced the expected transient in ABP and CBFV, which was largely complete within about 8-10 seconds, with CBFV recovering faster than ABP. Table 1 shows significant changes in most variables at LBNP transients. Surprisingly, LBNP induced a brief transient drop in HR at the onsets (p=4·10⁻⁸, Friedman test, comparing consecutive one-second intervals around the transients).

Table 1. Comparison of changes pre (1-2 s) and post (2-3 s) LBNP changes (Wilcoxon test)

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Units</th>
<th>PRE mean</th>
<th>PRE std</th>
<th>POST mean</th>
<th>POST std</th>
<th>p</th>
<th>LBNP ONSET</th>
<th>LBNP OFFSET</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABP</td>
<td>mmHg</td>
<td>86.49</td>
<td>13.16</td>
<td>80.24</td>
<td>12.77</td>
<td>&lt;10⁻⁵</td>
<td>80.95</td>
<td>12.47</td>
</tr>
<tr>
<td>CBFV</td>
<td>cm/s</td>
<td>64.85</td>
<td>11.07</td>
<td>60.23</td>
<td>10.19</td>
<td>&lt;10⁻⁵</td>
<td>62.13</td>
<td>10.70</td>
</tr>
<tr>
<td>HR</td>
<td>beats/min</td>
<td>65.15</td>
<td>9.94</td>
<td>66.69</td>
<td>10.07</td>
<td>0.0024</td>
<td>67.72</td>
<td>11.24</td>
</tr>
<tr>
<td>etCO₂</td>
<td>%</td>
<td>4.75</td>
<td>0.44</td>
<td>4.63</td>
<td>0.51</td>
<td>0.0003</td>
<td>4.62</td>
<td>0.48</td>
</tr>
<tr>
<td>RR</td>
<td>breaths/min</td>
<td>15.28</td>
<td>3.79</td>
<td>15.56</td>
<td>3.78</td>
<td>0.0092</td>
<td>15.29</td>
<td>3.60</td>
</tr>
</tbody>
</table>

Discussion and Conclusion. The relatively small changes in LBNP demonstrated a clear response in ABP and provoked cerebral autoregulation. Subjects found the procedure acceptably comfortable. Ten second intervals of LBNP would appear to be sufficient to allow the ABP and CBFV responses to be largely complete. Shorter intervals clearly demonstrate the well-known left-shift of CBFV relative to ABP. There is a clear evidence of intra-subject variability in the responses, with some subjects showing consistently much stronger changes than others. The application of LBNP does not just lead to a drop in ABP but also impacts on HR and etCO₂, which both show a transient effect at the onset of the steps, which may confound inferences. In previous work, an improvement in CA was seen during LBNP, which may be associated with the hypercapnia induced.

The change in ABP induced clearly has the potential to improve the assessment of CA, but whether this is an effective approach requires further investigation.
The effect of random step-wise lower-body negative pressure on cardio and cerebrovascular measures

Dragana Nikolić
Anthony Birch
Ronney Panerai
David Simpson
13-15 July 2015, CARNET, Southampton

Objective

To examine the influence of pseudo-random LBNP changes on:
- arterial blood pressure,
- cerebral blood flow,
- end-tidal CO₂,
- heart rate and
- respiratory rate.

Outline

• Methodology
  - Experimental protocol
  - Dataset recorded (LBNP)
  - Preprocessing and analysis
    - Data preprocessed and edited to remove artefacts
    - Coherence averaging method used to examine LBNP effect
  - Results
    - Influence of LBNP changes on mean ABP, mean CBFV, etCO₂ and HR
    - Consistency between repeated sessions
    - Consistency between two protocols (baseline and LBNP)
  - Summary

Methodology

EXPERIMENTAL SET-UP

Subject, in supine position with the head elevated, exposed to lower body negative pressure

Low body negative pressure (LBNP)

• CA observed during augmented ABP variations
• 20 step-wise changes of LBNP (from –15 to –100 mmHg) with a duration of 5, 10 and 20 s were applied over 5 minute.

SAMPLE RECORDING
The effect of random step-wise lower-body negative pressure on cardio and cerebrovascular measures

D Nikolic, University of Southampton, UK

Data set used for examining LBNP effects

- **Data analysed**
  - data recorded at the Southampton General Hospital
  - signals simultaneously recorded and sampled at 250 Hz (MP150, BIOPAC)
  - extracted baseline and LBNP segments approximately 5 minutes long
  - coherent averaged mean ABP, mean CBFV, etCO2 and HR signals used to examine the effects caused by rapid changes of LBNP

- **Subjects**
  - 15 healthy volunteers
    - age 32 ± 10 years, height 171 ± 8 cm, weight 73 ± 15 kg, 7 female
  - recordings repeated on 2 separate occasions between 2 and 25 days apart (30 LBNP segments in total)

Results.
The effect of random step-wise lower-body negative pressure on cardio and cerebrovascular measures
D Nikolic, University of Southampton, UK

LBNP effect on mean ABP

LBNP effect on mean CBFV

LBNP effect on end-tidal CO₂
The effect of random step-wise lower-body negative pressure on cardio and cerebrovascular measures
D Nikolic, University of Southampton, UK

### Results

**LBNP effect on heart rate**

- **ABP**
- **CBFV**
- **CBOV**
- **RRI**
- **LBNP onset**

**LBNP effect on heart rate**

- **ABP**
- **CBFV**
- **CBOV**
- **RRI**
- **LBNP onset**

### Results

**LBNP effect on cardio and cerebral measures**

Pre and post changes of mean values during LBNP onsets and offsets

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Units</th>
<th>BASELINE</th>
<th>LBNP</th>
<th>LBNP-BASELINE (Wilcoxon test)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>mean</td>
<td>std</td>
<td>mean</td>
</tr>
<tr>
<td>ABP</td>
<td>[mmHg]</td>
<td>86.49</td>
<td>13.28</td>
<td>80.24</td>
</tr>
<tr>
<td>CBFV</td>
<td>[cm/s]</td>
<td>62.65</td>
<td>10.98</td>
<td>60.51</td>
</tr>
<tr>
<td>eCO2 [%]</td>
<td></td>
<td>4.75</td>
<td>0.45</td>
<td>4.26</td>
</tr>
<tr>
<td>HR [beats/min]</td>
<td></td>
<td>67.95</td>
<td>11.74</td>
<td>65.37</td>
</tr>
</tbody>
</table>

### Results

**LBNP vs BASELINE data comparison (1/3)**

Mean values of cardio and cerebral measures

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Units</th>
<th>BASELINE</th>
<th>LBNP</th>
<th>LBNP-BASELINE (Wilcoxon test)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>mean</td>
<td>std</td>
<td>mean</td>
</tr>
<tr>
<td>ABP</td>
<td>[mmHg]</td>
<td>86.49</td>
<td>13.28</td>
<td>80.24</td>
</tr>
<tr>
<td>CBFV</td>
<td>[cm/s]</td>
<td>62.65</td>
<td>10.98</td>
<td>60.51</td>
</tr>
<tr>
<td>eCO2 [%]</td>
<td></td>
<td>4.75</td>
<td>0.45</td>
<td>4.26</td>
</tr>
<tr>
<td>HR [beats/min]</td>
<td></td>
<td>67.95</td>
<td>11.74</td>
<td>65.37</td>
</tr>
</tbody>
</table>

### Results

**LBNP vs BASELINE data comparison (2/3)**

Consistency between two separate sessions

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Units</th>
<th>BASELINE</th>
<th>LBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>mean</td>
<td>std</td>
</tr>
<tr>
<td>ABP</td>
<td>[mmHg]</td>
<td>0.38</td>
<td>0.03</td>
</tr>
<tr>
<td>CBFV</td>
<td>[cm/s]</td>
<td>0.80</td>
<td>0.02</td>
</tr>
<tr>
<td>eCO2 [%]</td>
<td></td>
<td>0.79</td>
<td>0.03</td>
</tr>
<tr>
<td>HR [beats/min]</td>
<td></td>
<td>0.70</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Results

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Units</th>
<th>BASELINE vs LBNP</th>
<th>ICC</th>
<th>p</th>
<th>ICC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABP</td>
<td>mmHg</td>
<td>0.69</td>
<td>0.000008</td>
<td>0.70</td>
<td>0.000008</td>
<td></td>
</tr>
<tr>
<td>CBV</td>
<td>cm³/s</td>
<td>0.84</td>
<td>&lt;0.0001</td>
<td>0.94</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>etCO₂</td>
<td>[ % ]</td>
<td>0.05</td>
<td>&lt;0.0001</td>
<td>0.46</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>beats/min</td>
<td>0.67</td>
<td>&lt;0.0001</td>
<td>0.83</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Summary

- The relatively small changes in LBNP demonstrated a clear response in ABP and provoked cerebral autoregulation.
- The application of LBNP has also impacts on etCO₂ and HR, which both show a transient effect at the onset of the steps, which may confound inferences. In previous work, an improvement in CA was seen during LBNP, which may be associated with the hypercapnia induced.
- There is a clear evidence of intra-subject variability in the responses, with some subjects showing consistently much stronger changes than others.
- The change in ABP induced clearly has the potential to improve the assessment of CA, but whether this is an effective approach requires further investigation.

Thank you.
Lymphatic drainage of the brain and pathogenesis of Alzheimer’s disease


Institute for Life Sciences, University of Southampton, UK.

Open University, UK.

**Background:** With increasing age and in Alzheimer’s disease, amyloid-β (Aβ) accumulates as insoluble plaques in the brain and deposits in blood vessel walls as cerebral amyloid angiopathy (CAA) (1). The severity of CAA correlates with the degree of cognitive decline in dementia. The distribution of Aβ in the walls of capillaries and arteries in CAA suggests that Aβ is deposited in the perivascular pathways by which interstitial fluid drains from the brain (2). Soluble Aβ within the extracellular spaces of the brain is degraded by enzymes, cleared across the endothelium, is taken up by perivascular cells and also enters the basement membranes of capillaries to drain towards leptomeningeal arteries along the arterial basement membranes that surround smooth muscle cells (3).

**Methods:** Using immunocytochemistry on human brains, experimental studies in mice with confocal and electron microscopy techniques as well as mathematical modelling and atomic force microscopy we have established that morphological, biophysical and biochemical changes associated with arteriosclerosis, aging and possession of apolipoprotein E4 genotype lead to a failure of perivascular drainage of soluble proteins, including Aβ. Mathematical and computational modeling suggests that strength of arterial pulsations coupled with the valve-effects of the proteins that make up the basement membranes provide the motive force necessary for the efficient clearance of fluid and amyloid-β from the brain.

**Results:** Cerebrovascular basement membranes change with age, hypercholesterolaemia and possession of Apolipoprotein E4 genotype (4-6). The basement membranes of capillaries and arteries are the lymphatic drainage pathways of the brain, restricted to the clearance of solutes and do not allow the drainage of particles, cells, immune complexes or lipoproteins (7).

**Conclusions:** The failure of perivascular clearance of Aβ appears to be a major factor in the accumulation of Aβ in CAA and may have significant implications for the design of therapeutics for the treatment of Alzheimer’s disease (8)

**References**


Aβ drains out of the brain along basement membranes of capillaries and arteries.

Aβ in basement membranes of capillaries and arteries

Subarachnoid Space

Capillary

Artery

Smooth muscle cell

Brain

Leptomeningeal artery

= Basement membrane containing no Aβ

= pia mater
DYNAMIC CEREBRAL AUTOREGULATION IS IMPAIRED IN IDIOPATHIC PARKINSON’S DISEASE

1 Haunton VJ, 1Hanby M, 2Lo N, 1Panerai R, 1Robinson TG, 1Department of Cardiovascular Sciences, University of Leicester, UK. 2University Hospitals of Leicester NHS Trust, Leicester, UK

Background. Idiopathic Parkinson’s disease (IPD) is a common neurodegenerative disorder characterised by neuronal loss and depletion of the neurotransmitter dopamine. It is hypothesised that cerebral autoregulation (CA) may be impaired in PD but, to date, there have been very few studies exploring this. This study evaluated CA indices in both the ‘on’ and ‘off’ states of the disease using transcranial Doppler (TCD) ultrasonography.

Methods. 45 patients with IPD (male=33, mean age 67.6 years, right handed = 42, median disease duration 3.9 years [range 0.3-13.1 years]), treated with usual dopaminergic medications, and 45 age and sex matched healthy controls (HC), underwent supine recordings of simultaneous bilateral middle cerebral artery cerebral blood flow velocity (CBFV), beat-to-beat blood pressure, electrocardiography and end-tidal CO2. Exclusion criteria were a history of diabetes, dementia, stroke, ischaemic heart disease, deep brain stimulation, and peripheral neuropathy. IPD patients were scanned in both their on (medicated) and off (un-medicating) states on two separate mornings, no more than two weeks apart. For the recordings made in the off state, patients were required to abstain from their anti-Parkinsonian medications for either 12 hours (short-acting preparations) or 24 hours (long-acting preparations) before attending for the measurement. On and off states were objectively evaluated using the Unified Parkinson’s Disease Rating Scale (UPDRS)1. Autoregulation index (ARI) values were calculated using transfer function analysis3 and the ‘best fit’ least squares method of matching CBFV step responses to one of the 10 model curves proposed by Tiecks2.

Results. No significant differences were observed in peripheral haemodynamic data (arterial blood pressure, heart rate and end-tidal CO2) between the IPD on state, IPD off state and HC groups. In IPD patients, MCBFV and ARI values did not differ significantly between brain hemispheres, or between on and off states. However, both MCBFV and ARI values were significantly lower in IPD patients than in HC. Mean ARI for IPD patients in their on state was 4.5, in their off state 4.7, compared to 5.0 for HC (ANOVA F=3.539, p <0.05). Frequency domain parameters including coherence, phase and gain also demonstrated statistically significant differences between IPD patients and HC at low, middle and high frequency ranges.

Discussion. This is the first study to have reported CA in IPD in terms of an ARI, and demonstrates that CA is impaired in the disease. That MCBFV is lower in patients with IPD is largely in disagreement with the limited existing literature. The relatively low median disease duration in this study suggests that CA impairment appears early in the disease. Dopaminergic medications do not appear to significantly affect CA in IPD.

Conclusion. Further studies exploring the specific effects of disease stage, disease phenotype, and individual classes of dopaminergic medications on CA in PD would be helpful, and may have significant clinical implications.

Key references

2 Tiecks FP et al. Stroke 1995;26:1014-1019
Dynamic cerebral autoregulation is impaired in idiopathic Parkinson’s disease
V Haunton, University of Leicester, UK

Cerebral Autoregulation in Idiopathic Parkinson’s Disease
Dr Victoria Haunton
NIHR Academic Clinical Lecturer
On behalf of the CHIASM group, Cardiovascular Sciences, University of Leicester

Talk Outline
- Parkinson’s Disease
- Why study CA in Parkinson’s disease?
- TCD studies in Parkinson’s disease
- Leicester work
- Questions and discussion

Prevalence
- 0.6% 65-69
- 3.5% 80-89

Aetiology
- Poorly understood
  - Genetics
  - Environmental factors
- Cellular mechanisms
  - Oxidative stress
  - Mitochondrial dysfunction
  - Glutamate excitotoxicity
  - Apoptosis

Pathophysiology

Clinical Presentation
- Non-motor features
  - Autonomic dysfunction
  - Psychiatric disturbances
  - Pain
- Sleep disorders
- Fatigue
- Unilateral onset
- Progressive
- 80% of patients will develop dementia
Dynamic cerebral autoregulation is impaired in idiopathic Parkinson’s disease

V Haunton, University of Leicester, UK

### Diagnosis

- Clinical Evaluation
  - Needs specialist evaluation

- Brain imaging
  - DaT scanning
  - TCCS

### Substantia Nigra TCCS

![Healthy Control vs Parkinson's Disease](image)


### Treatment

- Nil curative
- Dopaminergic drug therapies
- Deep brain stimulation
- Multidisciplinary team care

### Why study CA in Parkinson’s?

- Understand neurovascular pathways in neurodegeneration
- Dementia
- Role of dopamine in CBF and CA
- Understand the autonomic component of the disease
  - Orthostatic hypotension

### Rodent models

- Study of oxidative stress in a rat model of chronic brain hyperperfusion
- Studies on astroglial and cognitive effects of chronic cerebral hyperperfusion in the rat: A model for chronic cerebral hyperperfusion-related

- Cerebrovascular autoregulation is profoundly impaired in mice overexpressing amyloid precursor protein

### Dopamine

- **DOPAMINE INVOLVED IN REGULATION OF CBF**
  - Dopaminergic neuronal terminals arise from the basal forebrain nucleus, raphé nuclei and the LC (Iadecola et al 1998)
  - Close proximity to penetrating arteries, capillaries and pericytes (Krimer et al 1998)
  - Dopamine has direct and indirect effects on vascular resistance via pericytes (Choi 1998)

- **DOPAMINE VASODILATORY**
  - PET studies report resting CBF to be higher in medicated than un-medicated patients (Lesnikow et al 1998, Placentini et al 2000, Rotenberg et al 1999)

- **DOPAMINE VASOCONSTRICTORY**
  - In-vitro studies of monkeys (Krimer et al 1998) and cats (Gibson et al 1998)
  - Perivascular application of dopamine results in 20% vasoconstriction.

- **REASONS FOR CONTRADICTIONS**
  - Dopamine receptor sub-types: D1-D5
  - D2 and D3 vasodilatation, or D2/D5 vasoconstriction (Zha et al 2004)
Dynamic cerebral autoregulation is impaired in idiopathic Parkinson’s disease
V Haunton, University of Leicester, UK

Orthostatic hypotension
- 40% of patients with PD
- Felt to be an independent risk factor for cognitive decline, increased mortality and requirement for institutional care
- Mechanisms in PD not fully understood
  - Degeneration of both central and peripheral autonomic centres

What is already known?

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Group</th>
<th>Method of CBF measurement</th>
<th>Intervention</th>
<th>On/Off</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamdy et al.</td>
<td>15 PD patients</td>
<td>TCD of MCA</td>
<td>Breath hold</td>
<td>ON AND OFF</td>
<td>CA Impaired</td>
</tr>
<tr>
<td>Niehaus et al.</td>
<td>15 PD patients</td>
<td>TCD of MCA</td>
<td>Baseline supine recording</td>
<td>Passive 70° tilt</td>
<td>ON</td>
</tr>
<tr>
<td>Troisi et al.</td>
<td>12 PD patients</td>
<td>TCD of MCA</td>
<td>Baseline supine recording</td>
<td>Emotional stimulation via picture cards</td>
<td>ON AND OFF</td>
</tr>
<tr>
<td>Angeli et al.</td>
<td>19 PD patients</td>
<td>TCD of MCA</td>
<td>Baseline supine recording</td>
<td>Passive 70° tilt</td>
<td>ON</td>
</tr>
<tr>
<td>Gurevich et al.</td>
<td>9 PD patients</td>
<td>TCD of MCA and VA</td>
<td>Baseline supine recording</td>
<td>Diamox (Acetazolamide) test</td>
<td>UNCLEAR</td>
</tr>
<tr>
<td>Vokach et al.</td>
<td>14 PD patients</td>
<td>TCD of MCA</td>
<td>Baseline supine recording</td>
<td>Thigh cuff release test</td>
<td>ON AND OFF</td>
</tr>
<tr>
<td>Tsai et al.</td>
<td>49 PD patients</td>
<td>TCD of MCA</td>
<td>Baseline supine recording</td>
<td>Cold pressor test</td>
<td>ON</td>
</tr>
<tr>
<td>Rätsep et al.</td>
<td>7 patients</td>
<td>TCD of MCA</td>
<td>Baseline supine recording</td>
<td>Cold pressor test OFF</td>
<td>CA impaired</td>
</tr>
<tr>
<td>Michi et al.</td>
<td>30 PD patients</td>
<td>TCD of MCA</td>
<td>Baseline supine recording</td>
<td>Passive 90° tilt</td>
<td>ON</td>
</tr>
<tr>
<td>Vokach et al.</td>
<td>14 PD patients</td>
<td>TCD of MCA</td>
<td>Baseline supine recording</td>
<td>Thigh cuff release test</td>
<td>ON AND OFF</td>
</tr>
<tr>
<td>Rosengarten et al.</td>
<td>175 PD patients</td>
<td>TCD of PCA</td>
<td>Visual evoked paradigm</td>
<td>ON</td>
<td>CA Intact</td>
</tr>
<tr>
<td>Zamani et al.</td>
<td>44 PD patients</td>
<td>TCD of MCA</td>
<td>Baseline supine recording</td>
<td>Period of forced hypercapnia</td>
<td>UNCLEAR</td>
</tr>
<tr>
<td>Schwalen et al.</td>
<td>32 PD patients</td>
<td>TCD of MCA</td>
<td>Head up tilt</td>
<td>UNCLEAR</td>
<td>CA Intact</td>
</tr>
<tr>
<td>Azevedo et al.</td>
<td>20 PD patients</td>
<td>f-TCD of PCA</td>
<td>Visual evoked paradigm</td>
<td>ON</td>
<td>CA Intact</td>
</tr>
</tbody>
</table>

Ethical approval for the study was obtained

Patients with a history of idiopathic PD, treated with dopaminergic medications, were recruited from the outpatient clinic at Leicester General Hospital, and by Parkinson’s UK

Exclusion criteria:
- Diabetes
- Stroke / TIA
- Ischaemic Heart Disease
- Peripheral Neuropathy
- Deep Brain Stimulation
- Dementia
- Recently diagnosed and treated HTN

Attended the research laboratory on 2 separate mornings, no more than 2 weeks apart, once in ‘on’ state, once in ‘off’ state

To achieve off state, required to have abstained from usual PD medications for 12-24 hours

Patients were also requested to abstain from caffeine, smoking and large meals for the four hours prior to each measurement

Healthy control group who attended once only

Baseline demographic data collected

- Assessment scales
  - Edinburgh Handedness Inventory
  - Hoehn and Yahr Scale
  - NMS Quest
  - UPDRS score
  - Mentation
  - Activities of daily living
  - Motor examination
  - Complications of therapy
Dynamic cerebral autoregulation is impaired in idiopathic Parkinson’s disease
V Haunton, University of Leicester, UK

Study Protocol

- TCD study
  - Bilateral MCA insonation
  - Nasal capnography
  - Beat to beat BP measurement with Finometer
  - 3 lead ECG recording

- Period of stabilisation

- Two, five-minute baseline recordings

Data analysis

- The ABP signal was calibrated at the start of each recording.
- Data inspected for quality, spikes were removed by linear interpolation.
- R-R interval was automatically marked using the ECG trace and continuous HR plotted against time.
- MAP and CBFV calculated for each cardiac cycle with linear interpolation used to obtain estimates of ETCO2 synchronised to the end of each cardiac cycle.
- Instantaneous relationship between CBFV and MAP was used to obtain estimates of critical closing pressure (CCP) and resistance area product (RAP) for each cardiac cycle using the first harmonic method.
- Beat-to-beat data were then spline interpolated and re-sampled at 5 samples/s to create time-series with a uniform time base.
- Autoregulation index (ARI) values were calculated using transfer function analysis and the “best fit” least squares method of matching CBFV step responses to one of the 10 model curves proposed by Tiecks*.

Statistical considerations

- Fisher’s exact test for categorical variables
- Shapiro-Wilk test for normality
- Paired and unpaired t-tests
- Bonferroni correction

Results

- 61 PD patients recruited
  - 13 no windows
  - 3 didn’t tolerate protocol / generated noisy data
    - $N = 45$

- Healthy Age and Sex Matched Controls recruited
  - 15 no windows
  - 5 noisy data
    - $N = 45$
Results

<table>
<thead>
<tr>
<th>PD PATIENTS</th>
<th>HEALTHY CONTROLS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>33 (73%)</td>
<td>29 (55%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.6</td>
<td>65.0</td>
</tr>
<tr>
<td>Right handed</td>
<td>4 (10%)</td>
<td>4 (10%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PD PATIENTS (ON)</th>
<th>PD PATIENTS (OFF)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration (years)</td>
<td>3 (0.5 - 13.1)</td>
<td>3 (0.5 - 13.1)</td>
</tr>
<tr>
<td>H&amp;Y Stage</td>
<td>2 (0 - 4)</td>
<td>2 (0 - 4)</td>
</tr>
<tr>
<td>UPDRS</td>
<td>34 (24-40, 12-61)</td>
<td>39 (32-46, 8-39)</td>
</tr>
<tr>
<td>Motor UPDRS</td>
<td>14 (8-20, 1-28)</td>
<td>20.5 (15-44, 8-39)</td>
</tr>
<tr>
<td>LEDD (mg)</td>
<td>568</td>
<td>568</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PD PATIENTS ON</th>
<th>PD PATIENTS OFF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>62.4</td>
<td>63.9</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>150.1</td>
<td>134.0</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>71.5</td>
<td>71.5</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>90.3</td>
<td>90.1</td>
</tr>
<tr>
<td>PTCO2 (mmHg)</td>
<td>37.6</td>
<td>36.6</td>
</tr>
</tbody>
</table>

CBFV data

<table>
<thead>
<tr>
<th>PD PATIENTS (ON)</th>
<th>PD PATIENTS (OFF)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBFV (cm/s)</td>
<td>46.3</td>
<td>47.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PD PATIENTS</th>
<th>HEALTHY CONTROLS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARI</td>
<td>0.01</td>
<td>0.25</td>
</tr>
<tr>
<td>GCS</td>
<td>9.6</td>
<td>9.6</td>
</tr>
<tr>
<td>RAP</td>
<td>1.24</td>
<td>1.25</td>
</tr>
</tbody>
</table>

Key findings

- BP lower in PD on state
- Resting mean CBFV lower in PD patients in their on state c.f. healthy controls
- No evidence of laterality – CBFV and ARI values same both sides
- Lower ARI in PD on state
- Frequency domain parameters suggest significant differences between all three groups, especially PD off state

Study limitations

- Certainty of PD diagnosis
- Disease phenotype – Tremor dominant vs. PIGD
- Lack of brain imaging to rule out CVD
- Lack of carotid imaging to exclude stenosis
- Heterogeneity of PD medications
- Relative lack of representation from patients at the later stages of PD
- Author not blinded at data analysis stage
Dynamic cerebral autoregulation is impaired in idiopathic Parkinson’s disease
V Haunton, University of Leicester, UK

Conclusions
- Peripheral haemodynamics (BP) affected by dopaminergic medications – well reported in the literature
- MCFBV lower in PD (medicated) patients – contradicts (limited) existing literature
- No evidence of laterality despite being a disease of laterality – more evidence of systemic nature of disease?
- ARI lower in PD on state – first time CA reported this way
- CrCP and RAP no significant differences – intact myogenic mechanisms?
- Frequency domain parameters suggest significant differences across all three groups
  - Bilateral role of dopaminergic medications
- Cerebral haemodynamics altered in idiopathic Parkinson’s disease – evidence of impaired CA

Further work
- TO BE EXPLORED AT CLINICAL SCIENCE LAB 15/07/2015!
  - Explore effects of medication type – clarify role of exogenous dopamine
  - Disease stage
  - Disease phenotype
    - Tremor predominant
    - PIGD
  - Cognitive impairment
  - Natural history study
  - Combined study with Transcranial Ultrasound
  - Merit in studying PD patients ON medication
  - Merit in unilateral data
  - Use CA for diagnostic / prognostication purposes

Summary
- Parkinson’s Disease
- Why study CA in Parkinson’s disease?
- TCD studies in Parkinson’s disease
- Leicester CHIASM work in PD
- Conclusions and future directions

Any questions?

She

“He therefore considered it to be a duty to submit his opinions to the examination of others…..”

her

James Parkinson 1817

Acknowledgements
- CHIASM group
  - Prof Tom Robinson
  - Prof Ronney Panerai
- Dr Martha Hanby, ACF
- Dr Nelson Lo
- Jean Martey and Liz Hillman, PDNS
- Dr Angela SM Salinet
- Dr Nazia Saeed
- Harry Hall
- Study participants
Dynamic Cerebral Autoregulation Impairment In Stroke Patients with Coexistent Large artery and Small vessel Disease

TIAN G1*, PhD; CHEN XY1*, PhD; LAN LF1, PhD; XIONG L1, PhD; LIN WH1, PhD; WANG W2; WANG LJ3, MD; LEUNG WH1, MD; MOK CT1, MD, Liu J4, PhD and WONG KS1, MD

1 Division of Neurology, Department of Medicine & Therapeutics, Chinese University of Hong Kong, Hong Kong, China; 2 Department of Neurology, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China; 3 Neuroscience Center, Department of Neurology, the First Norman Bethune Hospital of Jilin University, Chang Chun, China; 4 Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Xueyuan Avenue, Shenzhen University Town, Shenzhen, China,

* Ge TIAN and Xiangyan CHEN are the co-first authors.

Background: Dynamic cerebral autoregulation (dCA) may become impaired after stroke. However, the patterns of dCA in stroke patients may be heterogenous depending on the underlying pathophysiology leading to ischemic stroke. In this study, we explored the dCA among stroke patients with coexistent large artery and small vessel disease as compared to other stroke subtypes.

Methods: Among consecutively recruited stroke patients, simultaneous monitoring of cerebral blood flow velocity (CBFV) and beat-to-beat arterial blood pressure (ABP) was performed to evaluate dCA by using transfer function analysis (TFA).

Results: Forty-two patients and 12 non-stroke controls were enrolled. Among patients with large artery disease, phase degree (PD) in affected hemisphere (32.37±40.79) was significantly lower than the unaffected hemisphere (58.27±39.96, P<0.05), and non-stroke control (65.14±30.68, P<0.05); PD in the unaffected hemisphere was similar to that in controls (P>0.05). Among the patients with small vessel disease, the values of PD were similar between bilateral hemispheres (27.67±36.31 vs 27.62±39.31, P>0.05), which were significantly lower than non-stroke controls (P<0.05, respectively). In the subgroup of stroke patients with coexistent large artery and small vessel disease, there was no significant difference in the values of PD between bilateral hemispheres (13.53±31.10 vs 20.17±42.81, P>0.05). PD in both hemispheres in this subgroups were significantly lower than that in controls (P<0.05, respectively). PD in the unaffected hemisphere in stroke patients with coexistent large artery and small vessel disease was lower than that in the unaffected hemisphere of patients with large artery disease (20.17±42.81 vs 58.27±39.96, p=0.022).

Conclusion: The pathophysiology of different stroke subtypes may affect the patterns of dynamic cerebral autoregulation. Large artery disease does not aggravate the severity of dCA impairment in patients coexistent with small-vessel disease.
White paper on transfer function analysis: a consensus guideline.

Claassen JA, Panerai RP, Simpson D

1 Donders Institute, Radboud University Medical Center, Netherlands.
2 Department of Engineering, University of Leicester, UK.
3 ISVR/Faculty of Engineering and the Environment University of Southampton, UK

Background

Previous CARNet research has identified strong variability in published cerebral autoregulation studies that used transfer function analysis. Follow-up research identified that between-center variability in transfer function methodology is a source of strong variation in TFA outcome. We have summarized which settings vary most between centers and explain the largest part of between-center variability in TFA data.

Aim

The aim was to provide a consensus guideline that is widely supported by the CARNet community and thus can reduce one source of between-centre variability. Because further evidence needs to be collected before all recommendations can be supported by solid evidence, we have chosen to present the consensus paper as a white paper with recommendations.

White paper

The following topics are addressed in the white paper, with a total of 17 recommendations:

General experimental conditions: temperature, body position, equipment, minimum duration (signal length).

Data preparation and pre-processing: sampling frequency, signal quality (e.g. missing segments, ectopic beats), detrending, filtering.

TFA methodology: window type, window length and overlap, spectral smoothing, coherence (minimal acceptable coherence settings)

Parameter extraction: reporting units, frequency ranges, dealing with negative phase, standards of reporting.

The goal of the paper is to promote harmonization between centers using TFA, and to provide guidance for both existing and new users of TFA. An important part of the paper is the so called validation database. The paper provides a table with TFA outcomes for an on-line dataset. Readers can analyse this dataset and use the Table to verify results from their analysis software.

Conclusion

We hope that the white paper will enhance consistency in TFA and in the reporting of results, and thus strengthen the power to gain insights across multiple studies from the many centres undertaking research in cerebral autoregulation.
Background. One of the challenges in the measurement of dynamic cerebral autoregulation (CA) is sometimes poor repeatability between measurements taken over time. For CA estimates carried out under only spontaneous fluctuations of ABP, low variability of ABP has been associated with reduced repeatability. Therefore, pseudorandom step-wise lower-body negative pressure (LBNP) was introduced with aim to provoke a small increase in blood pressure variability. We report on the impact this protocol has on the repeatability of CA measurements taken in healthy adults on different days.

Methods. Thirty approximately 5 minutes long recordings were acquired during two sessions between 2 and 25 days apart, from 15 healthy subjects (aged 32±10 years, 7 female, height 171.3±8.0 cm, weight 72.9±15.2 kg), in supine rest. In each recording, a total of 20 LBNP periods of 5, 10 and 20 s duration (changing approximately from −20 to −100 mmHg) were applied at random intervals. ABP was recorded with a Finometer, CBFV with transcranial Doppler ultrasound in the middle cerebral artery (bilateral, but only the better quality channel was selected), heart-rate (HR) using an ECG and end-tidal CO2 (etCO2) from a capnograph. For each subject, 5 minutes of baseline data (no LBNP) were also acquired. Data segments identified as strongly contaminated by artefact were removed and left as gaps in the signals (not interpolated, nor were good data segments concatenated). Both a single input (only ABP) and multiple input (ABP and etCO2) model was used, with CBFV as the output. CA was estimated using the phase and gain in the low frequency (LF) range 0.07-0.2 Hz, estimated using finite impulse response filters with a length of 10 s for ABP-CBFV and 25 s for etCO2-CBFV.

Results. No significant change in autoregulation was noted (LF gain and phase, uni- and multivariate models, p>0.3, Wilcoxon) between baseline and LBNP, though there was a drop in EtCO2 averaged over the 5 minutes recordings from 5.00 to 4.68% (p<5·10⁻⁵; 28 out of 30 recordings showed a decrease). The intra-class correlation coefficient (ICC (2,1)) between the two recording sessions was low (<0.6), and not significant during baseline. It increased for both gain and phase with LBNP, but only reached significance for phase (ICC=0.47). The multivariate model tended to give slightly higher ICC values than the univariate model. The LBNP also provided significantly improved model fit applied to the normalized rms error (p<5·10⁻³, Wilcoxon): 62% and 48% for baseline and the uni- and multivariate models respectively, decreasing to 44% and 37% for LBNP. When the first and second half of each recording at rest (i.e. approximately 150 s) were used to assess repeatability of measures within the same recording session, ICC for gain decreased from 0.62 for the univariate model to 0.56 (p<10⁻³) for the multivariate model while phase decreased from 0.73 to 0.64 (p<10⁻⁴).

Discussion and Conclusion. The introduction of LBNP clearly improved model fit and provided some improvement in repeatability. However, the latter still remained poor. For comparison, the ICC for mean HR between the two recording sessions was 0.72 and 0.78 (p<2·10⁻²) for baseline and LBNP respectively. The use of the multivariate model provided some additional improvement over the results from the univariate model. The low ICC is probably partly due to the relatively small scatter of values, all taken from healthy adult volunteers, and rather higher values might be expected if subjects with a wider range of CA function were included. While a larger sample number will provide more robust results and likely lead to more of the ICCs becoming statistically significant, the main inference that repeatability is rather poor is not likely to change. Whether this poor repeatability is due to noise in measurements, inadequate choice of model or the input signals included, the selection of parameter (LF phase and gain), or reflects time-varying physiological function, remains a key question for the assessment of CA.
Pseudorandom steps in lower body negative pressure can improve repeatability in the assessment of cerebral autoregulation

Dragana Nikolić
David Simpson
Anthony Birch
Ronney Panerai

13-15 July 2015, CARNET, Southampton

Objective

To examine the impact LBNP protocol has on the repeatability of CA measurements taken in healthy adults on different days.

Outline

• Methodology
  – Experimental protocol
  – Data sets (baseline and LBNP)
• Preprocessing and analysis
  – Data preprocessed and edited to remove artefacts
  – Univariate and multivariate models used to estimate CA measures
• Results
  – Gain and phase in low frequency range
  – Consistency between repeated sessions
  – Consistency between two consecutive segments in the same recording
• Summary

Experimental protocol

• ABP measured with a finger cuff device (Finapres 2300, Ohmeda).
• CBFV recorded from the middle cerebral artery with a TCD ultrasound and a 2 MHz transducer (Multidop-4, DWL).
• Respiratory pCO2 recorded with an infrared capnograph (Capnocheck, BCI).
• Surface ECG measured with Diasonics, Simonsen & Weel.
• 20 step-wise changes of LBNP (from –15 to –100 mmHg) with a duration of 5, 10 and 20 s were applied over 5 minute.

Data description

• Data analysed
  – data recorded at the Southampton General Hospital
  – signals simultaneously recorded and sampled at 250 Hz (MP150, BIOPAC)
  – extracted baseline and LBNP segments approximately 5 minutes long
• Subjects
  – 15 healthy volunteers
    (age: 32 ± 10 years, height 171 ± 8 cm, weight 73 ± 15 kg, 7 female)
  – recordings repeated on 2 separate occasions between 2 and 25 days apart
    (30 baseline and 30 LBNP segments in total)
Pseudorandom steps in lower body negative pressure can improve the repeatability in the assessment of cerebral autoregulation

D M Simpson, University of Southampton, UK

Data preprocessing and analysis.

Data preprocessing

- R peaks detected from ECG signal and used for calculating HR
- End-tidal CO$_2$ calculated from CO$_2$ signal
- Automatic and manual detection of R and CO$_2$ peaks
- Low-pass filtered above 20Hz, median filtered (CBFV only), downsampled to 10Hz, edited to remove artifacts (spikes, bad data sections) and linearly interpolated
- Beat-to-beat average values of ABP and CBFV calculated

Data analysis

- Single input (only ABP) and multiple input (ABP and etCO$_2$) model used, with CBFV as the output.
- Mean ABP and mean CBFV downsampled to 1 Hz and normalized by mean
- etCO$_2$ down-sampled to 0.2 Hz, mean removed
- The gain and phase in the very low frequency (VLF) range 0.02-0.07 Hz and the low frequency (LF) range 0.07-0.2 Hz estimated using FIR filters.

System modelling

UNIVARIATE MODEL

\[
\begin{align*}
    p &\rightarrow h_{pv} &\rightarrow v \\
    v &= h_{pv} \cdot p \\
    h_{pv} &= R_{pv}^{1/2}R_{p}
\end{align*}
\]

MULTIVARIATE MODEL

\[
\begin{align*}
    p &\rightarrow h_{pv} &\rightarrow v \\
    c &\rightarrow h_{cv} &\rightarrow v \\
    v &= h_{pv} \cdot p + h_{cv} \cdot c \\
    h_{pv} &= \begin{bmatrix} R_{p} & R_{cp} & R_{pv} \\ R_{pc} & R_{c} & R_{pcv} \\ R_{pv} & R_{pcv} & R_{cv} \end{bmatrix}^{-1} \begin{bmatrix} R_{p} \\ R_{pc} \\ R_{cv} \end{bmatrix}
\end{align*}
\]
Pseudorandom steps in lower body negative pressure can improve the repeatability in the assessment of cerebral autoregulation

D M Simpson, University of Southampton, UK

Results.

UV vs MV model comparison (1/4)

Mean and std values calculated for the whole data segment

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Units</th>
<th>BASELINE</th>
<th>LBNP</th>
<th>BASELINE vs LBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>mean</td>
<td>std</td>
<td>mean</td>
</tr>
<tr>
<td>Gain [%/%]</td>
<td></td>
<td>1.35</td>
<td>0.34</td>
<td>1.41</td>
</tr>
<tr>
<td>Phase [º]</td>
<td></td>
<td>35.16</td>
<td>11.57</td>
<td>36.67</td>
</tr>
<tr>
<td>Gain [%/%]</td>
<td></td>
<td>1.36</td>
<td>0.35</td>
<td>1.41</td>
</tr>
<tr>
<td>Phase [º]</td>
<td></td>
<td>35.83</td>
<td>11.70</td>
<td>37.06</td>
</tr>
<tr>
<td>ABP [mmHg]</td>
<td></td>
<td>87.15</td>
<td>11.31</td>
<td>83.95</td>
</tr>
<tr>
<td>CBFV [cm/s]</td>
<td></td>
<td>67.44</td>
<td>11.58</td>
<td>63.47</td>
</tr>
</tbody>
</table>

Mean and std values calculated for the whole data segment

Results

UV vs MV model comparison (2/4)

Consistency between two recording sessions

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Range</th>
<th>UNIVARIATE MODEL</th>
<th>MULTIVARIATE MODEL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ICC p</td>
<td>ICC p</td>
</tr>
<tr>
<td>Gain [%/%]</td>
<td></td>
<td>0.37</td>
<td>0.404</td>
</tr>
<tr>
<td>Phase [º]</td>
<td></td>
<td>0.36</td>
<td>0.201</td>
</tr>
<tr>
<td></td>
<td>VLF</td>
<td>0.36</td>
<td>0.201</td>
</tr>
<tr>
<td></td>
<td>LF</td>
<td>0.36</td>
<td>0.201</td>
</tr>
</tbody>
</table>

UV vs MV model comparison (3/4)

Consistency between two consecutive segments

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Range</th>
<th>UNIVARIATE MODEL</th>
<th>MULTIVARIATE MODEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gain [%/%]</td>
<td></td>
<td>0.60</td>
<td>0.63</td>
</tr>
<tr>
<td>Phase [º]</td>
<td></td>
<td>0.73</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>VLF</td>
<td>0.73</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>LF</td>
<td>0.73</td>
<td>0.76</td>
</tr>
</tbody>
</table>

UV vs MV model comparison (4/4)

Model fit error

<table>
<thead>
<tr>
<th>Quantity</th>
<th>UNIVARIATE MODEL</th>
<th>MULTIVARIATE MODEL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BASELINE</td>
<td>LBNP</td>
</tr>
<tr>
<td></td>
<td>mean</td>
<td>std</td>
</tr>
<tr>
<td>NMSE</td>
<td>0.615</td>
<td>0.125</td>
</tr>
</tbody>
</table>

NMSE(LBNP)<NMSE(BASELINE), \(p<0.01\), Wilcoxon test

Summary.
Summary

- The introduction of LBNP clearly improved model fit and provided some improvement in repeatability. However, the latter still remained poor.
- The use of the multivariate model provided some additional improvement over the results from the univariate model. The low ICC is probably partly due to the relatively small scatter of values, all taken from healthy adult volunteers.
- Whether this poor repeatability is due to noise in measurements, inadequate choice of model or the input signals included, the selection of parameter (LF gain and phase), or reflects time-varying physiological function, remains a key question for the assessment of CA.
CONTRIBUTION OF IDENTIFIABILITY TECHNIQUES TO CEREBRAL AUTOREGULATION

Mahdi A, Payne SJ
Institute of Biomedical Engineering, University of Oxford, UK
email: adam.mahdi@eng.ox.ac.uk

Background. Model-based approaches to cerebral autoregulation (CA) assessment, including autoregulation index (ARI), have now been used for decades. Once a framework has been chosen, the identification is performed in order to estimate model parameters from noisy input/output (I/O) physiological data (e.g. arterial blood pressure (BP) and cerebral blood flow velocity (FV)). Subsequently either the fit is analyzed or the estimated parameters are projected on some agreed scale reflecting CA performance. For the above projection to be physiologically consistent it would be desirable to require that different I/O time series give rise to distinct sets of parameters. This is the problem of structural and practical identifiability, which will be studied here in the context of model-assisted approaches to CA.

Methods. For linear single-input single-output models the identifiability can be determined by considering the transfer function (TF) from which the so-called coefficient map (CM) between the parameters of the model and the coefficients of the TF is formed. Then, the structural identifiability is studied by inspecting if CM is one-to-one (i.e. if it maps two different parameter vectors to different sets of TF coefficients). For nonlinear models an approach to identifiability based on the analysis of the sensitivity matrix (the so-called practical identifiability) is typically more feasible. The data used in this work, for the consideration of practical identifiability, were collected continuously during postural change from sitting to standing for three subject groups: healthy young, healthy elderly, and hypertensive elderly humans.

Results. First, linear approaches to CA have been considered. It has been shown that ARI, ARMA/ARX and TF models are structurally identifiable almost everywhere in the parameter space but not all input signals suffice to excite all the modes (i.e. allow to estimate all model parameters uniquely). Second, the structural and practical identifiability was established for some recently developed nonlinear BP/FV models. The computational complexity related with checking if CM is one-to-one is normally a challenging problem, which here was addressed by using symbolic packages (e.g. Mathematica) and Rosenfeld-Groebner algorithm (implemented in Maple). The application of sensitivity analysis made it possible to additionally identify the dynamic parameters, i.e. those that can be estimated only during the transient portion of the experiment. Finally, a method for constructing a structurally identifiable physiologically-based CA models defined by electric circuit analog has been developed.

Discussion. There has been growing interest in data-driven and physiologically-based computational approaches to CA. Model simulation, using both synthetic and physiological data, has so far been the most common way to evaluate the performance. Structural identifiability can provide an insight into the model structure a priori, before the data are taken into account. Since the method is data independent it often reveals aspects of the model not captured by the simulation. Moreover, it has been recognized that even if the uniqueness of the parameters with respect to I/O data is not essential, the identifiability of the model is important for the optimization procedures to be more reliable and efficient.

Conclusion. Both structural and practical identifiability techniques are proposed and studied for computational approaches to CA. Some of the advantages of using this validation tool, in addition to the traditional simulation approaches, were discussed.

Key references.
Reproducibility of dynamic cerebral autoregulation measurement methods: a retrospective multicenter study

Elting JW, Sanders ML, Claassen J, Panerai RB

1 Department of Neurology, University of Groningen, University Medical Center Groningen, The Netherlands
2 Department of Geriatric Medicine, Donders Institute for Brain, Cognition and Behaviour, Alzheimer Centre Nijmegen, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
3 Department of Cardiovascular Sciences, University of Leicester, and National Institute for Health Research Biomedical Research Unit in Cardiovascular Science, Glenfield Hospital, Leicester, United Kingdom

email: j.w.j.elting@neuro.umcg.nl
On behalf of the CARNet group

Background.

Different methods to calculate dCA parameters are available and currently in development. If dCA analysis is to be used in a clinical setting, there are at least two problems that need to be addressed. First, It has not been established if any method of dCA analysis is superior in terms of higher within subject reproducibility and lower within group variability. Second, It is unclear what level of improvement would be needed for dCA analysis to become clinically useful. In view of these problems, it is desirable to move towards more standardized methodology for dCA assessments. The aim of this study is to analyze reproducibility and variability of different dCA methods and parameters in a retrospective multicenter study for analysis methods that have been reported in the literature.

Methods.

Five centers provided measurement data that consisted of 2 measurements on 15 healthy volunteers, for a total of 75 healthy subjects. Data sets consisted of five minutes beat-to-beat transcranial Doppler (TCD), blood pressure (BP) and end-tidal CO₂ measurements during rest. When TCD data was unilateral, the original Tiecks curves were used to generate artificial data based on the BP signal. Data validation was performed using predefined limits and included checking for plausibility and consistency. After data anonymization, data analysis was performed by 14 participating centers on 150 datasets (75 sets with 2 measurements). The following dCA analysis methods were used: Transfer function analysis (TFA), Laguerre-Volterra kernels, Wavelet analysis, IR-filter based methods, Autoregulation index (ARI), ARMA based ARI methods and variant ARI methods, and correlation coefficient-like indices.

The preliminary results of the different dCA analysis methods are based on 3 types of reproducibility analyses: coefficient of variation (CV), intraclass correlation coefficient (ICC) and Bland-Altman plots. More extensive statistical analyses are under way.

Preliminary interpretations

1. High variability exists between subjects and between measurements for all dCA parameters, regardless of the analysis method.
2. CV and ICC results indicate a much better reproducibility for artificial data compared to physiological data in almost all methods.
3. Newer methods, including time varying and multivariate methods, seem to have similar or worse reproducibility and variability compared to standard TFA and ARI methods.
4. In methods that results in gain and phase variables, the phase variables seem to have higher CV and lower ICC compared to gain variables in similar frequency bands.
5. For ICC, methods that split up the dCA analysis into different components (such as frequency bands) seem to perform somewhat better than methods that summarize dCA into one single variable.
6. For most TFA-like and ARI-like methods, a modest increase in reproducibility can be achieved by filtering out cases with low BP variability. Variability between subjects is reduced only for gain parameters, not for phase and ARI indices.
Discussion.
This preliminary analysis was based on visual interpretation of graphic results. Statistical significance will need to be confirmed by further analyses. Only healthy volunteers were included. Further studies are needed with measurements of longer duration, under different physiological conditions or in patients with different pathologies.

The effect of manoeuvres that increase BP variability needs to be addressed. Some earlier studies suggest that this is worth investigating on a larger scale.

Comparison with hypercapnic data and patient data may be useful to evaluate which level of reproducibility is needed for a meaningful clinical application.

Conclusion.
dCA analysis yields highly variable results in healthy volunteers, with limited reproducibility. If this conclusion is supported by more indepth analyses, the fact that a wide range of analytical techniques have been included, suggests that further improvements in reproducibility and reliability might rely more on different measurement protocols than on the search for more advanced methods of data analysis.
THE BRAIN CONTROLS PHYSICAL EXERCISE BUT IS ALSO CHALLENGED BY IT

1Acute Internal Medicine & Clinical Cardiovascular Physiology, University of Amsterdam, NL.
2School of Life Sciences, The Medical School, University of Nottingham, UK
email: j.j.vanlieshout@amc.uva.nl | Johannes.Vanlieshout@nottingham.ac.uk

Invited talks - an abstract summarising you presentation is welcome including any images or tables.

In humans regulation of blood flow to the activated brain is different from the control of flow to working skeletal muscles. Comparable to the experience from functional MRI, cerebral activation by a motor task like physical exercise results in an increased cerebral blood flow. This enhances cerebral oxygenation while muscle oxygenation progressively decreases with work rate. Sufficient blood flow to the brain is critical for maintaining cerebral oxygen and substrate supply. In the early stages of exercise, cerebral oxygenation may actually exceed the increase in brain O2 demand as it is secured by several mechanisms, of which the partial pressure of arterial carbon dioxide, the cerebral perfusion pressure or mean arterial pressure at brain level as a surrogate, and cerebral metabolism are the most important.

Thus relative cerebral hyperperfusion may be an important precaution since brain function deteriorates when its oxygenation is reduced by more than 10% from the resting level. A problem is that aging is associated with reductions in global and regional cerebral blood flow and cerebral metabolism affecting grey matter flow with a ~15% reduction between the 3rd and 5th decade. In addition, the systemic and cerebral vascular conductance responses to exercise are mitigated with aging.

Development of fatigue, defined as an exercise-induced loss of muscle force generating capacity, is common to all humans but may become a problem in subjects with type 2 diabetes. Reduced exercise tolerance in type 2 diabetes is incompletely understood, and has traditionally been attributed to impaired muscle metabolism, and also to cardiac impairment. Rating of perceived exertion (RPE) increases with work rate as muscle oxygenation decreases, but a reduction in cerebral blood flow and/or oxygenation could also be important determinants of RPE. There are several reasons why in T2DM patients the physiological response to exercise, i.e. increased cerebral blood flow and cerebral oxygenation, may become impaired, and if so, set a limit to their exercise capacity. Against this background the response of cerebral blood flow/oxygenation and metabolism to brain activation by exercise will be discussed in physically trained subjects with type 2 diabetes.
Cerebral autoregulation in different hypertensive disorders of pregnancy
Teelkien R van Veen, MDab, Ronney B Panerai, PhDc, Sina Haeri, MDb,d, Jasbir Singh, MDb, Jasvant A Adusumalli, MDb, Gerda G Zeeman, MD PhDa and Michael A Belfort, MD PhDb

aUniversity of Groningen, University Medical Center Groningen, Department of Obstetrics and Gynecology, Groningen, the Netherlands;
bBaylor College of Medicine, Department of Obstetrics and Gynecology, Houston, Texas;
cUniversity of Leicester, Department of Cardiovascular Sciences, Leicester, United Kingdom;
dSt. David’s Women’s Center of Texas, North Austin Maternal-Fetal Medicine, Austin, Texas

Abstract
Background: Cerebrovascular complications associated with hypertensive disorders of pregnancy (preeclampsia (PE), chronic hypertension (CHTN) and gestational hypertension (GHTN)) are believed to be associated with impaired cerebral autoregulation (AR), a physiological process that maintains blood flow at an appropriate level despite changes in blood pressure. The nature of AR dysfunction in these conditions is unclear. We therefore evaluated AR in 30 patients with PE, 30 with CHTN and 20 with GHTN, and compared them to a control group of 30 normal pregnant women.

Methods: Cerebral blood flow velocity (CBFV) in the middle cerebral artery (transcranial Doppler ultrasound), blood pressure (noninvasive arterial volume clamping), and end-tidal carbon dioxide were simultaneously recorded during a 7-minute period of rest. Autoregulation Index (ARI) was determined from the CBFV responses to spontaneous fluctuations in mean arterial BP. Segments of 512 samples and 50% superposition were transformed with the fast Fourier transform (FFT) algorithm to obtain the transfer function parameters and the inverse FFT was then performed to estimate the impulse and step responses. ARI values of 0 and 9 indicate absent and perfect autoregulation, respectively. Statistics: ANOVA with Bonferroni test versus control group. Data are presented as mean±SD.

Results: ARI was significantly reduced in PE (ARI 5.5±1.6,P=0.002) and CHTN (5.6±1.7, P=0.004) but not in GHTN (6.7±0.8, P=1.0) when compared to controls (6.7±0.8). ARI was more decreased in patients with CHTN who subsequently developed PE than in those who did not (3.9±1.9 vs. 6.1±1.2, P=0.001). This was not true for women with GHTN or controls who later developed PE. Furthermore, the ARI of women with superimposed PE was significantly lower than in those with new onset PE (3.9 ± 2.2 vs. 6.0 ± 1.1, P=0.002)

Conclusion: Pregnant women with CHTN or PE (even after excluding superimposed PE) have impaired AR when compared to women with GHTN or normal pregnancy. Whether the decreased ARI in patients with CHTN who later develop PE is due to preexistent differences or early affected cerebral circulation remains to be determined.
Cerebral autoregulation in different hypertensive disorders of pregnancy

T van Veen, University Medical Center Groningen, The Netherlands

TR van Veen, RB Panerai, S Haeri, J Singh, JA Adusumalli
GG Zeeman and MA Belfort

University Medical Center Groningen, Groningen, the Netherlands
Baylor College of Medicine & Texas Children’s Hospital, Houston, United States
University of Leicester, Leicester Royal Infirmary, Leicester, United Kingdom
St. David’s Women’s Center of Texas, Austin, United States

Introduction

- Hypertension most common complication of pregnancy
  - Chronic hypertension (CHTN)
  - Gestational hypertension (GHTN)
  - Preeclampsia (PE)
  - Superimposed preeclampsia (SiPE)
- Risk for cerebrovascular complications during pregnancy is increased with all hypertensive disorders, most pronounced with severe PE and SiPE
- In preeclampsia, cerebral symptoms can occur despite minimal alterations in blood pressure

Aim

To evaluate cerebral autoregulation in hypertensive disorders of pregnancy (SiPE, PE, CHTN, and GHTN) and to compare this with a control group of normal pregnant women

Methods

- Prospective cohort study
- Pregnant patients with gestational age >20 weeks
- Exclusion criteria:
  - Cerebrovascular disease
  - Epilepsy
  - Smoking, drugs use
  - Initiation of antihypertensive therapy <48h
  - Magnesium sulfate
  - Active labor

Data Analysis

- Median filter to CBFV signal
- Butterworth filter (cut off 20Hz)
- Fast Fourier Transform (FFT) algorithm (512 samples, 50% superposition) to obtain transfer function parameters in the frequency domain
- Low frequency range (<0.1 Hz)
- Inverse FFT to estimate step response
- Compared to Tiecks’ template curves
- Rejection: coherence < 0.5 for any frequency <0.25 Hz.
Cerebral autoregulation in different hypertensive disorders of pregnancy
T van Veen, University Medical Center Groningen, The Netherlands

Statistics

- Analysis of variance with Bonferroni’s post-hoc test and analysis of variance on ranks with Dunn’s post hoc test vs the control group
- χ² without Yates correction for analysis between groups.
- Student t test or Mann-Whitney Rank Sum test for subgroup analysis.
- Univariate regression for the relationship between autoregulation and BP.
- Significance: 2-tailed probability value of < .05

Results

- 110 patients enrolled
  - 30 preeclampsia (7 superimposed preeclampsia),
  - 30 chronic hypertension
  - 20 gestational hypertension
  - 30 controls
- Similar demographics, except gestational age, BMI and parity
- Development of preeclampsia after measurement:
  - 7 chronic hypertension
  - 5 gestational hypertension
  - 2 control

### Table: Average CBFV step responses of all groups

<table>
<thead>
<tr>
<th>Time (s)</th>
<th>PE</th>
<th>CHTN</th>
<th>GHTN</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Error bars represent ±1, standard error of the mean.

### Table: Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preeclampsia (n=30)</th>
<th>Chronic Hypertension (n=30)</th>
<th>Gestational Hypertension (n=20)</th>
<th>Control (n=30)</th>
<th>P-value (MANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age</td>
<td>30 ± 7</td>
<td>27 ± 5</td>
<td>21 ± 5</td>
<td>30 ± 6</td>
<td>0.03</td>
</tr>
<tr>
<td>(weeks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-gestational</td>
<td>29 ± 0</td>
<td>34 ± 7</td>
<td>31 ± 8</td>
<td>31 ± 5</td>
<td>-0.821</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>6 (20%)</td>
<td>6 (20%)</td>
<td>2 (10%)</td>
<td>0</td>
<td>0.061</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>23 (77%)</td>
<td>11 (37%)</td>
<td>12 (60%)</td>
<td>17 (57%)</td>
<td>0.122</td>
</tr>
<tr>
<td>Risk at study</td>
<td>35 (20 – 69)</td>
<td>37 (20 – 40)</td>
<td>37 (20 – 48)</td>
<td>36 (20 – 40)</td>
<td>0.802</td>
</tr>
<tr>
<td>(median)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBFV at delivery</td>
<td>35 (24 – 44)</td>
<td>37 (24 – 39)</td>
<td>38 (22 – 44)</td>
<td>39 (23 – 45)</td>
<td>-0.001</td>
</tr>
<tr>
<td>(median)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No association between ARI and arterial blood pressure

### Table: Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preeclampsia (n=30)</th>
<th>Chronic Hypertension (n=30)</th>
<th>Gestational Hypertension (n=20)</th>
<th>Control (n=30)</th>
<th>P-value (MANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age</td>
<td>20 ± 7</td>
<td>27 ± 6</td>
<td>21 ± 5</td>
<td>30 ± 6</td>
<td>0.03</td>
</tr>
<tr>
<td>(weeks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-gestational</td>
<td>29 ± 0</td>
<td>34 ± 7</td>
<td>31 ± 8</td>
<td>31 ± 5</td>
<td>-0.821</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>6 (20%)</td>
<td>6 (20%)</td>
<td>2 (10%)</td>
<td>0</td>
<td>0.061</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>23 (77%)</td>
<td>11 (37%)</td>
<td>12 (60%)</td>
<td>17 (57%)</td>
<td>0.122</td>
</tr>
<tr>
<td>Risk at study</td>
<td>35 (20 – 69)</td>
<td>37 (20 – 40)</td>
<td>37 (20 – 48)</td>
<td>36 (20 – 40)</td>
<td>0.802</td>
</tr>
<tr>
<td>(median)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBFV at delivery</td>
<td>35 (24 – 44)</td>
<td>37 (24 – 39)</td>
<td>38 (22 – 44)</td>
<td>39 (23 – 45)</td>
<td>-0.001</td>
</tr>
<tr>
<td>(median)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cerebral autoregulation is impaired in pregnant women with CHTN, PE and SiPE

Might reflect a range of endothelial impairment.

No association between ARI and arterial blood pressure

ARI is impaired in women with CHTN who later develop SiPE

– Early manifestation of PE, or

– Indication of baseline endothelial dysfunction
# Cerebrovascular autoregulation during and after surgical ligation of the ductus arteriosus using two surgical approaches in preterm infants

1Kooi EMW, 2Van der Laan ME, 3Accord RE, 2Roofthoof MTR, 3Aries MJ, 4Elting JWJ  
1Div. of Neonatology, Beatrix Children’s Hospital, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands.  
2Center of Congenital Heart Diseases, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands.  
3Dep. of Intensive Care, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands.  
4Dep. of Neurology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands.

## Background

Cerebrovascular autoregulation (CAR) is often disturbed in preterm infants and can be assessed continuously using Near-infrared Spectroscopy (NIRS) (4). During ligation of an NSAID-resistant hemodynamically significant patent ductus arteriosus, CAR may deteriorate unnoticed, (1,2,5) possibly inducing hypoxic-ischemic cerebral damage. Impaired CAR has been described in a limited number of preterm infants undergoing posterolateral thoracotomy, a procedure after which a reduction in cardiac output has been observed (3). It is unknown whether CAR is also impaired after ductal ligation using a sternotomy. The aim of this observational study was to compare CAR in preterm infants during and after ductal ligation using the two surgical approaches.

## Methods

Observational cohort study. Preterm infants <32 weeks of gestational age (GA) requiring ductal ligation between July 2011 and September 2014 were considered eligible for inclusion. Halfway this timeframe the standard surgical approach changed in our hospital from posterolateral thoracotomy to sternotomy. Only infants with both cerebral NIRS measurement and invasive mean arterial blood pressure (MABP) measurements for at least 1 hour before, during and at least 12 hours after ligation, were included in the study. Regional cerebral tissue oxygen saturation (rSO₂) and MABP data were collected with a sample frequency of 0.2Hz, and stored offline for analysis. Artefacts were removed with linear interpolation and by applying a median filter. Dynamic CAR was quantified using the TOx parameter, which is a moving correlation coefficient between 10 sec averaged values of rSO₂ and MABP in a 5 min window. Afterwards, we averaged the TOx values over the following epochs: 1. pre-ligation (max 4 hours), 2. during ligation, 3. 0-4 hours post-ligation, 4. 4-8 hours post-ligation, 5. 8-12 hours post-ligation. Changes in TOx over time and between the surgical approaches were evaluated using repeated measurements ANOVA.

## Results

Data were complete for 9/14 infants with both NIRS and invasive MABP measurements. The first four were approached by posterolateral thoracotomy, the latter five by sternotomy. Median GA was 26 weeks (range:24.9-27.9), BW 800 grams (640-960) and PNA 18 days (15-30). We did not observe changes in MABP (p=0.24) or rSO₂ (p=0.09) during the study periods. TOx changed significantly over time (F=9.95;p=0.024), with higher TOx values during and after surgery for all defined epochs. Although the two surgical groups differed in baseline TOx, the posterolateral thoracotomy group showed a higher increase in TOx from baseline (surgery:0.32, 4h:0.36, 8h:0.32,12h:0.31) compared to the sternotomy group (surgery:0.20, 4h:0.05, 8h:0.15, 12h:0.11) (F=6.50;p=0.038).

## Discussion

Ductal ligation is associated with prolonged worsening of CAR estimates. The impairment was more obvious in the posterolateral thoracotomy approach. We hypothesize that during this approach, venous congestion with secondary decreased cerebral perfusion pressure may play a role.

## Conclusion

In preterm infants, CAR capacity was reduced during and up to 12 hours after ductal ligation, significantly more so when using posterolateral thoracotomy, compared to sternotomy.

## Key references

3. Lien R, Hsu KH, Chu JJ, Chang YS. Hemodynamic alterations recorded by electrical
ahead of print]
4. Verhagen EA, Hummel LA, Bos AF, Kooi EM. Near-infrared spectroscopy to detect absence of
5. Zaramella P1, Freato F, Quaresima V, et al. Surgical closure of patent ductus arteriosus reduces
the cerebral tissue oxygenation index in preterm infants: a near-infrared spectroscopy and Doppler
Is this autoregulation?
Crístine Sortica da Costa¹; Marek Czosnyka²; Subhabrata Mitra¹; Peter Smielewski²; Helen O’Reilly²; Ken Brady⁴, Topun Austin, PhD¹

¹ Neonatal Unit, Rosie Hospital, Cambridge University Hospitals NHS Foundation Trust, UK.
² Brain Physics Lab, Academic Neurosurgical Unit, University of Cambridge, Cambridge, UK
³ Neonatal Unit, Norfolk and Norwich University Hospitals, Norwich, UK
⁴ Department of Anesthesiology and Critical Care Medicine, Texas Children’s Hospital, Houston

Objective: Near-infrared spectroscopy (NIRS) allows non-invasive assessment of cerebral hemodynamics in preterm newborns. Over past decade we aimed to assess brain autoregulation using various estimators of cerebrovascular reactivity in a cohort of preterm infants. We investigated the relationship between NIRS-derived indices and correlate them with severity of clinical illness.

Methods: NIRS tissue oxygenation index (TOI) along with other physiological variables were continuously recorded for a minimum of two hours. Sixty preterm infants born at median gestational age (GA) 26+2 weeks (23+2 – 32+1), who had indwelling arterial catheters, were studied at a median 34 hours (5h to 228h) of age. Moving correlation coefficients between measurements of cerebral perfusion (TOI) and heart rate (TOHRx) and mean arterial blood pressure (TOx) respectively were calculated. We tested hypothesis that positive TOHRx indicates dependence of brain oxygenation on cardiac output, being the surrogate of disturbed autoregulation. Optimal arterial pressure was calculated as observed or predicted level of MABP at which autoregulation is the best, i.e. averaged TOHRx or TOx reach minimal values. MABP_{OPTHR} was defined by dividing MABP into 2mmHg bins and averaging TOHRx within those bins. MABP_{OPTTOx} was calculated in the same way, averaging values of TOx instead of TOHRx. A measurement of divergence from MABP_{OPT} was calculated as the absolute difference between mean MABP and mean MABP_{OPT} both estimators from the total study time.

Results: TOHRx demonstrated a significant correlation with gestational age (R=-0.4, p<0.005), birth weight (R=-0.45, p=0.003) and CRIB II (R= 0.55, p=0.0015). Surprisingly, no significant correlations between TOx and clinical parameters were confirmed. Individual MABP_{OPT} was defined in 80% of the patients for both TOHRx and TOx. A measurement of divergence from MABP_{OPTHR} was significantly greater in those patients who died (mean 4.2 (CI 3.33, 4.96) compared with those who survived 2.1(CI 1.64, 2.56), p=0.013). Patients who had MABP lower than MABP_{OPTHR} by 4mmHg or more had greater mortality rate (40%) than those with MABP close to or above MABP_{OPTHR} (13%), P=0.049. Patients with MABP greater than MABP_{OPTHR} by 4mmHg had significantly greater intraventricular haemorrhage (IVH) scores, P=0.042. No significant correlation between MABP related to MABP_{OPTTOx} and clinical outcome or status was observed.

Conclusion: HR has a key influence on cerebral haemodynamics in preterm infants. Continuous monitoring of TOHRx allows the determination of MABP_{OPT} in preterm neonates. Significant deviation below MABP_{OPT} was observed in those infants who died. Deviation of MABP above optimal level was observed in those who developed more severe IVH. Although TOHRx may be of diagnostic value in identifying premature infants with impaired cerebrovascular reactivity leading to worse clinical outcome, we still do not know whether it is really an index of cerebral autoregulation.

Invited Talk: Managing an integrated database and large-scale collaboration: The Pain and the Pleasure.

Ian Piper

1Clinical Physics, South Glasgow University Hospital, Glasgow, UK.

The Brain Monitoring with Information Technology (BrainIT) group [1] was founded in 1997. Three periods of EU funding allowed the group to define a core dataset, develop tools for data collection and analyse the data [2]. This presentation will share with the CarNet group our thoughts and experiences on meeting challenges and lessons learned over the 18 years since the group was formed.

Key references.

[1] www.brainit.org
TITLE OF STUDY
Reduced dynamic cerebral vasomotor reactivity in patients with mild cognitive impairment
Submitted to Fifth International Meeting on Cerebral Haemodynamic Regulation, Southampton, UK

1Marmarelis V, 1Shin D, 2Orme M, 3Tarumi, 3Zhang R
1Department of Biomedical Engineering, University of Southern California, US
2Sonovation Inc., Los Angeles, California, US
3UT Southwestern Medical Center, Dallas, Texas, US
email: vzm@usc.edu, tel: 001-310-880-8200

Aims. This study has a dual purpose: (1) to introduce indices of dynamic CO2 vasomotor reactivity, obtained from resting-state data via predictive models utilizing the novel method of Principal Dynamic Modes (PDMs) [1-2]; (2) to examine the hypothesis that patients with mild cognitive impairment (MCI) exhibit reduced dynamic cerebral vasomotor reactivity – also observed recently in Alzheimer’s disease [3].

Methods. Beat-to-beat measurements of cerebral blood flow velocity at the middle cerebral artery (CBFV), arterial blood pressure (ABP) and end-tidal CO2 (ETCO2) were collected in 46 amnestic MCI patients (based on the modified Peterson criteria) and 20 control subjects similar in age and education. Subjects with clinical histories of stroke, psychiatric disorders, heart disease, hypertension and diabetes mellitus were excluded. The time-series data were analysed using PDMs [1] to obtain predictive dynamic models of cerebral autoregulation and CO2 vasomotor reactivity for each subject. These two-input (ABP, ETCO2) and one-output (CBFV) models were subsequently used to compute subject-specific indices of dynamic cerebral autoregulation (DCA) and dynamic cerebral vasomotor reactivity (DCVR) as described in [2-4].

Results. Using 4 PDMs for each input, the average normalized mean-square error of the model prediction was 36% of output variance. The predictive model for each subject was used to compute the CBFV response in two cases: (1) to an ABP pulse stimulus, while the ETCO2 is kept at baseline (isocapnic conditions); (2) to an ETCO2 pulse stimulus, while the ABP is kept at baseline (isobaric conditions). This is illustrated in Figure 1 for a control subject (left) and an MCI patient (right) in the case of ETCO2 pulse input. It is evident that the CO2 vasomotor reactivity of the MCI patient is impaired. The time-average of these computed responses, divided by the respective input pulse value, is the DCA index (for case 1) and the DCVR index (for case 2) of each subject. The obtained DCA indices were not statistically different for controls and patients (p=0.23), while the DCVR indices were significantly smaller for patients (μ=0.65, σ=1.16) than controls (μ=1.63, σ=0.90), corresponding to a t-statistic of 3.71 and p-value of 0.0002.

Figure 1: Model-predicted CBFV responses (blue) to 30-sec ETCO2 input pulse (red) for a control subject (left) and an MCI patient (right). The DCVR impairment is evident in the patient. The average of the color-shaded area (divided by the pulse level) is the DCVR index of each subject.
**Conclusion.** Model-based indices of dynamic cerebral vasomotor reactivity (DCVR) are reduced significantly in MCI patients relative to controls (p=0.0002).

**Key references.**


MODEL-ASSISTED ASSESSMENT OF EFFECTS OF AGE AND HYPERTENSION ON CEREBRAL BLOOD FLOW VELOCITY

Mader G, Olufsen M, Mahdi A, Ottesen J, Timmermann, S

1 Department of Mathematics, NC State University, NC, USA
2 Insti of Biomedical Engineering, University of Oxford, UK
3 Department of Science, Systems, and Models, Roskilde University, Denmark
4 Department of Quantitative Pharmacology, H. Lundbeck A/S, Denmark

Background. Both aging and hypertension impair arterial blood pressure (ABP) regulation, potentially making hypertensive elderly subjects vulnerable to cerebral hypoperfusion and syncope during orthostatic stress. Cerebral autoregulation (CA) is a term used to describe the brain’s ability to locally control cerebral blood flow (CBF) amidst changes in ABP through myogenic, metabolic, shear-dependent, and neurovascular regulation. Generally CA is studied from two perspectives: static and dynamic. Static CA refers to the net effect a change in ABP has on CBF, represented by the CA curve\(\text{[2]}\). Dynamic CA refers to the time-varying response to an ABP perturbation. Numerous authors have tried to explain both static and dynamic aspects of CA, proposing physiologically-based models\(\text{[6,7]}\) or statistical approaches\(\text{[1,5]}\). This study combines the two methodologies, deriving a simple nonlinear model that can accurately predict CBF velocity as a function of measured ABP.

Methods. The experimental data analyzed in this study was collected continuously during postural change from sitting to standing for three subject groups: healthy young, healthy elderly, and hypertensive elderly humans\(\text{[3]}\). The model is motivated by viscoelastic-like behavior observed in experimental data and dynamic CA is described using a mechanical model consisting of two viscoelastic Voigt body elements combined with a spring. The CBF velocity of the subject is estimated by combining the dynamic CA (model output) with the patient-specific baseline CBF velocity. Structural and practical identifiability as well as sensitivity analysis were performed on the model to ensure uniquely estimable parameters. Parameters were estimated using both nonlinear least squares minimization and nonlinear mixed effects analysis.

Results. Qualitative testing of the model involved analysis of dynamic responses to step-changes in pressure both within and outside the autoregulatory range, while quantitative testing was used to show that the model can fit dynamics observed in data measured from each of the subgroups. Results showed that the model is able to reproduce observed overshoot and adaptation as well as predict the different autoregulatory responses across the three subgroups.

Discussion. This simple nonlinear model is validated against both filtered and pulsatile experimental data. Both nonlinear least squares and nonlinear mixed effects estimated different parameter values across the three subject groups. Preliminary results show significant differences in parameters between young and elderly, with little to no difference between elderly normotensive and elderly hypertensive subjects. The model can also be used to identify outliers within each of the three subgroups, suggesting that those individuals be additionally tested.

Conclusion. This work is an extension of recently published research\(\text{[4]}\). Results for all subject data indicate that the model is able to characterize and quantify the effects of aging and hypertension on cerebral ABP and CBF regulation.

Key references.
The time-dependent variability of arterial CO2 influences the nonstationary properties of
dynamic CO2 reactivity estimates during resting conditions

Kostoglou K,1,2 Poulin M.J.,1,2 Mitsis G.D.,2

1Department of Electrical and Computer Engineering, McGill University, Montreal, Quebec, Canada
2Department of Physiology & Pharmacology, Faculty of Medicine, University of Calgary, AB, Canada.

Background. In our previous work [1-2] we have shown that cerebral blood flow velocity (CBFV) is related to mean arterial blood pressure (MABP) and end-tidal CO2 (PETCO2) in a linear time-varying manner. However, the relationship between PETCO2 and CBFV was found to exhibit larger variability with respect to time when compared to MABP-CBFV. The main scope of the present study was to examine this phenomenon more rigorously and explain the observed variations quantitatively.

Methods. Cerebral autoregulation under free-breathing conditions was modelled as a multivariate time-varying system with MABP and PETCO2 as inputs and CBFV as output. We employed the Laguerre expansion technique to model the system, which performs data-driven estimation of the system dynamics. Linear finite impulse response models that describe the effect of past input values on the output were estimated by expanding the MABP and PETCO2 impulse responses in terms of an orthonormal basis of discrete Laguerre functions. In order to take into account possible nonstationarities, the model parameters were updated at each time step using an adaptive Kalman filter approach. This resulted in MABP and PETCO2 system components that exhibited time-varying characteristics. The variability of the two impulse responses at each time step was quantified as the percentage change from its overall mean value.

Results. We found that the variability of the PETCO2 impulse response was negatively correlated (significant Kendall tau rank correlation coefficient with mean±std value of r=-0.202±0.069 and range -0.26<r<-0.14, p<3.067e-20 for all subjects) with the power of the PETCO2 signal, computed as an exponential moving average in time frames equal to the memory of the algorithm (Fig.1). This phenomenon was not observed as strongly in the MABP case (significant Kendall tau rank correlation coefficient with mean±std value of r=-0.032±0.041 and range -0.065<r<-0.067, p<0.04 for 9/13 subjects). The low power of the PETCO2 signal leads to an increase in the condition number of the covariance matrix used in the recursive algorithm, affecting computationally the extracted time-varying model parameters. The influence of additional features of the PETCO2 signal was also examined. We observed a weak positive correlation between the variability of the PETCO2 impulse response and the time lag of the maximum instantaneous effect of PETCO2 on CBFV. This indicates that either time-varying pure time delays or time-varying model orders may lead also to variable estimates.

Conclusions: Based on the aforementioned results, low PETCO2 excitation may induce high variability in the obtained system estimates with respect to time. This implies that the time-varying relationship between PETCO2 and CBFV should be carefully interpreted, taking into account the underlying properties of the PETCO2 signal.

Figure 1: MABP power and MABP kernel variability (left panel); PETCO\textsubscript{2} power and PETCO\textsubscript{2} kernel variability (right panel) as a function of time for two representative subjects (subject 1: first row, subject 2: second row). For visualization purposes, all variables are normalized between zero and one separately for each subject.
TITLE OF STUDY
Comparison of cerebral tissue oxygenation with cerebral arterial flow velocity responses to spontaneous changes in blood CO2 and pressure in older adults.
Submitted to Fifth International Meeting on Cerebral Haemodynamic Regulation, Southampton, UK

1Marmarelis V, 1Shin D, 2Orme M, 3Tarumi, 3Zhang R

1Department of Biomedical Engineering, University of Southern California, US
2Sonovation Inc., Los Angeles, California, US
3UT Southwestern Medical Center, Dallas, Texas, US
email: vzm@usc.edu , tel: 001-310-80-8200

Aims. This study examines the combined dynamic effects of changes in blood CO2 and pressure upon cerebral tissue oxygenation, measured via near-infrared spectroscopy (NIRS), and compares them with the concurrent effects on cerebral blood flow velocity (CBFV) measured at the middle cerebral artery via transcranial Doppler (TCD). Our working hypothesis is that measurements of cerebral tissue oxygenation may be a reliable surrogate of CBFV measurements for the purpose of model-based estimation of dynamic cerebral vasomotor reactivity (DCVR), which has been shown recently to be impaired in patients with mild cognitive impairment (MCI) or Alzheimer’s disease (AD) [1-2].

Methods. Beat-to-beat NIRS measurements of cerebral tissue oxygenation index (TOI), TCD measurements of CBFV at the middle cerebral artery, arterial blood pressure (ABP) and end-tidal CO2 (ETCO2) were collected in 38 amnestic MCI patients (based on the modified Peterson criteria) and 14 control subjects similar in age and education. The time-series data were analysed using the novel method of Principal Dynamic Modes (PDMs) [3-4] to obtain predictive dynamic models of the relationship between the two “inputs” of ABP and ETCO2 and the two “outputs” of TOI and CBFV. The obtained models were subsequently used to compute subject-specific indices of DCVR either for the CBFV output (FV-DCVR) or the TOI output (TO-DCVR), following the procedure described in [1-3], as the average predicted response of CBFV or TOI to a 30-sec ETCO2 pulse stimulus, while the ABP was kept at baseline (isobaric conditions).

Results. The obtained DCVR indices were significantly smaller for MCI patients in both output cases ($\mu=0.65, \sigma=1.16$ for FV-DCVR; $\mu=0.39, \sigma=1.83$ for TO-DCVR) than controls ($\mu=1.63, \sigma=0.90$ for FV-DCVR; $\mu=1.76, \sigma=1.66$ for TO-DCVR), corresponding to p-value of 0.0002 in both cases. The scatter-plot of the obtained DCVR indices for the two cases is shown in Figure 1. The regression of TO-DCVR values against the neurocognitive Memory Recall scores is shown in the right panel of Figure 1 and indicate a positive correlation with slope 1.16 and $r^2=0.07$.

Figure 1. Left: Scatter-plot of model-based indices of DCVR for 14 controls (blue) and 38 MCI patients (red), using CBFV output (FV-DCVR, abscissa) or TOI output (ordinate). Both types of DCVR values are larger for controls ($p=0.0002$). Right: regression of TO-DCVR vs Recall scores.
**Conclusion.** Model-based indices of dynamic cerebral vasomotor reactivity, obtained from either cerebral blood flow velocity or brain tissue oxygenation measurements, are significantly smaller in MCI patients relative to controls of similar age and education (p=0.0002).

**Key references.**


Effects of ageing, and measurement method, on gross and cortical cerebral autoregulatory upper limits


Cardiovascular & Respiratory Sciences, School of Clinical & Experimental Medicine, College of Medical & Dental Sciences, University of Birmingham, UK, B15 2TT.

Cerebral blood flow (CBF) and autoregulation is evaluated by various techniques including transcranial Doppler ultrasound, laser speckle imaging, vascular flow probes, as well as mathematical computer modelling systems. Different methods are also used to induce arterial blood pressure (ABP) changes, such as lower body negative/positive pressure, and use of pharmacological agents. This can lead to contrasting data e.g. the slope of the autoregulatory curve, and definition of the UL. Developing a consistent method for both the experiment, and the analysis, is therefore key when investigating the effect of a physiological process on autoregulation, such as ageing.

Ageing leads to impaired endothelium-dependent vasodilatation and sympathetically-mediated vasoconstriction in many tissues, including the brain. We hypothesised that cerebral autoregulation is modulated by these influences, and therefore ageing would be associated with impaired autoregulation at the upper limit (UL). We assessed this using 2 methods of flow measurement: a Transonic flow probe on the carotid artery, after external carotid ligation, to assess gross changes in CBF, as well as laser speckle imaging to assess cortical red cell flux (cRCF, using an rFLPI-2 camera, Moor Instruments Ltd).

Anaesthetised young (Y, 6-8 weeks, n=25) and old (O, 52-58 weeks, n=12) male Wistar rats had phenylephrine infused (0.1–200µg.kg.min⁻¹ i.v.) to raise ABP. Cerebral vascular resistance (CVR) was calculated online (CVR=MABP/MCBF), and blood gasses were monitored throughout, ensuring PaCO₂ was kept within the normal range. Dual-line linear regression analysis of the ‘plateau’ and ‘rising’ phases of the autoregulatory curves was used to calculate ULs.

The slopes of both Y and O gross plateau phases showed negative slopes (-0.006±0.001 and -0.005±0.003 respectively). The gross CBF UL for Y rats was 168±2mmHg. In 8 Y rats where cRCF was simultaneously monitored, the gross CBF UL was 166±4mmHg, whilst the cRCF UL was significantly higher at 170±5mmHg*. By contrast in O rats, the gross CBF UL was 180±3mmHg* (vs Y rats), and the cRCF UL was identical. Beyond the UL, the gross rising phases showed positive slopes, reflecting the increase in CBF (which was accompanied by a fall in CVR). However the O rising slope was significantly blunted vs Y (0.02±0.007 vs 0.08±0.01 respectively).

We suggest that in Y rats, a higher UL for cCBF vs gross CBF reflects further capacity for autoregulatory constriction of smaller cerebral vessels after larger, proximal vessels have reached their UL. This may protect cortical tissue circulation. Around 50% of O rats showed basal hypertension compared to Y rats, which has been shown to induce a rightwards shift in the autoregulatory curve. This may explain the higher gross CBF UL in O rats, however, as the UL for cRCF and gross CBF were the same in O rats, it seems the extended autoregulatory range for smaller cerebral vessels is lost with ageing. This could result in fragile cortical vessels being exposed to increased pressure when ABP rises, increasing the risk of haemorrhagic stroke.

British Heart Foundation funding is gratefully acknowledged.
Effects of ageing, and measurement method, on gross and cortical cerebral autoregulatory upper limits

Emma Thompson
Centre for Cardiovascular Sciences
College of Medical and Dental Sciences
University of Birmingham
elt735@bham.ac.uk
Supervisors: Professor Janice Marshall & Dr Andrew Coney

Introduction
- Cerebral autoregulation: cerebral blood flow (CBF) maintained across range of arterial blood pressures (ABP)
- Various measurement methods:
  - Transcranial Doppler, laser speckle, vascular flow probes, hydrogen clearance, microspheres, mathematical modelling,......
- Various techniques to induce ABP changes:
  - LBNP/LBPP, rapid cuff deflation, tilt tables, pharmacological agents, artery clips......
- Defining the ‘plateau’ and upper/lower limits
- Human volunteers vs. animal studies

Methods
- Aflaxan-anaesthetised (12-30mg.kg.hr⁻¹) male Wistar rats
- Young (Y, n=25, 6-8 weeks) or Old (O, n=12, 52-64 weeks)
- Procedures complied with current UK guidelines
- Simultaneously assessed CBF at gross and cortical levels (Y n=8):
  - Internal carotid arteries vascularly isolated = index of CBF via Transonic flow probe
  - Cranial bone thinned until vessels visible = index of cortical CBF via Laser speckle imaging camera (rFLPI-2, Moor Instruments Ltd.)
- Autoregulatory capacity challenged by infusion of phenylephrine (PE: 0.1-200µg.kg.min⁻¹) to raise ABP until UL reached
- Cerebrovascular resistance (CVR) calculated online (=MABP/MCBF)
- Arterial blood gases and body temperature monitored
- \( P_{a\text{Co}_2} \) within normal range throughout
- Statistics: paired or unpaired t-test as appropriate. Significance taken as P<0.05

Hypotheses
- Ageing is associated with impaired autoregulation at the UL
  - Lower UL in Old vs Young rats
  - Increased chance of haemorrhagic stroke in Old rats
- Hypothesis 2: Cortical UL higher than gross

Data analysis
- How to define upper limit (UL)?
  - % rise in CBF, absolute increase above baseline, increase in CBF with no further increase in ABP......
  - Dual-line linear regression
  - Adapted from Samsel and Schumacker (1988), previously used in our lab (Edmunds and Marshall, 2001)
- Young control UL: 168±2mmHg

Results: Young vs Old basal characteristics
- No significant difference between Y and O in MABP, \( P_{a\text{O}_2} \) or \( P_{a\text{CO}_2} \)
- Significantly lower HR, \( P_{a\text{O}_2} \), and trend for lower Hct in O rats
- Significantly lower CVR, and higher CBF, in O rats

Ageing:
- Altered CBF, structural vascular changes, oxidative stress, hypertension
- Endothelial dysfunction, reduced innervation density
- Cerebral autoregulation is normally modulated by endothelium-dependent vasodilatation and sympathetically-mediated vasoconstriction
- Impaired autoregulation at the upper limit (UL)?
- Linked to increased risk of stroke in older people?

Hypotheses
- Ageing is associated with impaired autoregulation at the UL
  - Lower UL in Old vs Young rats
  - Increased chance of haemorrhagic stroke in Old rats
Effects of ageing, and measurement method, on gross and cortical cerebral autoregulatory upper limits
E Thompson, University of Birmingham, UK

Results: Upper limit in Young vs Old
- Gross UL significantly higher in O vs Y
- Gross UL significantly higher in O vs Y
- Cortical UL identical to gross in O

Results: Changes in cerebrovascular resistance
- CVR rises during plateau phase: autoregulatory vasoconstriction
- Beyond UL CVR falls
- Blunted in O

Results: Slopes of regression lines
- Y and O gross plateau slopes –ve, cortical slopes +ve
- Gross and cortical rising slopes +ve: CBF increasing beyond UL
- O blunted vs Y

Discussion & Conclusions
- Baseline CBF is higher in Old vs Young rats
- Lower CVR – increased vascularity?
- Higher Cortical vs Gross upper limit in Young adults
- This suggests further autoregulatory capacity of smaller vessels after larger vessels have reached upper limit
- We propose this is a mechanism that protects cortical circulation
- Not seen with ageing – loss of protective mechanism, increased risk of haemorrhage
- Higher Gross upper limit in Old vs Young adults
- Vascular structural changes, increased stiffness?
- Hypertension – seen in ~50% of O group
- Change in active dilator mechanisms at UL?....

Emma Thompson
elt735@bham.ac.uk
Centre for Cardiovascular Sciences, College of Medical and Dental Sciences, University of Birmingham
Aging is associated with Maintained Cerebral Autoregulation Despite Impaired Cerebrovascular Dilatory Response to Carbon Dioxide

JM Serrador, LA Reyes, FA Sorond, LA Lipsitz

Background: Our lab has previously examined the effect of aging on cerebral autoregulation and cerebrovascular reactivity in a large group of community dwelling elderly individuals. This work demonstrated that autoregulation remained intact with aging and that cerebrovascular reactivity was lower in the elderly than in previously reported literature from younger healthy populations. In addition we found that females had better autoregulation and cerebrovascular reactivity. While the control of vascular tone is performed at the smooth muscle level, activation of the smooth muscle is completed through different mechanisms. During cerebral autoregulation, a myogenic stretch response occurs in response to changes in pressure. During cerebrovascular reactivity testing, the addition of CO$_2$ causes activation of a pathway that dilates the smooth muscle through an endothelial mechanism. Thus, if the smooth muscle function is impaired, both autoregulation and cerebrovascular reactivity would be impaired. Previous data in the peripheral vasculature has demonstrated that populations with impaired endothelial function show an inability to dilate but are still able to constrict in response to a constrictive stimulation. The goal of this work was to examine whether cerebrovascular response to a dilatory stimulus (hypercapnia) would be different to a constrictor stimulus (hypocapnia) and if either would be correlated to autoregulation.

Methods: We used TCD to evaluate cerebrovascular reactivity in 419 (186 males) subjects over the age of 70 recruited as part of the MOBILIZE Boston study (MBS). The MBS is a prospective cohort study of a unique set of risk factors for falls in seniors in the Boston area. We assessed CO$_2$ vasoactivity during both hypercapnia (8% inspired CO$_2$) and hypocapnia (mild hyperventilation) as well as cerebral autoregulation (sit to stand maneuver).

Results: Male subjects had significantly lower CO$_2$ vasoactivity (Males: 2.8±0.7, Females: 3.1±0.8 %/mmHg CO$_2$, p<0.001) as we have previously reported. Examination of their response to reduced end tidal CO$_2$ (hypocapnia) found that there was no difference in the reduction of cerebral flow velocity or vasoconstrictor response (Males: 3.7±3.7, Females: 3.5±4.0 %/mmHg CO$_2$, p=0.6). In contrast, while both sexes had an impaired ability to vasodilate to CO$_2$, males demonstrated an even greater impairment than females (Males: 0.0±1.3, Females: 0.5±2.1 %/mmHg CO$_2$, p<0.006). Interestingly, there was no correlation between the vasodilatory or vasoconstrictor response and measures of cerebral autoregulation. In addition, controlling for diabetes, hyperlipidaemia or hypertension did not change the results.

Conclusion: These data suggest that an impaired response to a dilatory cerebrovascular stimulus (hypercapnia) may indicate that cerebral endothelial dysfunction is present in aging. In contrast smooth muscle regulation of the vasculature remains intact since cerebral vessels were able to constrict during hypocapnia and dilate during a hypotensive stimulus while standing. Thus, improving endothelial function may result in improved dilation of vessels during stimuli that activate the endothelial pathways such as hypercapnia.

References: Deegan et al, Stroke. 2011 Jul;42(7):1988-93
Acute Stages of Sport Concussion: Heart Rate Variability and Blood Pressure Suppression During Postural Hemodynamic Drives

Scott Bishop, 1Ryan Dech, 1Kaishan Aravinthan, 1Taylor Baker, 1Matthew Butz, 1J. Patrick Neary
1Kinesiology and Health Studies, University of Regina, Regina, Canada

BACKGROUND: Previous research used thigh-cuff deflation techniques to assess dynamic cerebral autoregulation (dCA) in a ‘medium risk’ brain injury cohort (4,7). The results showed an Autoregulation Index (ARI) impairment, and patients with the worst ARI scores had lower mean arterial pressure (MAP). The ARI was also used in healthy professional boxers, and showed ‘selectively lower’ scores that were indicative of impaired dCA that was attributed to the boxer’s training volume (5). Other research utilized beat-to-beat (R-R) Fourier-transformed heart rate variability (HRV) to gauge brain injury severity and ‘recovery’ (2-3, 6, 9). Parasympathetic (high frequency, HF 0.15-0.4Hz) and either sympathetic or baroreflex (low frequency, LF 0.04-0.15Hz) innervations have been used to assess post-injury autonomic function (6). Based on this research, we monitored participants who were within 24-72hrs of recovery following a sport concussion (mTBI) to assess autoregulation and cardiovascular metrics.

METHODS: Male hockey athletes (n=170; aged 17-24yrs) were recruited for baseline assessment from within the university, the Canadian Western Hockey League, and the Regina Junior Hockey League. Concussed participants (n=13) were recruited from within these leagues, and were symptomatic at time of testing (24 - 72 hours post-injury). All participants had finger plethysmography, electrocardiography, and expired gases analyzed. A cyclical postural challenge consisting of 10s body-weight squatting, and 10s of standing (0.05 Hz driving frequency) was performed. The average peak pressure was calculated from 4-7s during squatting and standing; as was the 10s average for both squatting and standing. R-R intervals were taken for the entire squat-stand (SS) duration, and were processed through HRV software (10). The SS R-R intervals were also transformed into both heart rates (HR) and HR standard deviations (HRSD), and were analyzed to ‘match’ the blood pressure responses for both squatting and standing (HRpeakmean, HRpeakSD, HRTotalaverage, HRTotalSD).

RESULTS: During the squat phase, peak average pressure for systolic (166.2mmHg vs. 148.3mmHg; p<.01), diastolic (89.8mmHg vs. 84.1mmHg; p<0.05), and MAP (115.2mmHg vs. 105.5mmHg; p<.01) were all significantly lower in the mTBI group compared to control baseline. Overall 10s averages when squatting for systolic (154.2mmHg vs. 137.3mmHg; p < 0.01), diastolic (84.7mmHg vs. 79.0mmHg; p<0.05), and MAP (107.8mmHg vs. 98.4mmHg; p<.01), were also significantly suppressed in the mTBI group. Additionally, the 10s average for systolic pressure during the stand phase (118.8mmHg vs. 107.8mmHg; p<0.05) was reduced with concussion, as was the standing peak systolic average pressure (108.5mmHg vs. 98.8mmHg; p<0.05). Concussions produced increased LF (84.9% vs. 85.6%; p=0.086), decreased HF (15.1% vs. 14.4%; p=0.086), and increased LF:HF ratio (5.7 vs. 6.0; p=0.083). The standing HRSD (14.0 vs. 10.8; p<0.05), and standing HRPeakSD (10.9 vs. 7.3; p<0.05) were both suppressed following mTBI.

DISCUSSION: These findings support other mTBI research indicating perturbed cerebrovascular regulation after mTBI(1-5). Specifically, relatively fit individuals in the acute stage of recovery can experience decreased pressure during squatting, and decreased systolic pressure during standing. The decreased standing HRSd, was interpreted as an increased likelihood of HR remaining elevated so as to compensate for the lowered standing systolic pressure. This is corroborated by the heightened LF values, which represent baroreflex activity.

KEY REFERENCES:


Autoregulation-based optimal cerebral perfusion pressure in a prospective traumatic brain injury cohort

Donnelly J¹, Smielewski P¹, Aries MJH², Liu X¹, Cabeliera M¹, Cardim D¹ Czosnyka M¹,³

1. Division of Neurosurgery, Department of Clinical Neurosciences, Addenbrooke’s Hospital, University of Cambridge, Cambridge, UK
2. University of Groningen, Netherlands
3. Institute of Electronic Systems, Warsaw University of Technology, Poland

Key words: Traumatic brain injury, intracranial pressure, cerebral haemodynamics, autoregulation, brain chemistry, cerebral perfusion pressure

Corresponding author: Joseph Donnelly

Division of Neurosurgery, Department of Clinical Neurosciences, Addenbrooke’s Hospital, University of Cambridge, Hills Road, Cambridge CB2 0QQ, UK
Fax: +44 (0) 1223 216926, Tel: +44 (0) 1223 336946
**Background:** An autoregulation-based method has been proposed to determine an optimal cerebral perfusion pressure in traumatic brain injured (TBI) patients with ICP monitoring. Retrospective data indicate that deviation from the continuously calculated ‘optimal’ CPP (CPPopt) is associated with worse patient outcome (Aries et al. 2012). In this prospective study we aimed to confirm this relationship in a prospective TBI cohort and refine the methods to investigate the relationship between CPP and CPPopt.

**Methods:** We prospectively collected ICP monitoring data from severe consecutive TBI patients admitted between 2010 and 2013 in Addenbrooke’s Hospital, UK. Treatment was guided by absolute values of ICP and CPP. CPPopt was determined using automatic curve fitting procedure of the relationship between pressure reactivity index (PRx) and CPP as described previously. The relationship of the deviation from CPPopt and outcome was assessed by calculating the time spent with CPP more than 5 mm Hg above or below CPPopt in survivors and non-survivors (assessed at 6 months post ictus).

**Results:** ICP monitoring data from 136 patients was available. Mean ICP, CPP, and CPPopt were 13.7 +/- 5.5, 78.2 +/- 7.8, and 77.7 +/- 7.7 mm Hg respectively. Patients spent significant amounts of time with CPP below CPPopt, particularly in non-survivors compared with survivors (42% vs. 28%; P=0.0005). Mean PRx and time spent with CPP below CPPopt were able to distinguish between survivors and non survivors (ROC area under the curve 0.70 and 0.73).

**Conclusions:** In a recent retrospective cohort of severe TBI patients we confirm an association between deviation from CPPopt and survival. Despite aggressive CPP and ICP oriented therapies, TBI patients with fatal outcome spend a significant time with a CPP below CPPopt, indicating a possible therapeutic target. Whether this deviation from CPPopt can be ameliorated with a CPPopt oriented therapy should be studied with a multicenter trial.
Figure 1 CPPopt determination after TBI

Figure 1 A demonstrates how CPPopt can be calculated as a continuous variable over a 4 hour epoch with multimodality monitoring. Pressure reactivity index (PRx) is shown in the top panel and CPP (solid line) in the middle panel. When PRx is averaged in CPP intervals and plotted we often see a ‘U-shaped’ curve as in this example; the minimum of the curve indicates that autoregulation is optimal for this patient at this point of time, when CPP is ~92 mm Hg. Figure B shows an example 48-hour recording from a patient with a fatal outcome. PRx is often significantly positive (top panel), particularly when CPP is below CPPopt (middle panel). The histogram in the bottom panel indicates the patient spent a significant amount of time with CPP more than 5 mm Hg below CPPopt.
Figure 2 Time spent with deviation of CPP from CPPopt in survivors (left) and non-survivors (right)

Non-survivors spent more time with CPP below CPPopt indicating possible hypoperfusion.

Reference


Conflict of interest

ICM+ is a software licensed by Cambridge Enterprise Ltd, UK. PS and MC have financial interest in 30% of licensing fee.
Introduction. Cerebrovascular pressure reactivity (PRx: moving correlation coefficient between 30 samples of consecutive 10 second averages of ICP and arterial blood pressure) independently correlates with outcome after traumatic brain injury (TBI). However, as an index plotted in time domain, PRx is rather noisy, and requires at least 30-minutes averaging (unless there is a strong haemodynamic stimulus like plateau waves of ICP, arterial hypotension, hyperventilation, etc). An alternative method of dealing with the noise is by plotting PRx against observed values of cerebral perfusion pressure (CPP), which additionally allows assessment of ‘optimal CPP’. However, the relationship between PRx and ICP is unclear.

Method. We analysed 651 recordings of TBI patients monitored in years 1997-2013 using ICM+ software and studied relationship between PRx and ICP. Then we identified 7 patients who died from refractory hypertension and examined time-varying values of PRx along with ICP and CPP. To ‘organize’ PRx and make it better interpretable, colour coding of values, with green, when PRx<0 and red when PRx>0.3 has been introduced as horizontal line of ICM+ screen. This idea was transposed from ‘traffic lights’ (three diodes: red, yellow, green connected to printer output of bedside computer running old ICM version (1991-2003)).

Results. The relationship between mean PRx and mean ICP was significant (p<0.0001) and showed flat distribution for PRx lower than 0.3 (mean ICP was 14+/−7.1 mm Hg). For higher values of PRx mean ICP was increasing to reach ICP 40+/−17 mm Hg at PRx=0.8 – see Fig Left. Then 7 patients after TBI who died in scenario of refractory intracranial hypertension were selected. In 4 cases initial ICP was below 20 mm Hg and final well above 60 mmHg, with CPP less than 20 mm Hg. In 3 cases initial ICP at start of monitoring was already elevated above 20 mm Hg but final ICP was very high (above 50 mm Hg), with CPP below 30 mmHg. ‘Solid red line’ (PRx constantly above 0.3) was observed in all cases preceding rise of ICP above 40 mmHg from minutes to hours – Fig Right.

Conclusion. Disturbed pressure-reactivity is associated with incidence of intracranial hypertension. ‘Solid red line’ is a mathematical consequence of mean ICP being stronger than usual and persistently positively correlated with MAP. It may indicate deteriorated autoregulation, or it may be present at high ICP as epiphenomenon of Cushing response. If such a state is detected for longer period by monitoring system, it should be considered as an indicator of profound cerebrovascular deterioration threatening with terminal rise of ICP.

Figure Left. Distribution of mean ICP in 651 TBI patients vs levels of Pressure Reactivity Index (PRx) indicates that for greater values of PRx (>0.3) incidence of intracranial hypertension rises

Figure Right. Patient who had normal ICP for three days after TBI and died on day 4 because of refractory intracranial hypertension. Deterioration of PRx can be seen as ‘solid rate line’ (PRx>0.3) all the time since day 1.
**Association of the outcome of traumatic brain injury patients with cerebrovascular autoregulation impairment events**

1^R^agauskas A, 1^P^etkus V, 1^K^rakauskaite S, 1^C^homskis R, 2^P^reiksaitis A, 2^R^ocka S.  
1Health Telematics Science Institute, Kaunas University of Technology, Lithuania.  
2Republic’s Vilnius University Hospital, Vilnius University, Clinics of Neurology and Neurosurgery, Lithuania.

**Background.** The aim of the prospective study was to explore associations of TBI patient specific cerebrovascular autoregulation (CA) dynamic and “optimal cerebral perfusion pressure” (optCPP) management \([1,2]\) with the outcome of severe TBI patients. Information on patients’ age and grade of diffuse axonal injury (DAI) was also included into the analysis.

**Methods.** CA monitoring of 33 severe TBI patients was performed by using ICM+ software (Cambridge, UK) in Republic’s Vilnius University Hospital. CA status estimating pressure reactivity index (PRx(t)) and CPP(t) data were processed in order to obtain diagnostic information for making patient-specific treatment decisions by using management of the optCPP \([1]\). The analysis of CA status dynamic was performed and the relationship between duration of the longest CA impairment (LCAI) event and patients’ outcome was investigated.

**Results.** Association of Glasgow outcome scale (GOS) with the averaged value of PRx(t) showed negative correlation \((r = -0.40)\). The averaged value \((PRx) > 0.24\) was associated with mortality. The correlation between GOS and the difference \(\Delta\text{optCPP} = \text{CPP} - \text{optCPP}\) was \(r = 0.484\). The critical value of CPP(t) declination from optCPP per - 6 mmHg was associated with mortality. Multiple correlation between GOS, \(\Delta\text{optCPP}\) and age was \(r = -0.79\). Durations of the longest single critical CA impairment events responsible for mortality were: 25 min when PRx(t)>0.8; 40 min when PRx(t)>0.7 and 80 min when PRx(t)=0.6. Multiple correlations between GOS, LCAI and age and between GOS, LCAI and DAI grade were \(r = -0.73\) and \(r = -0.59\), respectively.

**Discussion.** The preliminary prospective study on TBI patients shows that unfavorable outcome of TBI patients is more significantly associated with duration of a single longest CA impairment episode but not with the time average of all CA impairments including relatively short secondary insults. This finding contradicts the present integrative approach of association between CA impairments and unfavorable outcomes of severe TBI patients. The pharmaceutical patient-specific management (adrenominetic, nitrite, thiopental, hypertonic saline, etc.), respiratory gas adjustment or decompressive craniectomy are available tools for maintaining CPP close to optCPP. OptCPP-targeted therapy allows eliminating too long single CA impairments and leads to a more favourable outcome of severe TBI patients.

**Conclusion.** The analysis of GOS association with duration of LCAI events showed that the outcomes of severe TBI patients are significantly associated with duration of the single longest CA impairment event, age and DAI grade. Multidimensional representation of GOS plots showed that better outcomes were obtained for younger patients (<47 years) with lower DAI grades (1 or 2), for those whose LCAI event was shorter than 40 min when PRx(t) was above 0.7 within that CA impairment event and for patients whose CPP(t) was kept within the interval from optCPP to (optCPPopt +10 mmHg).

**Key references.**


Acknowledgement: This research has been funded by the grant MIP-118/2012 from the Research Council of Lithuania and the Swiss – Lithuanian grant No.CH-3-SMM-01/06.
Association of the outcome of traumatic brain injury patients with cerebrovascular autoregulation impairment events

V Petkus, Kaunas University of Technology, Lithuania

Association of the outcome of traumatic brain injury patients with cerebrovascular autoregulation impairment events

A Ragauskas, V Petkus, S Krakauskaite, R Chomskis, A Preiksaitis, S Rocka

Health Telematics Science Institute, Kaunas University of Technology, Lithuania

Republic’s Vilnius University Hospital, Vilnius University, Clinics of Neurology & Neurosurgery, Lithuania

Background

The aim of the prospective study was to investigate the associations of TBI patient-specific cerebrovascular autoregulation (CA) dynamics and “optimal cerebral perfusion pressure” (optCPP) management with the outcome of severe TBI patients.

Identification of critical durations of relatively long CA impairments in association with severe TBI patients’ outcomes was also the aim of prospective clinical study.

Methods

Fig. 1. ICM+ software (Cambridge, UK) windows used for continuous CA monitoring data presentation and “optimal CPP” determination.

Parameters included into analysis:

• Longest CA impairments LCAI episode when PRx(t) continuously exceeded high positive values of 0.5; 0.6; 0.7; and 0.8 were estimated for each patient.

• The “optimal CPP” values were calculated by plotting the CPP values vs PRx values and fitting the “U-shape” curve over the plotted points taken from 6 hrs monitoring window. The minimum point of the “U-shape” was kept as “optCPP” value.

• ∆CPPopt=CPP-optCPP – the difference between the real-time CPP and the “optimal CPP”

• PRx(t) - the moving linear correlation coefficient between ABP(t) and ICP(t) slow waves. PRx(t) calculated within 10 min moving averaging time window.

Prospective study in Vilnius university hospital

33 patients after severe TBI (GCS 8 or less when Motor Response 5 or less).

<table>
<thead>
<tr>
<th>Parameters included into analysis:</th>
<th>Patients with favorable outcome (GOS 6M = 4 - 5)</th>
<th>Patients with unfavorable outcome (GOS 6M = 1-3)</th>
<th>Patients with unfavorable outcome (GOS 6M = 2-3)</th>
<th>Patients with unfavorable outcome (GOS 6M = 1)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>16</td>
<td>8</td>
<td>9</td>
<td>3</td>
<td>33</td>
</tr>
<tr>
<td>Sex</td>
<td>13 / 3</td>
<td>6 / 2</td>
<td>8 / 1</td>
<td>27 / 6</td>
<td></td>
</tr>
<tr>
<td>Age, year</td>
<td>Mean (SD) 25.3 (9.7)</td>
<td>46.3 (18.4)</td>
<td>49 (7.6)</td>
<td>36.8 (16.2)</td>
<td></td>
</tr>
<tr>
<td>Initial Glasgow Coma Score, Median (IQR)</td>
<td>6 (4-7)</td>
<td>5 (4-8)</td>
<td>5 (5-6)</td>
<td>5 (4-7)</td>
<td></td>
</tr>
<tr>
<td>Patient’s No. with DAI grades I/II/III</td>
<td>3 / 12 / 1</td>
<td>1 / 6 / 1</td>
<td>0 / 5 / 4</td>
<td>4 / 23 / 6</td>
<td></td>
</tr>
<tr>
<td>Averaged PRx, Mean (SD)</td>
<td>0.08 (0.11)</td>
<td>0.12 (0.17)</td>
<td>0.26 (0.30)</td>
<td>0.14 (0.20)</td>
<td></td>
</tr>
<tr>
<td>LCAI (PRx&gt;0.5), min</td>
<td>57.7 (42.6)</td>
<td>93.5 (79.2)</td>
<td>235.3 (252.7)</td>
<td>114.8 (155.0)</td>
<td></td>
</tr>
<tr>
<td>LCAI (PRx&gt;0.6), min</td>
<td>41.6 (32.6)</td>
<td>71.1 (67.7)</td>
<td>202.1 (227.8)</td>
<td>92.5 (138.8)</td>
<td></td>
</tr>
<tr>
<td>LCAI (PRx&gt;0.7), min</td>
<td>24.0 (12.8)</td>
<td>38.8 (32.2)</td>
<td>149.5 (164.8)</td>
<td>61.8 (100.5)</td>
<td></td>
</tr>
<tr>
<td>LCAI (PRx&gt;0.8), min</td>
<td>14.6 (11.8)</td>
<td>29.1 (28.6)</td>
<td>95.3 (123.3)</td>
<td>40.1 (72.3)</td>
<td></td>
</tr>
</tbody>
</table>

Methods

Fig. 2. Association between GOS and PRx. GOS after 6 months correlates negatively with PRx (r=-0.397, P=0.009). Threshold value of PRx>0.24 (GOS ≥ 5.527, P=0.0188) is associated with mortality.
Association of the outcome of traumatic brain injury patients with cerebrovascular autoregulation impairment events
V Petkus, Kaunas University of Technology, Lithuania

Fig. 3. Association between GOS and ∆CPPopt. The correlation coefficient between the GOS after 6 months and ∆CPPopt is r=0.471 (P=0.004).

ΔCPP opt < -6 mmHg associated with mortality

Results

Fig. 4. Association between GOS after 6 months and duration of CA impairment under conditions when PRx >0.7 (r=-0.499, P=0.001<0.05). CA impairment duration > 40 min (∛ =5.991, P=0.014<0.05) when PRx>0.7 is associated with mortality.

Results

Fig. 5. Linear dependence between the critical longest duration of CA impairment event and the critical PRx thresholds associated with mortality. The correlation coefficient r=0.985 (P=0.008).

Results

Fig. 6. Association between GOS after 6 months and age (r=0.626, P<0.001). The age > 47 years (∛ =8.397, P=0.004) is associated with poor outcome (GOS 1..3).

Results

Fig. 7. Association between GOS after 6 months and DAI grade (r=-0.468, P<0.005). DAI grade 3 is associated with poor outcome (GOS =1, 2 or 3).

Results

Fig. 8. Contour plots of GOS dependences on the duration of CA impairment at PRx level above 0.7, and age. Better outcome is associated with younger patients and for those whose prolonged duration of CA impairment was not observed. The multiple correlation coefficient between GOS and two input factors (LCAI, age) was r=0.730 (P<0.001).
Association of the outcome of traumatic brain injury patients with cerebrovascular autoregulation impairment events
V Petkus, Kaunas University of Technology, Lithuania

Results
Multi-dimensional analysis of outcome (II):
GOS vs Duration of longest CA impairment and DAI grade

Fig. 9. Contour plots of GOS dependences on the duration of CA impairment at PRx level above 0.7, and DAI grade. Better outcome is associated with patients with lower DAI grade and for those whose prolonged duration of CA impairment was not observed. The multiple correlation coefficient between GOS and LCAI together with DAI grade was r = -0.589 (P=0.001)

Results
Multi-dimensional analysis of outcome (III):
GOS vs ∆CPPopt and age

Fig. 10. Contour plots of GOS dependences on the declination form “optimal CPP” and age. Better outcome is associated with younger patients and for those whose CPP was kept within the range from “optimal CPP” to “optimal CPP”+10 mmHg. The multiple correlation coefficient between GOS and ∆CPPopt together with Age was r = - 0.619 (P<0.001)

Results
Multi-dimensional analysis of outcome (IV):
GOS vs ∆CPPopt and DAI grade

Fig. 11. Contour plots of GOS dependences on the declination form “optimal CPP” and DAI grade. Better outcome is associated with patients with lower DAI grade and whose CPP was kept within the range from “optimal CPP” to “optimal CPP”+10 mmHg. The multiple correlation coefficient between GOS and ∆CPPopt together with DAI grade was r = - 0.559 (P=0.002)

Vegetative state GOS 2

Unfavorable outcome case
• 18yo female
• Traffic accident 2013 December 20 (pedestrian)
• GCS – 4
• Maximal wide of right pupil
• CT and MRI – severe DAI (grade III)
• Cerebrovascular autoregulation data:
  – Average PRx -0.02

VOS 2

Favorable outcome
• 24yo male
• Traffic accident 2013 November 23 (passenger)
• GCS – 6
• Pupils normal
• CT and MRI – severe DAI (grade III)
• Cerebrovascular autoregulation data:
  – Average PRx +0.18

GOS 5
Association of the outcome of traumatic brain injury patients with cerebrovascular autoregulation impairment events
V Petkus, Kaunas University of Technology, Lithuania

Conclusions

- GOS of severe TBI patients (Vilnius centre prospective study of 33 patients) is multi-factorial function that significantly correlates with:
  - Duration of longest CA impairment event (according to time when PRx exceeds critical level),
  - Declination from ‘Optimal CPP’,
  - Age,
  - DAI grade, etc.

Conclusions

- PRx and CPP thresholds associated with mortality:
  a) critical duration of CA impairment:
     - > 25 min when PRx>0.8
     - > 40 min when PRx>0.7
     - > 80 min when PRx>0.6
     - > 100 min when PRx>0.5
  b) CPP - “optimal CPP”< -6 mmHg

Conclusions

- Patient specific CPP management between ‘Optimal CPP’ to ‘Optimal CPP’+10 mmHg is the best choice for treatment of severe TBI.

Acknowledgments

The study has been funded by Swiss-Lithuanian clinical project BrainCare, FP7 Project TBICare and Lithuanian Science Council project MIP 118/2012-14.

THANK YOU!
Poster Abstracts
Static and dynamic cerebral autoregulation – are we measuring the same thing?

Daan LK de Jong¹, Olga V Meulenbroek¹, Takashi Tarumi²,³, Jurgen AHR Claassen¹, R Zhang²,³,⁴

¹Department of Geriatric Medicine, Radboud Alzheimer Centre, Radboud University Nijmegen Medical Centre; Donders Institute for Brain, Cognition and Behavior, Nijmegen, The Netherlands; ²Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital Dallas; ³Department of Internal Medicine; ⁴Department of Neurology and Neurotherapeutics, Alzheimer’s Disease Center, University of Texas Southwestern Medical Center

Mail: Daan.dejong@radboudumc.nl

Background

The increase in temporal resolution of measuring cerebral blood flow (CBF) has had, and will continue to have, a high impact on cerebral autoregulation research. Most of previous studies measured static cerebral autoregulation (sCA) [1, 2], while dynamic cerebral autoregulation (dCA) can be assessed with high temporal resolution CBF measurements [3-5]. However, research into the relation between sCA and dCA is remarkably limited, although it has been commonly assumed that sCA and dCA are closely related [4, 6, 7]. Better understanding of the relationship between sCA and dCA is fundamentally important both for research and clinical care. Therefore, in this study we compared measurements of sCA and dCA to determine if assessments of sCA are correlated with dCA.

Methodology

For this study 24 healthy older adults (55-78 yrs) were tested. dCA measures were quantified using transfer-function analysis of spontaneous oscillations in blood pressure (BP) and CBF velocity (CBFV) measured in the middle cerebral artery (8 minute, supine resting conditions), and ARI-analysis of transient decrease and increase in BP and CBFV induced by bolus injection of sodium nitroprusside followed by bolus of phenylephrine (the modified Oxford method). sCA was quantified by a linear regression slope between percentual changes in cerebrovascular resistance index (CVR = MAP/CBFV) and mean BP. Steady-state changes in BP were induced using stepwise intravenous administration of sodium nitroprusside (0.25, 0.5, 0.75 and 1.0 µg /min) and phenylephrine (0.5, 1.0 and 1.5 µg /min). Steady-state changes in CBF were measured using color-coded duplex ultrasonography from the internal carotid artery and vertebral artery.

Results

Table 1 shows the correlation between sCA and dCA measures. Only sCA in the posterior circulation (VA) showed a significant correlation with one dCA parameter, LF-phase (ρ=0.501; p=0.01). None of the other dCA parameters correlated with sCA in ICA or VA.

<table>
<thead>
<tr>
<th>dCA parameters</th>
<th>sCA (ICA)</th>
<th>sCA (VA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LF-gain</td>
<td>0.151</td>
<td>0.095</td>
</tr>
<tr>
<td>LF-phase</td>
<td>0.108</td>
<td>0.501*</td>
</tr>
<tr>
<td>ARI-nitroprusside</td>
<td>0.333</td>
<td>-0.121</td>
</tr>
<tr>
<td>ARI-phenyl</td>
<td>0.367</td>
<td>0.262</td>
</tr>
</tbody>
</table>

Table 1: Correlation (Spearman’s ρ) between different dCA parameters and the sCA of the anterior (ICA) and posterior (VA) circulation

Figure 1: Scatter plot between low-frequency phase (dCA) and the posterior sCA
Conclusion

There was only a weak correlation between sCA and dCA measures, limited to the LF phase. These results suggest that sCA and dCA may reflect different properties of cerebrovascular function. Further data analysis will be performed to confirm these preliminary findings.

References

Static and dynamic cerebral autoregulation – are we measuring the same thing?

Daan LK de Jong¹, Olga V Meulbroek¹, Takashi Tarumi², Jurgen AHR Claassen¹, R Zhang²,³,⁴

¹Department of Geriatric Medicine, Radboud Alzheimer Centre, Radboud University Nijmegen Medical Centre, Donders Institute for Brain, Cognition and Behavior, Nijmegen, The Netherlands; ²Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital Dallas; ³Department of Internal Medicine; ⁴Department of Neurology and Neurotherapeutics, Alzheimer’s Disease Center, University of Texas Southwestern Medical Center

Introduction

Dynamic cerebral autoregulation (dCA)
- Dynamic response to changes in blood pressure

Static cerebral autoregulation (sCA)
- Equilibrium situations of BP and cerebral blood flow

Weaker evidence that they are strongly related [1].

Objective

Assess the relation between static cerebral autoregulation and dynamic cerebral autoregulation

Methods

26 healthy elderly
- Administration of sodium nitroprusside and phenylephrine
- Bolus
- Continuous infusion

Outcome measures
- dCA parameters
  - TFA of 5 min baseline
  - ARI analysis after bolus injection
- sCA parameters
  - Linear regression slope

Baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/women (n)</td>
<td>13/13</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67±7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171±9</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>77±15</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26±4</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>123±16</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>76±11</td>
</tr>
<tr>
<td>HR (mmHg)</td>
<td>66±8</td>
</tr>
</tbody>
</table>

Table 1: Baseline characteristics of the participating subjects

Results

Figure 2: Boxplot of sCA values calculated from anterior and posterior circulation, with the subjects grouped in three different categories based on the ARI-score. Low is ARI < 4; normal is 4 ≥ARI≤6; high is ARI>6.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>sCA (ICA)</th>
<th>sCA (VA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LF-gain</td>
<td>0.127</td>
<td>0.119</td>
</tr>
<tr>
<td>LF-phase</td>
<td>0.023</td>
<td>0.477 *</td>
</tr>
<tr>
<td>ARI-nitroprusside</td>
<td>0.535*</td>
<td>-0.016</td>
</tr>
<tr>
<td>ARI-phenyl</td>
<td>0.343</td>
<td>0.281</td>
</tr>
</tbody>
</table>

Table 2: Correlation (Pearson’s r) between different dCA parameters and the sCA of the anterior (ICA) and posterior (VA) circulation

Figure 3: Parameter for static CA (Y axis, higher value = better sCA) plotted against parameter for dynamic CA (x-axis, higher value = better dCA)

Discussion

Conclusion
Although sCA and dCA show relation they likely reflect different elements of the regulatory mechanisms

Further research
- Influence larger vessels in sCA
- Effect of the drugs on CA properties
- Effect CO₂ on measurements
- Difference in CA during decrease or increase of BP

Contact: Daan de Jong
daan.dejong@radboudumc.nl

[1]: Tiecks et al. (1995), Stroke

*This study was supported the ADDF # 20121210
Multimodal measurements of blood pressure and cerebral hemodynamic responses to hypercapnia in the MRI
Optoelectronics and Measurement Techniques Laboratory, University of Oulu, Oulu, Finland
Department of Diagnostic Radiology, Medical Research Center of Oulu, Oulu, Finland
Donders Institute for Brain Cognition and Behaviour, Radboud University Medical Centre, Netherlands

Introduction
MRI has great potential to augment the spatial resolution of dynamic cerebral hemodynamic measurements. Availability of MRI compatible measurements of blood pressure (BP) and near-infrared spectroscopy (NIRS) would allow simultaneous recordings and could progress cerebral autoregulation research. We report preliminary results of MRI-compatible measurements of BP pulse propagation between heart and carotid artery, assumed to reflect systemic BP, the driving force of blood flow to the brain. Gathered pulse transit time (PTT) values are compared to the blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) signals under vasodilatory challenges in human brain. In addition, we investigate quantitatively the changes of oxy- (HbO) and deoxy- (HbR) haemoglobin by using NIRS. All measurements were performed simultaneously in MRI.

Methods
BP propagation and NIRS were recorded using MRI compatible non-invasive methods [1]. Two fibre optic sensors were used for the continuous measurement of BP pulse propagation from heart to the carotid artery. One sensor was placed over the aortic valve on the sternum, the other over the carotid artery, and the PTT between the sensors was determined. Simultaneous BOLD fMRI experiments were performed with Siemens 3T SKYRA, in combination with 32-channel head coil. Respiration gases were recorded using GE anaesthesia monitor. To induce mild hypercapnia, a breath hold (BH) task is applied. For each run, the BH paradigm consisted blocks of [32 s BH + 88 s rest] repeated five times (N = 5). The data analysis was performed using Matlab, HoMER2 and FSL.

Results
Figure 1 shows the fluctuations of PTT and the heart rate (HR) and carbon dioxide (CO2) signals as a function of time during BH task. BH decreases PTT, which indicates an increase in blood flow. In agreement, BOLD fMRI showed increase in signal intensity at grey matter (GM) regions (Figure 2), which suggests increased blood flow. Preliminary analysis of PTT and fMRI signal indicated good positive correlation at GM regions (0.57) and, in contrast, negative correlation with CSF signals (0.70).
Fig. 1. BH task exhibits substantial changes in PTT, HR and CO2.

Fig. 2. BOLD fMRI showed increase in signal intensity at GM regions.

Figure 3 shows activation maps between both HbO and HbR and BOLD, when NIRS optode is placed on the subject’s upper left forehead.

Fig. 3. Hypercapnia shows low positive correlation between HbO and BOLD (top), but a high correlation of 0.89 between HbR and BOLD (bottom).

Preliminary hypercapnia analysis:
1. Positive correlation coefficient between MRI compatible BP and fMRI signal was 0.57 at GM regions.
2. Negative correlation coefficient between NIBP and CSF fMRI signal was 0.70.

Conclusion
We have shown, for the first time in humans, that PTT pulsations measured between the aortic valve and the carotid artery have high positive correlation with fMRI signal in GM (0.57). In contrast to GM, BP is negatively correlated with the CSF fMRI signal. This implies that CSF acts as a dynamic reservoir to regulate intracranial pressure. However, additional measurements need to be performed.

Key references
Multimodal measurements of blood pressure and cerebral hemodynamic responses to hypercapnia in the MRI

Introduction
Magnetic resonance imaging (MRI) has great potential to augment the spatial resolution of dynamic cerebral hemodynamic measurements. Availability of MRI compatible measurements of blood pressure (BP) and near-infrared spectroscopy (NIRS) would allow simultaneous recordings and could progress cerebral autoregulation research. We report preliminary results of MRI-compatible measurements of BP pulse propagation between heart and carotid artery, assumed to reflect systemic BP, the driving force of blood flow to the brain. Gathered pulse transit time (PTT) values are compared to the blood oxygen level dependent (BOLD) functional MRI signals under vasodilatory challenges in human brain. In addition, we investigate quantitatively the changes of oxy- (HbO) and deoxy- (HbR) haemoglobin by using NIRS. All measurements were performed simultaneously in MRI.

Methods
BP propagation and NIRS were recorded using MRI compatible non-invasive methods [1]. Two fibre optic sensors were used for the continuous measurement of BP pulse propagation from heart to the carotid artery. One sensor was placed over the aortic valve on the sternum, the other over the carotid artery, and the PTT between the sensors was determined. Simultaneous BOLD fMRI experiments were performed with Siemens 3T SKYRA, in combination with 32-channel head coil. Respiration gases were recorded using GE anaesthesia monitor. To induce mild hypercapnia, a breath hold (BH) task is applied. For each run, the BH paradigm consisted blocks of [32 s BH + 88 s rest] repeated five times (N = 5). The data analysis was performed using Matlab, HoMER2 and FSL.

Results
Figure 1 shows the fluctuations of PTT and the heart rate (HR) and carbon dioxide (CO2) signals as a function of time during BH task. BH decreases PTT, which indicates an increase in blood flow.

In agreement, BOLD fMRI showed increase in signal intensity at grey matter (GM) regions (Figure 2), which suggests increased blood flow. Preliminary analysis of PTT and fMRI signal indicated good positive correlation at GM regions (0.57) and, in contrast, negative correlation with CSF signals (0.70).

Conclusion
We have shown, for the first time in humans, that PTT pulsations measured between the aortic valve and the carotid artery have high positive correlation with fMRI signal in GM (0.57). In contrast to GM, BP is negatively correlated with the CSF fMRI signal. This implies that CSF acts as a dynamic reservoir to regulate intracranial pressure. However, additional measurements need to be performed.

Reference
Are Hormonal Changes Throughout the Menstrual Cycle Associated with Changes in Cerebral Autoregulation?

Michelle Favre; Apollonia Fox; Levy Reyes; Jorge M. Serrador

WRIISC, VAHCS, East Orange, NJ 07018 & Pharmacology & Physiology, Rutgers Biomedical Health Sciences, Newark, NJ

Previous reports have demonstrated enhanced cerebral autoregulation in females compared to males. It was the objective of this study to determine if menstrual cycle phase and ovarian hormones play a role in the enhancement of autoregulation in young females. Seven young, (mean age 22.9 ± 3.1 years) healthy women were tested at three time points during the menstrual cycle: menstruation (M), late follicular (F), and the luteal (L) phase. Each visit consisted of a cerebrovascular reactivity assessment and three sit-to-stand tests. Continuous measurements of heart rate, end-tidal CO₂, blood pressure, and cerebral blood flow velocity in the anterior and middle cerebral arteries were obtained. Saliva samples were collected for verification of menstrual cycle phase. Autoregulatory indices for both the anterior (M: 4.2 ± 1.2; F: 3.4 ±0.73; L: 3.8 ± 0.82) and middle (M: 4.3 ± 0.93; F: 3.2 ± 0.70; L: 3.5 ± 0.77) cerebral arteries during the sit-to-stand tests were significantly greater during menstruation compared to the late follicular phase (p= 0.04). Further results show that the average resting heart rate (M: 75 ± 1.5; F: 69 ± 1.0; L: 70 ± 1.4 bpm) while sitting was significantly elevated during menstruation compared to both the late follicular phase (p= 0.002) and the luteal phase (p= 0.012). Mean arterial pressure (M: 90 ± 4.4; F: 79 ± 6.4; L: 81 ± 8.8 mmHg) while sitting was also significantly higher during menstruation compared to the late follicular phase (p= 0.044). However, cerebrovascular reactivity (M: 2.7 ± 0.15; F: 3.6 ± 0.25; L: 3.3 ± 0.53 %mmHg) was significantly lower in the anterior cerebral artery during menstruation compared to the late follicular phase (p= 0.017). End-tidal CO₂ (M: 35.5 ± 0.93; F: 37.1 ± 0.95; L: 34.4 ± 0.93 mmHg) was significantly lower during the luteal phase compared to the late follicular phase (p= 0.046). Despite the small sample size, these results support that autoregulation is affected throughout the menstrual cycle. The improvements in autoregulation during menstruation may be due to the increase in mean arterial pressure.
Cerebrovascular responsiveness to carbon dioxide in atrial fibrillation.

Igor D. Braz¹, Samuel J. E. Lucas¹, Johannes J. van Lieshout²,³, Paramjit Gill⁴, Gregory Y. H. Lip⁵ and James P. Fisher¹

¹School of Sport, Exercise and Rehabilitation Sciences, College of Life and Environmental Sciences, University of Birmingham, UK
²Laboratory for Clinical Cardiovascular Physiology, Academic Medical Center, Amsterdam, The Netherlands
³School of Life Sciences, The Medical School, University of Nottingham, Queen’s Medical Centre, Nottingham, UK
⁴School of Health and Population Sciences, University of Birmingham, UK
⁵University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK

BACKGROUND. Atrial fibrillation (AF) is the most common heart rhythm abnormality and is a risk factor for severe stroke, cognitive decline and dementia. Elevated plasma biomarkers of vascular damage/dysfunction and reduced conduit (brachial) artery function have recently been identified in AF. In the present study we sought to test the hypothesis that patients with AF have lower cerebral vascular responsiveness in comparison to healthy age-matched control (HC) participants.

METHODS. Five AF patients (66±14yr [mean±standard deviation]) and four HC participants (69±3yr) were recruited. Middle cerebral artery mean velocity (MCA Vₘ, transcranial Doppler), mean arterial pressure (MAP, Finometer), heart rate (HR, ECG) and partial pressure of end-tidal carbon dioxide (PₑT₇CO₂) were recorded continuously. Cerebrovascular responsiveness was determined from the change in MCA Vₘ to a two-stepped hypercapnic protocol (CVR_CO₂). Incremental hypercapnia was delivered via the open circuit steady-state method, with 4-min stages of 4% and 7% CO₂ (in 21% oxygen, nitrogen balanced). CVR_CO₂ was calculated as the percentage change in MCA Vₘ per mm Hg change in PₑT₇CO₂.

RESULTS. Resting MCA Vₘ (AF 48.0±13.6, HC 64.8±20.5 cm·s⁻¹, P=0.181), MAP (AF 93.4±15.2, HC 97.1±15.0 mm Hg, P=0.727), HR (AF 63±16, HC 57±2 b·min⁻¹, P=0.478) and PₑT₇CO₂ (AF 35.3±7.3, HC 37.0±6.5 mm Hg, P=0.728) were not significantly different between groups. Incremental hypercapnia evoked similar increases in PₑT₇CO₂ and MAP between groups, yet CVR_CO₂ was significantly lower in AF patients (2.9±0.8 %·mmHg⁻¹) compared to HC (5.8±2.6 %·mmHg⁻¹; P=0.046).

DISCUSSION AND CONCLUSION. These preliminary results indicate that AF patients have an impaired CVR_CO₂ when assessed at the middle cerebral artery. This blunted cerebral vasodilatory capacity may be associated with the increased risk of cerebrovascular events in this patient group. Future work is required to confirm these findings in a larger patient cohort and to elucidate the mechanisms underlying this dysfunction.
Background. Recently, astronauts have a risk of visual impairment such as optic disc oedema. It may be related to changes in cerebral circulation, increased intracranial pressure and/or other reasons. Cephalad fluid shift and exposure to carbon dioxide (CO\textsubscript{2}) are considered as factors of affecting the cerebral autoregulation during spaceflight. The physiological effects of hypercapnia are recognized as one of the important factors in cerebral autoregulation. Notably, the environment of international space station is high concentrations of CO\textsubscript{2} approximately 0.5%. Besides, astronauts also face a risk of inhaling high concentration of CO\textsubscript{2} pocket, because natural convection of the air does not occur under microgravity. Currently, there has been no report on the influence of CO\textsubscript{2} on dynamic cerebral autoregulation during head-down tilt (HDT) as a simulated-microgravity that produces cephalad fluid shift. Therefore, we test hypothesis that 1) exposure to high concentrations of CO\textsubscript{2} will impair dynamic cerebral autoregulation similarly as revealed previously, 2) exposure to CO\textsubscript{2} during HDT will cause an additive or a synergistic effect on dynamic cerebral autoregulation.

Methods. We are studying 15 healthy men for subjects at this point. Protocols consisted of four interventions labelled AIR (air inhalation in a supine), CO\textsubscript{2} (exposure to 3\%CO\textsubscript{2} in a supine), HDT (air inhalation during 10\degree HDT) and CO\textsubscript{2}HDT (exposure to 3\%CO\textsubscript{2} during 10\degree HDT). After 10-minute baseline (air inhalation in a supine), intervention periods were performed in each of the four protocols. Arterial blood pressure (ABP) using tonometry and cerebral blood flow (CBF) velocity in the middle cerebral artery using transcranial Doppler ultrasonography were recorded. Dynamic cerebral autoregulation was assessed by spectral and transfer function analysis.

Results. All results of intervention are shown in comparison with each baseline. There were no significant changes in AIR (n=10). Phase in the low frequency range (LF) decreased significantly (0.70 ± 0.06 → 0.52 ± 0.05 radians, P=0.004) in CO\textsubscript{2} (n=15). All indices of transfer function analysis did not change significantly in HDT (n=15). Phase LF decreased significantly (0.74 ± 0.09 → 0.46 ± 0.08 radians, P=0.036) and gain LF increased significantly (0.94 ± 0.08 → 1.10 ± 0.11 cm/s/mmHg, P=0.025) in CO\textsubscript{2}HDT (n=10).

Discussion. As expected, decreased phase LF by exposure to 3\%CO\textsubscript{2} indicates impaired temporal function of dynamic cerebral autoregulation. In addition to decreased phase LF, exposure to 3\%CO\textsubscript{2} during 10\degree HDT increased gain LF. Changes of gain LF were not recognized in CO\textsubscript{2} alone and in HDT alone. Hence, increased gain LF in CO\textsubscript{2}HDT is considered that other effects are generated through exposure to 3\%CO\textsubscript{2} during 10\degree HDT. These results indicate that temporal and suppressing function of ABP fluctuation to CBF are impaired by a combination of hypercapnia and cephalad fluid shift.

Conclusion. Exposure to 3\%CO\textsubscript{2} during 10\degree HDT decreased phase LF and increased gain LF. This result suggest that dynamic cerebral autoregulation is impaired by a combination of hypercapnia and cephalad fluid shift. Exposure to CO\textsubscript{2} during spaceflight would have a strong influence on cerebral autoregulation compared to on the earth.

Key references. Carbon dioxide, dynamic cerebral autoregulation, head-down tilt and transfer function analysis.
DOPAMINE INFUSIONS IMPROVES CEREBRAL AUTOREGULATION IN NEWBORN PIGLETS

Eriksen VR¹², Rasmussen M¹², Hahn GH¹³, Greisen G¹
¹Department of Neonatology, Copenhagen University Hospital - Rigshospitalet, Denmark.
²University of Copenhagen, Faculty of Health Sciences, Denmark.
³Department of Paediatrics and Adolescent Medicine, Copenhagen University Hospital - Rigshospitalet, Denmark.

Background
Hypotensive neonates who have been treated with dopamine have poorer neurodevelopmental outcome than those who have not been treated with dopamine. We speculate that dopamine therapy might stimulate adrenergic receptors on cerebral arteries and thereby inhibit vasodilation and limit autoregulation at low levels of blood pressures. We tested our hypothesis in a piglet model.

Materials and Methods
Cerebral autoregulation (CA) capacity was estimated at different mean arterial blood pressure (MAP) levels in 18 piglets with and without dopamine infusion. Piglets were randomised to start with or without dopamine and to infusion rates of 10, 25 or 40µg/kg/min. Stable levels of hypotension were induced by gradually inflating a balloon catheter placed in vena cava. At each MAP level small fluctuations in MAP were induced by repeated inflating a balloon catheter in aorta for 30 sec. Cerebral perfusion was monitored by laser doppler flowmetry through a craniotomy. The ratio between the % change of estimated cerebrovascular resistance and the % change of MAP was used to estimate CA capacity. Non-linear regression analysis was used to describe the relation between CA capacity and MAP.

Results
Eighteen piglets aging 4-66 hrs were examined. During measurements P₀CO₂ (4-6kPa) and arterial saturation (>95%) were stable. MAP ranged between 14 and 82mmHg. Overall, CA capacity improved with increasing MAP until a breakpoint. After that breakpoint the CA capacity was stationary (figure 1). The breakpoint was 40.5mmHg (95% range 36.8-42.6) for the piglets when they did not receive dopamine. Below the breakpoint CA capacity increased with the rate of dopamine infusion (+0.7%/µg*kg⁻¹*min⁻¹, 95% CI 0.3-1.1, p<0.01).

Conclusion
Surprisingly, dopamine infusion improved rather than impaired the CA capacity in ‘hypovolemic’, hypotensive newborn piglets. We speculate that this unexpected finding might be caused by the fact that dopamine reduces the endogenous sympathetic response to comparable low levels of cardiac output. Compared to high endogenous sympathetic tone dopamine might be more ‘brain-protective’ as dopamine only has minor effect on cerebral arteries.
**Figure 1.** Relation between mean arterial blood pressure and cerebral autoregulatory capacity without dopamine and increasing infusion rates of dopamine. The horizontal line represents the plateau where cerebral autoregulation capacity does not change despite changes in mean arterial blood pressure. The sloped lines represent the relation between cerebral autoregulation and mean arterial blood pressure below the breakpoint at the different dopamine infusion rates.
DOPAMINE INFUSION IMPROVES CEREBRAL AUTOREGULATION IN NEWBORN PIGLETS

Vibeke R. Eriksen1,2, Martin B. Rasmussen1,2, Gitte H. Hahn1,3 and Gorm Greisen1
1Department of Neonatology, Rigshospitalet, Copenhagen, Denmark. 
2Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. 
3Department of Paediatrics and Adolescent Medicine, Rigshospitalet, Denmark.

CONCLUSION

Dopamine does not impair CA in newborn, hypotensive piglets.

In fact, we observed a dose response with improved CA capacity at higher infusion rates of dopamine.

DISCUSSION

Surprisingly, we found the opposite effect of what we hypothesised.

We speculate that at low MAP dopamine infusion improves perfusion of vital organs and hereby, reduce endogenous sympathetic tone.

Compared to high endogenous sympathetic tone dopamine might be more ‘brain protective’ as dopamine only has minor effect on cerebral arteries.

ACKNOWLEDGEMENTS

This study was financially supported by Lundbeck Foundation and University of Copenhagen.
Measuring blood pressure oscillations in the MRI

Daan LK de Jong, Gerrita J van Spijker, Astrid Hoedemaekers, Olga V Meulenbroek, Jurgen AHR Claassen

1 Department of Geriatric Medicine, Radboud Alzheimer Centre, Radboud University Nijmegen Medical Centre, Donders Institute for Brain, Cognition and Behavior, Nijmegen, The Netherlands; 2 Departments of Intensive Care, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Background

The tremendous increase in temporal resolution of measurements of blood flow has had a strong impact on cerebral autoregulation research [1, 2]. On the other hand, spatial resolution of these measurements has hardly increased over time. With the development of new MR sequences it is now possible to achieve a spatial resolution of several millimeters, with also a reasonable temporal resolution [3, 4]. Also MR-sequences like arterial spin labeling (ASL) are developing rapidly. Thus far, this has been at the expense of the temporal resolution to such an extent that only static CA can be assessed [5]. With the expectation of further increases in the temporal resolution of ASL, non-invasive BP-measurements in the MRI with high temporal resolution become necessary. Recently, a new MR-compatible NIBP device became available, the CareTaker. The objective of this study was to validate the CareTaker for measuring oscillations in blood pressure.

Methods

5 healthy subjects (aged 19-27) received an arterial line, serving as the gold standard for continuous blood pressure recordings. The CareTaker was fixated at the flexion of the elbow, where the pulsation of the brachial artery was sensible. The measurement started with a 5-minute baseline recording, aimed at comparing recordings of absolute BP measures as well as recordings of spontaneous fluctuations in blood pressure. This was followed by 5 minutes of paced breathing (0.1 Hz) in order to compare recordings of induced, stronger fluctuations in BP (low frequency oscillations). In both signals, systolic, mean and diastolic BP were calculated through automatic peak detection followed by visual inspection. To compare CareTaker recordings with the gold standard, we calculated correlation and coherence between these signals and performed a Bland-Altman analysis.

Results

The correlation coefficient ranged between -0.29 – 0.12. Coherence between measurements with both devices is highest between the MAP and in the LF-band during paced-breathing(0.44±0.14). The Bland-Altman-plot shows a higher variation during paced breathing.

<table>
<thead>
<tr>
<th></th>
<th>Coherence (VLF)</th>
<th>Coherence (LF)</th>
<th>Coherence (HF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>base</td>
<td></td>
<td>base</td>
<td></td>
</tr>
<tr>
<td>PB</td>
<td>0.12</td>
<td>0.21±0.09</td>
<td>0.25±0.17</td>
</tr>
<tr>
<td>SBP</td>
<td></td>
<td>0.35±0.09</td>
<td>0.40±0.14</td>
</tr>
<tr>
<td>MAP</td>
<td>-0.06</td>
<td>0.26±0.09</td>
<td>0.24±0.12</td>
</tr>
<tr>
<td>DBP</td>
<td>-0.03</td>
<td>0.23±0.11</td>
<td>0.22±0.06</td>
</tr>
</tbody>
</table>

Table 1: Correlation coefficient and the coherence in the VLF (0.02-0.07Hz), LF (0.07-0.15Hz) and HF (0.15-0.4Hz) frequency bands between the intra-arterial BP-measurements and the CareTaker measurements, for SBP, MAP & DBP during rest in supine position (base) and during paced breathing (PB) at 0.1 Hz.
Conclusion

Correlation between the CareTaker and invasive BP signals was low. Highest coherence was found in the LF band during paced breathing, in line with expectations, as in this band the oscillations were induced. However, even then, the coherence was low. Although the systematic bias is 0, Bland-Altman analysis revealed a clear bias which depends on the direction of changes in the gold standard. In conclusion, the CareTaker is not a valid method for measuring blood pressure oscillations in the autoregulatory frequency range.

References


Figure 1: Bland Altman plot of intra-arterial BP measures (gold standard) and the CareTaker during baseline (left) and paced breathing (right), in 5 subjects.
Measuring blood pressure oscillations in the MRI

Daan LK de Jong1, Gerrita J van Spijker1, Astrid WE Hoedemaekers2, Olga V Meulenbroek1, Jurgen AHR Claassen1

1 Department of Geriatric Medicine, Radboud Alzheimer Centre, Radboud University Nijmegen Medical Centre, Donders Institute for Brain, Cognition and Behavior, Nijmegen, The Netherlands; 2 Departments of Intensive Care, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Introduction

In current dCA measurements spatial information is lacking

MRI-techniques have much spatial information, but
- Temporal resolution still low
- Blood pressure (BP) oscillations measurements not possible

Newly developed MR-compatible NIBP available: CareTaker
- Sensitivity for BP-oscillations not known

Objective

To validate the CareTaker for measuring oscillations in blood pressure

Methods

5 healthy subjects with
- Arterial line
- CareTaker

Measurement protocol
- 5-minute baseline
- 5-minute paced breathing at 0.1Hz

Analysis
- Correlation
- Coherence in 0-0.5 Hz

Results

![Graph showing blood pressure oscillations](image)

**Figure 3:** Data segment with beat-to-beat interval (top) and resulting SBP values (bottom)

<table>
<thead>
<tr>
<th></th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLF-Coherence</td>
<td>base 0,18 ± 0,05</td>
<td>0,18 ± 0,10</td>
</tr>
<tr>
<td></td>
<td>PB</td>
<td>0,24 ± 0,17</td>
</tr>
<tr>
<td>LF-Coherence</td>
<td>base 0,13 ± 0,05</td>
<td>0,12 ± 0,05</td>
</tr>
<tr>
<td></td>
<td>PB</td>
<td>0,23 ± 0,09</td>
</tr>
<tr>
<td>HF-Coherence</td>
<td>base 0,17 ± 0,02</td>
<td>0,15 ± 0,03</td>
</tr>
<tr>
<td></td>
<td>PB</td>
<td>0,17 ± 0,03</td>
</tr>
</tbody>
</table>

**Table 1:** Coherence in VLF (.02-.07Hz), LF (.07-.15Hz) and HF (.15-.4Hz) frequency bands between arterial line BP data and CareTaker BP data

Discussion

Conclusion

So far, the CareTaker is not a valid method for measuring blood pressure oscillations in the autoregulatory frequency range.

Points of attention:
- Length of tubing?
- Sensitivity of noise in MRI

Contact: Daan de Jong
Email: Daan.deJong@radboudumc.nl

*This study was supported by the ADDF # 20121210*
Neurovascular Coupling and the BOLD signal
David, T., Joel, E.
Bluefern Supercomputing Unit,
University of Canterbury, NZ.

Background. The ability of neurons to communicate with the cerebral blood vessels to increase perfusion is termed as neurovascular coupling. Disordered neurovascular coupling has been observed in several brain pathologies like hypertension, stroke and Alzheimer's disease [3]. Estimates show that at least half of the energy consumed in the brain is due to the Na\textsuperscript{+}/K\textsuperscript{+} ATP-ase exchange pump with about 90% of ATP used being produced by oxidative glucose metabolism. The normal functioning of brain cells depends on a continuous supply of oxygen and glucose through cerebral blood flow, seen through fMRI BOLD signals. However hypoxic conditions can induce a reversal of the BOLD signal [4].

Methods.
An eight compartment mathematical model comprising soma, dendrite (CA1 pyramidal cell), extracellular space, astrocyte, perivascular space, smooth muscle cells, endothelial cell and lumen compartments was formulated based on existing models [1,2] which describe the neurovascular coupling mechanism. Each compartment is coupled with other compartments using ODEs, solved using MATLAB. This provides simulation of cerebral blood flow (CBF) and oxygen consumption of the Na\textsuperscript{+}/K\textsuperscript{+} exchange pump to give cerebral metabolic rate of oxygen (CMRO\textsubscript{2}) from which provides an fMRI BOLD signal.

Results. The magnitude of the BOLD signal depends on the ratio of the fractional change of CBF to the fractional change in CMRO\textsubscript{2}. A value of more than one for this ratio will result in less oxygen extraction fraction. The decrease in oxygen extraction fraction decreases the deoxyhemoglobin in the tissue voxel and hence giving a positive BOLD signal change. The figure shows a simulation of BOLD signals from the neurovascular coupling model compared with the experiments of [4] in the hypoxic hippocampus.

Discussion: The high relative increase of CBF to CMRO\textsubscript{2} decreases the oxygen extraction fraction, decreasing the deoxyhaemoglobin content in the tissue voxel resulting in a positive BOLD signal. High neural activity increases the CMRO\textsubscript{2} due to the ATP-ase pump and generates a negative BOLD response.

Conclusion. A mathematical model simulating neurovascular coupling and the fMRI BOLD signal is presented. The model includes action potential generation, restoration of ionic gradients and its associated K\textsuperscript{+} signaling mechanisms resulting perfusion variations. Future modeling will focus on integrating synaptic and glial activities and their associated mechanisms to the existing model and to determine its fMRI BOLD response.

Key references.
Neurovascular coupling and the BOLD signal

Motivation

The mechanisms with which the neurons communicate with the vasculature to increase the blood flow, termed neurovascular coupling is still unclear primarily due to the complex interactions between many parameters and difficulty in accessing, monitoring and measuring them in the highly heterogeneous brain. Hence a solid theoretical framework based on existing experimental knowledge is necessary to study the relationship between neural activity, the associated vasoactive factors released and their effects on vasculature. Such a framework should also be related to widely available experimental data such as fMRI BOLD so that it can be validated with repetitive experiments and generate verifiable hypothesis.

Key aspects of the model

- Electrically excitable Hodgkin-Huxley type neuron model which opens the voltage dependent ion channels and increases the potassium ion concentration in the extracellular space upon activation.
- Cerebral blood flow increase through K⁺ signalling mechanism of neurovascular coupling which involves astrocytic BK channel and KIR channel in the smooth muscle cell [1].
- Oxygen consumption by sodium/potassium exchange pump in the neuron which restores ionic homeostasis after activation.
- Deoxyhemoglobin content determined from cerebral blood flow, oxygen consumption and cerebral blood volume.
- BOLD response determined by deoxyhemoglobin content in the tissue voxel and cerebral blood volume.
- Simulated BOLD response for different physiological scenarios such as high neural activity, low neural activity and hypoxic condition.

Results & Discussion

- We compared the simulated negative BOLD signal to experimental BOLD signal (Fig 1) observed in the hippocampus during hypoxia by Kannurpatti et al [2] and it showed a reasonably good agreement.
- The magnitude of the BOLD signal depends on the ratio of the fractional change of CBF to CMRO₂.
- A value of more than unity for this ratio will result in decrease in oxygen extraction fraction, decreasing the deoxyhemoglobin content in the tissue voxel resulting in a positive BOLD signal change. Similarly, a value of less than one results in a negative BOLD signal change.

Conclusion

- Our model predicts the variations of BOLD response such as initial dip, positive BOLD, negative BOLD, and post stimulus undershoot occurring due to the neurovascular and neurometabolic responses.
- This approach of combined quantitative modeling of neurovascular, neurometabolic and their BOLD responses will enable more specific assessment of a brain region and possibly enhance our understanding of the mechanism.
- While examining the BOLD signal from a particular voxel in a certain region of the brain, all the parameters must be modified according to the experimental data from that region.
- Future modeling will also focus on integrating synaptic and glial activities and their associated mechanisms to the existing model and to determine its fMRI BOLD response.

Acknowledgements

We would like to thank members of Brains Trust Group for their continuous support. Also, we would like to thank Bluefern Supercomputing Unit and University of Canterbury for funding this project.

References

Prospective comparative clinical study of non-invasive cerebrovascular autoregulation monitor

Ragauskas A, Petkus V, Krakauskaite S, Chomskis R, Preiksaitis A.

Health Telematics Science Institute, Kaunas University of Technology, Lithuania.

Republic’s Vilnius University Hospital, Vilnius University, Clinics of Neurology and Neurosurgery, Lithuania.

Background. The results are presented of prospective comparative study of simultaneous fully non-invasive (without ABP(t) line) and invasive cerebrovascular autoregulation (CA) monitoring on severe TBI patients. The aim of the study was to validate the non-invasive CA monitoring technology [1,2,3] and to explore its suitability for identification of CA and optimal cerebral perfusion pressure (optCPP).

Methods. The non-invasive CA monitor is based on the ultrasonic transintracranial “time-of-flight” (TOF) measurement of intracranial blood volume (IBV) pulsations and waves within the brain parenchyma [2]. The monitor provides the possibilities of non-invasive CA estimation with or without using the external arterial blood pressure (ABP(t)) monitoring line. CA status is estimated by the slow IBV waves extracted from the non-invasively measured TOF(t) and by the reference ABP(t) signal or by the non-invasively identified reference signal which replaces ABP(t) signal. The phase difference between the IBV(t) slow waves and the reference slow waves is used as the CA estimation index vPRx. The special envelope signal extracted from the non-invasively measured IBV pulse waves is proposed as a reference signal which is used instead of ABP(t) reference signals to calculate the CA estimation index vPRx [3].

The clinical assessment of non-invasive CA monitoring technology was carried out in Republic’s Vilnius University Hospital (Lithuania). The CA status was monitored for 28 severe TBI patients (22 males, 6 females, aged 18-66) simultaneously invasively by using ICM+ software tool (Cambridge, UK) and non-invasively by Vittamed 505 (Vittamed, Lithuania) monitor.

Results. The comparative invasive versus non-invasive CA monitoring study of 28 TBI patients showed that the correlation between the invasively measured PRx(t) data and the non-invasively measured vPRx(t) data was r=0.74 (with ABP measurement line) and r=0.72 (without ABP line). The analysis of the reference signals extracted from the envelope of the non-invasively measured IBV(t) pulse waves showed the agreement with the ABP(t) reference slow wave signals (r=0.68).

Discussion. The results of the ongoing clinical study demonstrated significant agreement between the invasive and non-invasive CA monitoring technologies under comparison. The non-invasive CA monitoring technology with or without the external ABP line provides similar diagnostic information on CA status thus showing the possibility to implement CA measurements in the cases when the invasive CA monitoring or the ABP line are not available.

Conclusion. The proposed non-invasive CA real-time monitoring technology provides the same diagnostic information as the invasive PRx(t) monitoring technology. The estimation of the CA status from the non-invasively recorded intracranial volume waves only exclude the ABP line’s errors and artefacts from the CA monitoring results.

Key references.


Acknowledgement: This research has been funded by the grant MIP-118/2012 from the Research Council of Lithuania and the Swiss – Lithuanian project No.CH-3-SMM-01/06.
Prospective comparative clinical study of non-invasive cerebrovascular autoregulation monitor
Arminas Ragauskas¹, Vytautas Petkus¹, Solventa Krakauskaitė¹ Romanas Chomskis¹, Aidanas Preikšaitis², Saulius Ročka²

¹ Health Telematics Science Institute, Kaunas University of Technology, Lithuania
² Vilnius University faculty of Medicine, Clinics of Neurology and Neurosurgery, Centre of Neuroangiography, Vilnius, Lithuania

Contact information: Barausko St. 59 A553-A561, LT-51423, Kaunas, Lithuania, E-mail: telematics@ktu.lt

Background
Impairment of cerebrovascular autoregulation (CA) has a strong impact on the outcome of patients with traumatic brain injury (TBI). Optimal TBI patients’ treatment requires continuous monitoring of CA status over a long period of time in order to regularly re-evaluate individualized treatment strategy. Current clinical practice is to monitor CA using invasive ICP and invasive arterial blood pressure (ABP) monitoring lines and estimating of the pressure-reactivity index (PRx) as the correlation coefficient between ABP(t) and ICP(t) slow waves. Reference signal’s ABP(t) monitoring line has errors and artifacts. In order to eliminate such errors and artifacts a novel technology for real-time non invasive CA monitoring, which does not need ABP monitoring line, is presented. All necessary information about the CA status can be obtained by processing non-invasively measured intracranial volumetric slow, respiratory and pulse waves only [1-3] and by linear measurement of the phase difference between informative and reference signals.

Materials and methods
The non-invasive CA monitor is based on the ultrasonic measurement of intracranial blood volume (IBV) pulsations and waves within the brain parenchyma [3]. The monitor provides the possibilities of non-invasive CA estimation with or without using the ABP(t) monitoring line. CA status is estimated by the slow waves extracted from the non-invasively measured IBV(t) and by the reference ABP(t) signal or by the non-invasively identified reference signal which replaces ABP(t) signal. The phase difference between the IBV(t) slow waves and the reference slow waves is used as fully non-invasive CA estimation index vPRx. The special envelope signal extracted from the non-invasively measured IBV(t) pulse waves is used instead of ABP(t) reference signals in order to calculate the CA estimation index vPRx [3].

Results
The clinical assessment of non-invasive CA monitoring technology was carried out in Republic’s Vilnius University Hospital (Lithuania). The CA status was monitored for 28 severe TBI patients (22 males, 6 females, aged 18-66) simultaneously invasively by using ICM+ software tool (Cambridge, UK) and non-invasively by Vittamed 505 (Vittamed Corp. Boston, USA) monitor. The comparative invasive versus non-invasive CA monitoring study of 28 TBI patients showed that the correlation between the invasively measured PRx(t) data and the non-invasively measured vPRx(t) data was r=0.74 (with ABP measurement line) and r=0.72 (without ABP line). The analysis of the reference signals extracted from the envelope of the non-invasively measured IBV(t) pulse waves showed the agreement with the ABP(t) reference slow wave signals (r=0.68).

Conclusion
Proposed non-invasive CA real-time monitoring technology (without the ABP line) reliably estimates CA status from the IBV(t) waves only as well as excludes the ABP line’s artifacts and errors from the measurement results.

Acknowledgments: This research has been funded by a grant MIP-118/2012 from the Research Council of Lithuania and the Swiss – Lithuanian project No.CH-3-SMM-01/06.

Fig. 1. Vittamed 505 non-invasive CA monitor and mechanical frame mounted on the volunteer’s head.

Fig. 2. Examples a) and b) of one-hour CA monitoring sessions on TBI patients by using invasive and non-invasive CA monitors. The correlation coefficients between the invasive PRx index and the non-invasive vPRx (without ABP line) are: a) r=0.80, b) r=0.78. Linear regression of CA monitoring comparative study of 28 patients within 35 hours shown on Fig 2, c). Overall correlation factor between PRx and non-invasively measured CA index (vPRx) is r=0.72.

References:
A NEW INDEX FOR DYNAMIC CEREBRAL AUTOREGULATION APPLIED TO THE SIT-TO-STAND MANEUVER
1Chacón M, 1Sun Ho-No, 1Jara JL
1Departamento de Ingeniería Informática, Universidad de Santiago de Chile, Chile.

Background. Dynamic Cerebral Autoregulation (dCA) has been frequently assessed for changes in arterial blood pressure (ABP) produced by the thigh-cuff maneuver, which is then used to estimate the dynamic autoregulation index (ARI) [2, 4]. A recently proposed alternative index, named model-free ARI (mfARI) [1], was evaluated with this maneuver finding similar but more robust values. Nonetheless, other types of maneuvers can induce changes in ABP that are more natural and less uncomfortable for patients, such as the sit-to-stand technique [3, 5]. In this study, mfARI was evaluated and compared to ARI for the sit-to-stand maneuver.

Methods. 19 subjects without any history of neurological or cardiovascular disease, aged between 21 and 41 years (27.6±5.4), were recruited and subjected to three repetitions of the sit-to-stand maneuver as in [3,5]. ABP was measured in the middle finger with a Finapres Ohmeda 23400, and cerebral blood flow velocity (CBFV) in the middle cerebral artery with a Doppler Box DWL. Both signals were filtered and averaged to a final frequency of 1.66 Hz. Only the stand section of the maneuver was utilized in the analysis, as this segment exhibits a drop in ABP as in the thigh-cuff maneuver. Statistical tests were considered significant for p<0.05.

Results. Individual mean ARI and mfARI values, in the same scale 0.0-9.0, were obtained from the stand segments recorded for each of the 19 subjects (57 maneuvers). Shapiro-Wilk normality tests did not find evidence against normality for both individual mean ARI (p=0.915) and individual mean mfARI (p=0.397). Table 1 presents mean±SD values and the coefficients of variation (CoV) calculated for each index.

<table>
<thead>
<tr>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Student t-test)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ARI</th>
<th>mfARI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>4.1 ± 1.5</td>
<td>5.7 ± 1.1</td>
</tr>
<tr>
<td>CoV</td>
<td>35.11%</td>
<td>19.35%</td>
</tr>
</tbody>
</table>

Discussion and Conclusion. The overall mean mfARI resulted significantly higher (1.6 points) than the overall mean ARI, and it also exhibited a significantly lower variability (45% reduction). Both findings seem more suitable in the case of a group composed of healthy subjects only. These initial results encourage performing a deeper analysis of the applicability and reproducibility of the new mfARI index in combination with the stand maneuver and its comparison with other dCA assessment techniques.

Key references.
5 van Beek AH, Olderekkert MG, Pasman JW, Hopman MT, Claassen JA (2010). Dynamic Cerebral Autoregulation in the Old Using a Repeated Sit-to-Stand maneuver, Ultrasound Med Biol 36(2).
BACKGROUND

Dynamic Cerebral Autoregulation (dCA) has been frequently assessed for changes in arterial blood pressure (ABP) produced by the thigh-cuff maneuver, which is then used to estimate the dynamic autoregulation index (ARI). A recently proposed alternative index, named model-free ARI (mfARI), was evaluated with this maneuver finding similar but more robust values. Nonetheless, other types of maneuvers can induce changes in ABP that are more natural and less uncomfortable for patients, such as the sit-to-stand technique. In this study, mfARI was evaluated and compared to ARI for the sit-to-stand maneuver.

METHODS

mfARI uses three parameters (Fig 1). Two of them from the CBFV signal: the transient response duration (\(\Delta t\)) and the steady-state response constant (Ks). The other one is the angle between ABP and CBFV (\(\phi\)). 19 subjects without any history of neurological or cardiovascular disease, aged between 21 and 41 years (27.6±5.4), were recruited and subjected to three repetitions of the sit-to-stand maneuver. ABP was measured in the middle finger with a Finapres Ohmeda 23400, and cerebral blood flow velocity (CBFV) in the middle cerebral artery with a Doppler Box DWL. Both signals were filtered and averaged to a final frequency of 1.66 Hz. Only the stand section of the maneuver was utilized in the analysis, as this segment exhibits a drop in ABP as in the thigh-cuff maneuver. Statistical tests were considered significant for \(p<0.05\).

mfARI = 1.59 + 3.8Ks - 0.13\(\Delta t\) + 0.11\(\phi\)

Equation 1: \(mfARI\) is estimated with this linear regression model between ARI values and the three parameters gauged from Aaslid-Tiecks’ theoretical templates

RESULTS

Individual mean ARI and mfARI values, in the same scale 0.0-9.0, were obtained from the stand segments recorded for each of the 19 subjects (57 maneuvers). Shapiro-Wilk normality tests did not find evidence against normality for both individual mean ARI \((p=0.915)\) and individual mean mfARI \((p=0.397)\). Table 1 presents mean±SD values and the coefficients of variation (CoV) calculated for each index.

<table>
<thead>
<tr>
<th>ARI</th>
<th>mfARI</th>
<th>P-value (t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>4.1 ± 1.5</td>
<td>5.7 ± 1.1</td>
</tr>
<tr>
<td>CoV</td>
<td>35.11%</td>
<td>19.35%</td>
</tr>
</tbody>
</table>

Table 1 Result classic ARI and mfARI

DISCUSSION and CONCLUSION

The overall mean \(mfARI\) resulted significantly higher (1.6 points) than the overall mean ARI, and it also exhibited a significantly lower variability (45% reduction). Both findings seem more suitable in the case of a group composed of healthy subjects only. These initial results encourage performing a deeper analysis of the applicability and reproducibility of the new \(mfARI\) index in combination with the stand maneuver and its comparison with other dCA assessment techniques.

Fig 1: \(mfARI\) parameters. ABP dotted line. CBFV continuous line
Background. Dynamic CA can change in response to respiratory manoeuvres (breath-holding, hyperventilation, Valsalva), posture and exercise, but the meaning of fluctuations in CA indices at rest, during baseline recordings, is not established (2, 5, 6, 7).

Methods. The reliability of three different techniques to estimate time-varying CA was studied in 58 healthy controls (age range 41–83 years), based on 115 five-minute supine recordings of bilateral MCA velocity, arterial BP (Finometer), ECG and end-tidal CO$_2$ at rest. Time-varying estimates of Tieck’s ARI index were obtained from ARMA modelling using a 60s moving window (ARI$^{t_{MW}}$) (2), or orthogonal decomposition (ARI$^{t_{OD}}$) (6). A new index, based on the normalised variability of resistance area product (RAP$^t$) was also tested. Initial validation of these indices was performed using the recorded BP signal to generate surrogated MCAV signals for each value of ARI from zero (impaired CA) to nine (best CA) for signal-to-noise ratios (SNR) of 20 and 5 dB. Cross-correlation (CC) analysis was performed to compare temporal patterns of ARI$^{t_{MW}}$, ARI$^{t_{OD}}$ and RAP$^t$ between hemispheres and inter-methods.

Results. With surrogate data, ARI$^{t_{MW}}$ performed better than the other methods with smaller coefficient of variation and less sensitivity to noise, compared to the ARI reference values. RAP$^t$ showed a sigmoidal relationship to the simulated ARI values and unacceptable bias when SNR was reduced to 5 dB. With real data, all three methods performed well in inter-hemisphere comparisons, with mean (SD) peak CC values of 0.63 (0.21), 0.56 (0.20) and 0.62 (0.21) for ARI$^{t_{MW}}$, ARI$^{t_{OD}}$ and RAP$^t$, respectively. The proportion of recordings with peak CC values above the 95% confidence limit was also high for all methods, ranging from 93.9 to 95.6%. The number of recordings with significant peak CC values for the right MCA was reduced for inter-method comparisons, when the ARI based methods were compared to RAP$^t$ (ARI$^{t_{MW}}$ 52.1%; ARI$^{t_{OD}}$ 60.0%), but remained elevated for the CC between ARI$^{t_{MW}}$ and ARI$^{t_{OD}}$ (84.3%). Similar values were obtained for the left MCA.

Discussion. Fluctuations in dynamic CA at rest could be caused by corresponding changes in neural activation or other physiological variables like PaCO$_2$, or be a consequence of noise or limitations in the bias and scatter of analytical methods. Inter-hemisphere agreement and analysis of surrogate data suggest the methods we studied are sensitive to CA changes and possibly reflect physiological influences. Nevertheless, RAP$^t$ is unlikely to be useful due to its high sensitivity to noise.

Conclusion. Further comparisons with alternative methods based on phase (4), multimodal pressure-flow (1), or neural networks (3) should be undertaken, jointly with improvements to identify or control neural activation at rest (7).

References

Can critical closing pressure replace EtCO2 as a determinant of CBFV in multivariate models?

Background. Dynamic cerebral autoregulation (dCA) under normocapnic conditions has been studied considering systemic arterial blood pressure (ABP) as the main input to predict cerebral blood flow velocity (CBFV). One of the best results has been obtained by using non-linear models with support vector machines (SVM) [1-2], in which end-tidal CO₂ (EtCO₂) was also included as input. The purpose of the present study was to assess the impact of replacing EtCO₂ by the critical closing pressure (CrCP) to these models in both their learning process and their ability to predict CBFV.

Methods. Sixteen healthy subjects aged 31.8 ± 8.5 years were studied. None of them had a history of any cardiovascular or neurological disease. The study was approved by the Leicester Research Ethics Committee. CBFV was recorded with a transcranial Doppler (Scimed QVL-120) using a 2MHz transducer. ABP was measured with a Finapress 2300 Ohmeda. CrCP was obtained by linear regression [3]. Recordings lasted 5 minutes, with 2.5 minutes of signal used to train the models and the other 2.5 minutes to test them using cross validation. Two subjects were rejected due to outliers in the CrCP signal. Four kinds of SVM models were trained with linear and non-linear kernels, and with and without CrCP.

Results. The mean values for the correlations of linear and non-linear models, with and without CrCP, are shown in table 1. Results showed a better accuracy for models with CrCP, linear and non-linear. Correlations showed deviation from normality, thus the Wilcoxon signed-rank test was used to compare them. No significant differences were found between linear multivariate and non-linear univariate models (p=0.510). There are differences between linear univariate and multivariate models (p=0.013), and between non-linear univariate and multivariate models (p=0.03)

Discussion and Conclusion
Statistical tests indicates that new information could be captured by adding the CrCP variable. For further studies, multivariate models trained under hypercapnia conditions with CrCP as input, instead of EtCO₂, might provide the possibility of detecting cerebrovascular diseases by capturing the relationship between the levels of CrCP and CO₂ in metabolic processes [4-5] or be used under conditions where CO₂ cannot be measured.

Key references.

CAN CRITICAL CLOSING PRESSURE REPLACE ETCO2 AS A DETERMINANT OF CBFV IN MULTIVARIATE MODELS?

PURPOSE
Dynamic cerebral autoregulation (dCA) under normocapnic conditions has been studied considering systemic arterial blood pressure (ABP) as the main input to predict cerebral blood flow velocity (CBFV). One of the best results has been obtained by using non-linear models with support vector machines (SVM), in which end-tidal CO2 (EtCO2) was also included as input. The purpose of the present study was to assess the impact of replacing EtCO2 by the critical closing pressure (CrCP) to these models in both their learning process and their ability to predict CBFV.

METHODS
Sixteen healthy subjects aged 31.8 ± 8.5 years were studied. None of them had a history of any cardiovascular or neurological disease. The study was approved by the Leicester Research Ethics Committee. CBFV was recorded with a transcranial Doppler (Scimed QVL-120) using a 2MHz transducer. ABP was measured with a Finapress 2300 Ohmeda. CrCP was obtained by linear regression. Recordings lasted 5 minutes, with 2.5 minutes of signal used to train the models and the other 2.5 minutes to test them using cross validation. Two subjects were rejected due to outliers in the CrCP signal. Four kinds of SVM models were trained with linear and non-linear kernels, and with and without CrCP, as shown in figures 1 and 2.

RESULTS
The mean values for the correlations of linear and non-linear models, with and without CrCP, are shown in table 1. Results showed a better accuracy for models with CrCP, linear and non-linear. Correlations showed deviation from normality, thus the Wilcoxon signed-rank test was used to compare them. No significant differences were found between linear multivariate and non-linear univariate models (p=0.510). There are differences between linear univariate and multivariate models (p=0.013), and between non-linear univariate and multivariate models (p=0.03).

DISCUSSION AND CONCLUSION
Statistical tests indicates that new information could be captured by adding the CrCP variable. For further studies, multivariate models trained under hypercapnia conditions with CrCP as input, instead of EtCO2, might provide the possibility of detecting cerebrovascular diseases by capturing the relationship between the levels of CrCP and CO2 in metabolic processes or be used under conditions where CO2 cannot be measured.
TITLE OF STUDY
Controlling for heart rate variability improves the estimation of cerebral autoregulation and vasomotor reactivity in older adults and MCI patients.
Submitted to Fifth International Meeting on Cerebral Haemodynamic Regulation, Southampton, UK

1Marmarelis V, 1Shin D, 2Orme M, 3Tarumi, 3Zhang R
1Department of Biomedical Engineering, University of Southern California, US
2Sonovation Inc., Los Angeles, California, US
3UT Southwestern Medical Center, Dallas, Texas, US
email: vzm@usc.edu, tel: 001-310-80-8200

Aims. This study explored the inclusion of heart rate variability (HRV) in our cerebral hemodynamic model that accounts for the combined dynamic effects of changes in arterial blood pressure (ABP) and end-tidal CO2 (ETCO2) upon cerebral blood flow velocity (CBFV) measured at the middle cerebral artery via transcranial Doppler (TCD). The effect of including HRV as a third input in the model was examined in control subjects and patients with mild cognitive impairment (MCI) in terms of the resulting p-values of model-based delineation of the two groups. Previous studies of the two-input model have shown statistically significant reduction of dynamic cerebral vasomotor reactivity (DCVR) in MCI and Alzheimer’s patients relative to age/education-matched controls [1-3].

Methods. Beat-to-beat TCD measurements of CBFV at the middle cerebral artery, ABP, ETCO2 and HRV time-series data were collected in 46 amnestic MCI patients based on the modified Peterson criteria (17 male and 29 female) and 18 control subjects (9 male and 9 female) similar in age and education. The time-series data were analysed using the method of Principal Dynamic Modes (PDMs) [3-4] to obtain predictive models of the dynamic effects of changes in the three “inputs” of ABP, ETCO2 and HRV upon the “output” CBFV. The obtained models were subsequently used to compute subject-specific indices of dynamic cerebral autoregulation (DCA) and DCVR, following the procedure described in [2-4]. These indices were compared with their counterparts for the two-input model.

Results. The obtained DCA and DCVR indices yielded smaller p-values in delineating the MCI patients from control subjects using a three-input, instead of a two-input, model (p=0.02 vs. p=0.08 for DCA, and p=0.001 vs. p=0.002 for DCVR). Both indices were statistically smaller for the MCI patients relative to controls. This finding is illustrated in Figure 1 via the respective scatter-plots for DCA and DCVR indices for the two types of models.

Figure 1. Scatter-plots of model-based indices of DCA (abscissa) and DCVR (ordinate) for 18 controls (blue) and 46 MCI patients (red), using models with two inputs (left) vs. three inputs (right). It is evident that the cluster of MCI patients is more concentrated for the three-input model, attesting to the ability of HRV to improve delineation of the two groups when included in the model.
Conclusion. Model-based indices of dynamic cerebral autoregulation (DCA) and vasomotor reactivity (DCVR) are statistically smaller for MCI patients and can delineate the latter from age/education-matched controls more reliably when heart rate variability (HRV) is included as a third input in the model.

Key references.


Absence of spontaneous blood pressure variability in patients after out-of-hospital cardiac arrest during the post-cardiac arrest syndrome.

van den Brule JMD, van der Hoeven JG, Vinke EJ, van Loon LM, Hoedemaekers CWE
Department of Intensive Care Medicine, Radboud University Nijmegen Medical Centre, the Netherlands.

Background: Out-of-hospital cardiac arrest (OHCA) is the leading cause of death in industrialized countries. Although in the past decades more patients have return of spontaneous circulation (ROSC), overall prognosis has not substantially improved and only a minority of patients survive with a favourable neurological recovery. The poor prognosis of patients after ROSC is related to the development of the so-called post-cardiac arrest syndrome (PCAS). The amount of brain damage after cardiac arrest strongly depends on the recovery of the cerebral circulation, but ROSC does not automatically restore normal cerebral circulation. Pressure autoregulation is an important determinant of cerebral blood flow velocity (CBFV). However, the state of autoregulation in patients after cardiac arrest is not well known. The aim of this study was to investigate pressure autoregulation in comatose patients successfully resuscitated from OHCA.

Methods: We performed a prospective observational study in 11 patients after OHCA. All patients were intubated and mechanically ventilated to obtain a PaO$_2$ > 75 and a PaCO$_2$ 34-41 mmHg. Mean arterial pressure was maintained between 80-100 mmHg. At specific time points after admission at the ICU the intra-arterial blood pressure and CBFV of the middle cerebral artery were measured. In the time domain, the coefficient of variation (CV), defined as SD of the (signal/mean of the signal)*100%, of the blood pressure and CBFV was calculated. In the frequency domain, the variation was calculated using the power over different frequency bands. The frequency bands were defined as very low frequency (0.02-0.07Hz), low frequency (0.07-0.15Hz) and high frequency (0.15-0.40Hz). Patients admitted to the ICU for pre-operative optimization served as normal controls. We present the preliminary data.

Results: We included 9 male and 2 female patients with a mean age of 58.1 years. The majority of the patients had a cardiac cause of the arrest. Median CV of the mean blood pressure immediately after the arrest was significantly lower in patients compared to normal controls (1.80 (1.17-2.18) mmHg vs 3.55 (2.50-3.91) mmHg, p=0.003). The CV of the CBFV was comparable between patients 6.74 (5.30-8.05) cm/sec and controls 4.90 (4.31-6.27) cm/sec, p=0.178. The loss of variation gradually restored towards normal values during the 72hrs observation period. No significant differences in the VLF, LF and HF power of the blood pressure and CBFV signals were measured between patients and controls at any point in time.

Conclusion: The spontaneous blood pressure variability is significantly reduced in patients immediately after OHCA, whereas variability in CBFV remained in the normal range. This lack in blood pressure variability was restored during admission and may be related to a (temporary) autonomic dysfunction in these patients. Lack of variability in the blood pressure signal prohibited reliable determination of the autoregulation using transfer function analysis.
The relationship between BP variability, White Matter Lesions and frailty in Alzheimer’s Disease patients

Gerrita J. van Spijker1, Olga V. Meulenbroek1, Maarten J.T. van Els1, Daan. L.K. de Jong1, Marcel G.M. Olde Rikkert1; Jurgen A.H.R. Claassen1

1 Department of Geriatric Medicine; Donders Institute for Brain, Cognition, and Behavior; Radboud Alzheimer Center; Radboud university medical center, Nijmegen, The Netherlands

Background. Findings from autopsy (1), as well as results from epidemiological and clinical studies (7) suggest a relationship between (cerebro)vascular disease and Alzheimer’s disease (AD). The causal cascade between these (cerebro)vascular risk factors and AD remains unknown. Research by Rothwell (5) indicates that blood pressure variability (BPV) may be more harmful than hypertension, whereas variability in systolic BP (SBP) demonstrated to be a predictor of cerebral ischemic events (6). Hypothetically, increased BPV may lead to episodes of lowered cerebral blood flow in AD patients (4), resulting in ischemia and consequently in white matter lesions (WMLs). Accumulation of WMLs over time can in turn disturb regulating systems. For instance, WMLs may disrupt central control mechanisms of blood pressure (e.g. baroreflex) resulting in higher BPV. Further, WMLs are associated with gait impairment (2) which is a very useful single indicator of frailty (3). At the same time, frail elderly may have a less active lifestyle; a risk factor for WMLs and BPV. Here, we study the relationship between these three variables: BPV, WMLs and frailty.

Methods. Baseline data of 47 mild to moderate AD patients (MMSE 12 and ≤ 26; aged 74.1±5.9 years; 62% female) in the NILVAD CBF add on study (www.nilvad.eu) will be analyzed. This includes BPV, frailty and WMLs (MRI). BPV will be calculated by means of a variation coefficient based on 7-day home-based blood pressure measurements of one week adjacent to the MRI visit. The frailty index is calculated from a composite score of 65 items based on several assessments Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-cog), Disability Assessment for dementia (DAD), Charlson Comorbidity Index (CCI), Lubbben Social Network Scale (LSNS), Gait Speed. WML volumes are estimated by averaging the manual annotations in FLAIR images by two raters. Relationship between the three variable pairs will be tested statistically with Spearman’s correlation coefficient, and relationship between all three variables with partial correlation.

Results. Currently, data is being processed. Results planned to be presented at the conference in July.

Discussion. We hypothesize that a larger volume of WML is associated with a higher BPV. We will explore whether frailty modifies this association..

Key references.
5. Rothwell PM(2010). Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. Lancet. 375: 938-948
Dynamic Cerebral Autoregulation in Patients with Hypertension

Nogueira RC1, Machado M1, Bor-Seng-Shu E2, Muela HSC3, Bortolotto LA3, Teixeira MJ2, Panerai RB4,5

1Department of Neurology, Hospital das Clinicas, University of São Paulo School of Medicine, São Paulo, Brazil
2Department of Neurosurgery, Hospital das Clinicas, University of São Paulo School of Medicine, São Paulo, Brazil
3Heart Institute, University of São Paulo School of Medicine, São Paulo, Brazil
4Department of Cardiovascular Sciences, University of Leicester, Robert Kilpatrick Clinical Sciences Building, PO Box 65, Leicester, England, LE2 7LX
5Biomedical Research Unit in Cardiovascular Science, Glenfield Hospital, Leicester, LE3 9QP.

Background. The cerebral blood flow control in hypertensive subjects is poorly understood. Previous work suggests that dynamic cerebral autoregulation is intact in controlled and uncontrolled hypertension subjects. This is a preliminary report of the first observational study with blinded analysis of dynamic cerebral autoregulation in hypertensive subjects and a healthy population.

Methods. The ongoing study is recruiting patients with diagnosis of hypertension at different stages of severity and a healthy population matched by age. Blood flow velocity of each MCA was collected using Transcranial Doppler and non-invasive ABP measured using an arterial volume-clamping device. Dynamic CA was assessed by transfer function analysis and the data was converted back to the time domain, estimating the autoregulation index (ARI). Two groups were created (group X and Y) and a researcher blinded for which group is health or with hypertension, made the analysis of dCA. For statistical analysis t-test was used to compare variables from two groups.

Results. The study recruited so far 65 subjects (40 group X and 25 group Y); as this is a preliminary analysis, the groups could not be revealed. The median age of group X was 51 years (range 33 – 71) and of group Y was 44 years (range 31 – 70) (p=0.03). Analysis of ARI revealed no significant difference from both groups (ARI group x = 5.86±1.7; ARI group y= 5.98±1.2; p=0.72).

Conclusion. Our results is in agreement with previous publication that dCA remains intact in patients with hypertension. Further analysis is needed with large population matched for age and sex for more robust conclusions.
Cerebral Hemodynamics in thrombolysis for Acute Ischemic Stroke: a systematic review and meta-analysis

Nogueira RC¹, Bor-Seng-Shu E², Saeed NP³, Teixeira MJ², Panerai RB³⁴, Robinson TG³⁴.

¹Department of Neurology, Hospital das Clinicas, University of São Paulo School of Medicine, São Paulo, Brazil
²Department of Neurosurgery, Hospital das Clinicas, University of São Paulo School of Medicine, São Paulo, Brazil
³ Department of Cardiovascular Sciences, University of Leicester, Robert Kilpatrick Clinical Sciences Building, PO Box 65, Leicester, England, LE2 7LX
⁴Biomedical Research Unit in Cardiovascular Science, Glenfield Hospital, Leicester, LE3 9QP.

Background. The present review investigated the role of cerebral hemodynamic imaging techniques in predicting clinical outcome and risk of symptomatic intracerebral haemorrhage (sICH) in patients who underwent intravenous thrombolytic treatment

Methods. Publications were searched and inclusion criteria were as follows: 1) published manuscripts, 2) patients with acute ischemic stroke managed with intravenous rtPA, and 3) availability of cerebral hemodynamic assessment prior to, during and/or after thrombolytic treatment to determine vessel patency, presence of collaterals or regulation of cerebral blood flow. Clinical outcomes were divided into neurological outcome (NIHSS within 7 days) and functional outcome (modified Rankin score in 2 – 3 months). sICH was defined as rtPA-related intracerebral bleeding associated with any worsening of NIHSS

Results. Recanalization was significantly associated with improved neurological and functional outcome (OR=7.83; 95% CI, 3.71 – 16.53 and OR=10.13; 95% CI, 5.31 – 19.33; p<0.001 respectively). Both tandem internal carotid artery/middle cerebral artery (ICA/MCA) occlusions and isolated ICA occlusion had worse functional outcome than isolated MCA occlusion (OR=0.26, 95% CI, 0.12 – 0.52; p<0.001 and OR=0.24, 95% CI, 0.07 – 0.77; p=0.016, respectively). Recurrence was associated with neurological deterioration (OR=6.48, 95% CI, 3.64 – 11.56; p<0.001) and early recanalization was associated with lower odds of sICH (OR=0.36, 95% CI, 0.18 – 0.70; p=0.003). No study of dynamic cerebral regulation were made before or during thrombolysis.

Conclusion. Brain hemodynamic data before, during and after thrombolysis may be useful for predicting clinical outcome. Cerebral arterial recanalization, presence and site of occlusion, and rec-occlusion are all important in predicting clinical outcome. The study of cerebral autoregulation during thrombolysis can help on clinical management and predicting outcome.
Background. It is generally accepted that cerebral autoregulation (CA) may become impaired after stroke (1,4). The worsening of autoregulation during both the acute vessel occlusion and reperfusion may render the penumbral areas particularly vulnerable in blood supply. Potential changes in autoregulatory capacity should be considered during interventions in the stroke unit such as mobilization and blood pressure (BP) manipulation. Impaired CA in stroke is related to acute neurological deterioration, necessity of decompressive surgery, and poor outcome (Aires et al. 2010). However, only few studies directly assessed the relationship either between stroke severity and CA, or stroke outcome and CA (2,4,5). The aim of this study was to assess the influence of the admission National Institute Health Stroke Scale (NIHSS) on CA in acute phase of stroke.

Methods. Stroke patients were assessed <48 h of stroke onset. The NIHSS scores on the admission and at the CA assessment were registered. The patients were divided in two groups depending on their admission NIHSS scores (G1 = NIHSS≥6 and G2 = NIHSS<6). Continuous recordings of bilateral cerebral blood flow velocity (CBFv) using TCD, BP using Finapres®, heart rate (3-lead ECG) and end-tidal CO2 (EtCO2, Capnograph) were obtained during 5 minutes baseline. A fast Fourier transform (FFT) was applied to the data, and the cross- and auto-spectra were estimated using the Welch method. The transfer function of the BP-CBFv dynamic relationship was calculated with FFT transform then applied to the complex transfer function, converting data back into the time domain, to calculate the CBFv step response (Katsogridakis et al. 2013). The autoregulatory index (ARI) was assigned to each recording by using the best least-squares fit between the CBFv step response and one of the 10 model ARI curves proposed by Tiecks et al. (6). ARI was calculated for each subject for both hemispheres at baseline.

Results. A total of 27 patients were included in this study. G1 comprised 13 participants with a mean age of 62.2y (10.0), NIHSS scores on the admission and at the CA monitoring were 10.5 (2.9) and 5.4 (1.7), respectively. Whereas 14 participants were included in G2 with mean age of 62.9y (10.9), NIHSS scores on the admission and at the CA monitoring were 3.2 (1.9) and 1.9 (1.1), respectively. The time between the stroke onset and the CA monitoring was 29.7h (14.1) and 30.3h (10.5), for G1 and G2, respectively. Patients with a higher admission NIHSS score (G1) presented lower ARI scores in the affected hemisphere (4.61 (2.6)) when compared to G2 (6.12 (1.7)). Higher ARI scores were found in the unaffected hemispheres of G1 (5.59 (1.7)) when compared to G2 (5.10 (2.2)). However, student’s t-test showed no statistically significant differences between groups.

Conclusion. This study revealed a trend towards an impairment of CA acutely in the affected hemisphere of patients with higher admission NIHSS. It may be of some importance to determine CA prognosis significance, as well as, to guide rehabilitation interventions that may have impact on peripheral haemodynamic variables. More work is required to increase the statistical power shedding light on the influence of CA impairment on clinical outcome and stroke location.

Exhibitors
ARTINIS MEDICAL SYSTEMS BV

Artinis Medical Systems is a small and innovative Dutch company. Artinis makes tissue oxygenation measurements with near infrared spectroscopy (NIRS) easy and affordable with fit to purpose solutions, R&D support, comprehensive training and effective after-sales support. We can do so based upon our extensive knowledge of the field and the close co-operation with expert groups in scientific institutions.

Artinis produces flexible, versatile and easily upgradeable laboratory equipment like the Oxymon MkIII. Measurements can be taken from 1 of up to 96 channels in various templates and MRI compatible with high temporal resolution.

Artinis also produces wireless NIRS equipment like the PortaMon the PortaLite, a device typically used on the human muscle and brain tissue respectively. These devices have the size of a cell phone, are very easy to use and can be used inside and outside with a range up to a 100 meters for online measurements using bluetooth. The devices are also equipped with an internal memory for offline measurements. Come and visit our booth for a demonstration!

A Einsteinweg 17
6662 PW Elst
The Netherlands
T +31 481 350 980
F +31 842 105 702
I www.artinis.com

LINTON INSTRUMENTATION

Steven Clifford
Sales & Support
Linton Instrumentation
Tel +44 (0) 1379 651344
Fax +44 (0) 1379 650970
Email: steve@lintoninst.co.uk
Visit our new website: www.lintoninst.co.uk
MOOR INSTRUMENTS LTD

Moor Instruments have specially developed systems to measure cerebral blood flow (CBF) and tissue oxygenation for applications which include:

- MCAO “Stroke” model
- Cerebral Ischemia / Reperfusion
- Cortical spreading depression
- Migraine
- Pain research

We would be very pleased to see you at our Stand in the exhibition hall

Moor Instruments specialise in equipment for the assessment of blood-flow and oxygenation for clinical and pre-clinical research.

Systems Include;

- Laser Doppler blood-flow imaging.
- Laser speckle contrast (LASCA) blood-flow imaging.
- Laser Doppler monitoring.
- Spectroscopic oxygenation measurement.
- TCPO2 transcutaneous oxygen measurement.
- Tissue oxygenation monitoring that uses near infrared spectroscopy (NIRS)

Please get in contact to learn more about the solutions we offer.

www.moor.co.uk / sales@moor.co.uk

RIMED LTD

Dotan Windman
Regional Sales & Marketing manager
Tel: +972-9-7484425 | Fax: +972-9-7484417
Mobile: +972-54-5498986 | Skype: Rimed-Marketing2
dotan@rimed.com | www.rimed.com
SMT MEDICAL TECHNOLOGY

Competence in medical technology, innovative products and an unparalleled service characterize SMT medical, a German based but internationally operating corporation. Besides diagnostic applications in the evaluation of metabolic syndrome, the company specializes in vascular testing, in particular cardio-vascular and neuro-vascular testing. The SMT medical team has extensive know-how in extra- and transcranial Doppler ultrasound testing modalities including cerebro-vascular monitoring and embolic signature detection. During recent years digital TCD technology has made significant advancement in offering cerebral blood flow information for the neuro-vascular lab, critical care and peri-operative environment. Current user interfaces are designed to simplify instrument operation, even in difficult clinical or research conditions.

At the 5th International Meeting on Cerebral Haemodynamic Regulation (CARNet) SMT medical exhibits the ‘Delica’ product line representing state-of-the-art transcranial Doppler technology featuring robotic monitoring probes and the EDS emboli detection based on artificial intelligence.

We will be pleased to serve you at our booth in the exhibition hall.
You are also invited to visit our website at www.smt-medical.com

SMT medical GmbH&Co.
Im Kreuz 9
97076 Wuerzburg
Germany
Tel. +49 931 3 29 33-0
Fax + 49 931 3 29 33-29
info@smt-medical.com
www.smt-medical.com
Delegate List

The following list includes all delegates attending this conference except for those who have requested that their details are not included.
### DELEGATE LIST

This list is the property of the Institute of Physics & Engineering in Medicine and must not be used for any commercial purpose without the written consent of the Chief Executive.

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
<th>Email Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Erik Gommer</td>
<td>Maastricht University Medical Centre, The Netherlands</td>
<td><a href="mailto:e.gommer@mumc.nl">e.gommer@mumc.nl</a></td>
</tr>
<tr>
<td>Dr Cornelia Hoedemaekers</td>
<td>Radboud University Medical Center, The Netherlands</td>
<td><a href="mailto:astrid.hoedemaekers@radboudumc.nl">astrid.hoedemaekers@radboudumc.nl</a></td>
</tr>
<tr>
<td>Ms Svenja Hüsch</td>
<td>University Hospital Aachen, Germany</td>
<td><a href="mailto:svenja.huesch@rwth-aachen.de">svenja.huesch@rwth-aachen.de</a></td>
</tr>
<tr>
<td>Dr Kenichi Iwasaki</td>
<td>Nihon University School of Medicine Japan, Japan</td>
<td><a href="mailto:iwasaki.kenichi@nihon-u.ac.jp">iwasaki.kenichi@nihon-u.ac.jp</a></td>
</tr>
<tr>
<td>Dr Sam Klein</td>
<td>University Hospitals Leuven, Belgium</td>
<td><a href="mailto:sam.klein@kuleuven.be">sam.klein@kuleuven.be</a></td>
</tr>
<tr>
<td>Dr Manda MY Lam</td>
<td>University of Leicester, UK</td>
<td><a href="mailto:ml376@le.ac.uk">ml376@le.ac.uk</a></td>
</tr>
<tr>
<td>Dr Linfang Lan</td>
<td>The Chinese University of Hong Kong, Hong Kong</td>
<td><a href="mailto:lanlinfang2006@163.com">lanlinfang2006@163.com</a></td>
</tr>
<tr>
<td>Miss Fernanda Lobos</td>
<td>Universidad de Santiago de Chile, Chile</td>
<td><a href="mailto:maria.lobos@usach.cl">maria.lobos@usach.cl</a></td>
</tr>
<tr>
<td>Dr Jatinder Minhas</td>
<td>University of Leicester, UK</td>
<td><a href="mailto:jatinder.minhas@hotmail.com">jatinder.minhas@hotmail.com</a></td>
</tr>
<tr>
<td>Mr Martin Müller</td>
<td>Kantonsspital Luzern, Switzerland</td>
<td><a href="mailto:martin.mueller@luks.ch">martin.mueller@luks.ch</a></td>
</tr>
<tr>
<td>Dr Natalie Nasr</td>
<td>University of Toulouse, France</td>
<td><a href="mailto:nasr.n@chu-toulouse.fr">nasr.n@chu-toulouse.fr</a></td>
</tr>
<tr>
<td>Dr Stephen John Payne</td>
<td>University of Oxford, UK</td>
<td><a href="mailto:stephen.payne@eng.ox.ac.uk">stephen.payne@eng.ox.ac.uk</a></td>
</tr>
<tr>
<td>Professor John Potter</td>
<td>University of East Anglia, UK</td>
<td><a href="mailto:john.potter@uea.ac.uk">john.potter@uea.ac.uk</a></td>
</tr>
<tr>
<td>Professor Arminas Ragauskas</td>
<td>Kaunas University of Technology, Lithuania</td>
<td><a href="mailto:telematics@ktu.lt">telematics@ktu.lt</a></td>
</tr>
<tr>
<td>Ms Marit Sanders</td>
<td>Radboud University Medical Center, The Netherlands</td>
<td><a href="mailto:marit.sanders@radboudumc.nl">marit.sanders@radboudumc.nl</a></td>
</tr>
<tr>
<td>Dr Martin Shaw</td>
<td>NHS Greater Glasgow and Clyde, UK</td>
<td><a href="mailto:martin.shaw@nhs.net">martin.shaw@nhs.net</a></td>
</tr>
<tr>
<td>Professor Johannes van der Hoeven</td>
<td>Radboud University Medical Center, The Netherlands</td>
<td><a href="mailto:j.vanderhoeven@radboudumc.nl">j.vanderhoeven@radboudumc.nl</a></td>
</tr>
</tbody>
</table>
# Programme Lead

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof David Simpson</td>
<td>University of Southampton, UK</td>
<td><a href="mailto:ds@isvr.soton.ac.uk">ds@isvr.soton.ac.uk</a></td>
</tr>
</tbody>
</table>

# Invited Speakers

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Roxana Carare</td>
<td>University of Southampton, UK</td>
<td><a href="mailto:r.o.carare@soton.ac.uk">r.o.carare@soton.ac.uk</a></td>
</tr>
<tr>
<td>Dr Edith Hamel</td>
<td>McGill University, Montreal, Canada</td>
<td><a href="mailto:edith.hamel@mcgill.ca">edith.hamel@mcgill.ca</a></td>
</tr>
<tr>
<td>Dr Ian Piper</td>
<td>South Glasgow University Hospital, UK</td>
<td><a href="mailto:ian.piper@brainit.org">ian.piper@brainit.org</a></td>
</tr>
<tr>
<td>Prof Thompson Robinson</td>
<td>University of Leicester, UK</td>
<td><a href="mailto:tgr2@leicester.ac.uk">tgr2@leicester.ac.uk</a></td>
</tr>
<tr>
<td>Dr Ilias Tachtsidis</td>
<td>University College London, UK</td>
<td><a href="mailto:i.tachtsidis@ucl.ac.uk">i.tachtsidis@ucl.ac.uk</a></td>
</tr>
<tr>
<td>Prof Johannes van Lieshout</td>
<td>University of Amsterdam, The Netherlands</td>
<td><a href="mailto:j.j.vanlieshout@amc.uva.nl">j.j.vanlieshout@amc.uva.nl</a></td>
</tr>
</tbody>
</table>

# Speakers

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mr Jurgen Claassen</td>
<td>Radboud University Medical Center, The Netherlands</td>
<td><a href="mailto:jurgen.claassen@radboudumc.nl">jurgen.claassen@radboudumc.nl</a></td>
</tr>
<tr>
<td>Professor Marek Czosnyka</td>
<td>University of Cambridge, UK</td>
<td><a href="mailto:mc141@medschl.cam.ac.uk">mc141@medschl.cam.ac.uk</a></td>
</tr>
<tr>
<td>Mr Joseph Donnelly</td>
<td>University of Cambridge, UK</td>
<td></td>
</tr>
<tr>
<td>Dr Jan Willem Elting</td>
<td>University Medical Center Groningen, The Netherlands</td>
<td><a href="mailto:j.w.j.elting@neuro.umcg.nl">j.w.j.elting@neuro.umcg.nl</a></td>
</tr>
<tr>
<td>Professor Christina Haubrich</td>
<td>University of Cambridge, UK</td>
<td><a href="mailto:christina.haubrich@t-online.de">christina.haubrich@t-online.de</a></td>
</tr>
<tr>
<td>Dr Victoria Haunton</td>
<td>University of Leicester, UK</td>
<td><a href="mailto:vjh12@le.ac.uk">vjh12@le.ac.uk</a></td>
</tr>
<tr>
<td>Dr Jose Jara</td>
<td>Universidad de Santiago de Chile, Chile</td>
<td><a href="mailto:joseluis.jara@usach.cl">joseluis.jara@usach.cl</a></td>
</tr>
<tr>
<td>Ms Mary Liu</td>
<td>University of Cambridge, UK</td>
<td></td>
</tr>
<tr>
<td>Mr Greg Mader</td>
<td>North Carolina State University, USA</td>
<td><a href="mailto:gcmader@ncsu.edu">gcmader@ncsu.edu</a></td>
</tr>
<tr>
<td>Dr Adam Mahdi</td>
<td>University of Oxford, UK</td>
<td><a href="mailto:adam.mahdi@eng.ox.ac.uk">adam.mahdi@eng.ox.ac.uk</a></td>
</tr>
<tr>
<td>Prof Vasilis Marmarelis</td>
<td>University of Southern California, USA</td>
<td><a href="mailto:vzm@usc.edu">vzm@usc.edu</a></td>
</tr>
<tr>
<td>Dr Georgios Mitsis</td>
<td>McGill University, Canada</td>
<td><a href="mailto:georgios.mitsis@mcgill.ca">georgios.mitsis@mcgill.ca</a></td>
</tr>
<tr>
<td>Dr Patrick Neary</td>
<td>University of Regina, Canada</td>
<td><a href="mailto:patrick.neary@uregina.ca">patrick.neary@uregina.ca</a></td>
</tr>
<tr>
<td>Dr Dragana Nikolic</td>
<td>University of Southampton, UK</td>
<td><a href="mailto:d.nikolic@soton.ac.uk">d.nikolic@soton.ac.uk</a></td>
</tr>
</tbody>
</table>
Mr Vytautas Petkus  
Kaunas University of Technology, Lithuania  
Email: vytautas.petkus@ktu.lt

Prof Jorge Serrador  
Rutgers Biomedical Health Sciences, USA  
Email: serradjo@njms.rutgers.edu

Ms Maria Skytioti  
University of Oslo, Norway  
Email: maria.skytioti@medisin.uio.no

Ms Emma Thompson  
University of Birmingham, UK  
Email: elf735@bham.ac.uk

Dr Ge Tian  
The Chinese University of Hong Kong, Hong Kong  
Email: tiangeminie@gmail.com

Mrs Teelkien van Veen  
University Medical Center Groningen, The Netherlands  
Email: teelkien@gmail.com

Poster presenters

Mr Felipe Bello  
Universidad de Santiago de Chile, Chile  
Email: felipe.bello@gmail.com

Mr Igor Braz  
University of Birmingham, UK  
Email: idx263@bham.ac.uk

Prof Max Chacon  
Universidad de Santiago de Chile, Chile  
Email: max.chacon@usach.cl

Prof Tim David  
University of Canterbury, New Zealand  
Email: tim.david@canterbury.ac.nz

Mr Daan de Jong  
Radboud University Medical Center, The Netherlands  
Email: Daan.dejong@radboudumc.nl

Ms Vibeke Eriksen  
Rigshospitalet, Denmark  
Email: vibeke.eriksen@dadi.net.dk

Ms Michelle Favre  
Rutgers Biomedical Health Sciences, USA  
Email: mef160@njms.rutgers.edu

Dr Takuya Kurazumi  
Nihon University School of Medicine Japan, Japan  
Email: takfromnarita@live.jp

Prof Vasilis Marmarelis  
University of Southern California, USA  
Email: vzm@usc.edu

Dr Teemu Myllyla  
University of Oulu, Finland  
Email: teemu.myllyla@ee.oulu.fi

Dr Ricardo Nogueira  
University of Sao Paulo, Brazil  
Email: rcnogueira28@gmail.com

Prof Ronney Panerai  
University of Leicester, UK  
Email: rp9@le.ac.uk

Mr Vytautas Petkus  
Kaunas University of Technology, Lithuania  
Email: vytautas.petkus@ktu.lt

Dr Angela Salinet  
University of Sao Paulo, Brazil  
Email: angelasmacedo@gmail.com

Dr Judith van den Brule  
Radboud University Medical Center, The Netherlands  
Email: j.vandenbrule@radboudumc.nl

Ms Gerrita van Spijker  
Radboud University Medical Center, The Netherlands  
Email: gerrita.vanspijker@radboudumc.nl
Notes

These pages have been left blank for you to make notes
This conference is kindly supported by
Artinis Medical Systems BV
Linton Instrumentation
Moor Instruments Ltd
Rimed Ltd
Smart Medical Ltd
SMT Medical Technology