Arrival Time Changes Demonstrate Active Cerebral Autoregulation in Normal Subjects using Lower Body Negative Pressure and Arterial Spin Labeling MRI

J. R. Cain[1], G. Thompson[1], L. M. Parkes[1], and A. Jackson[1]
[1]Imaging Science, University of Manchester, Manchester, United Kingdom

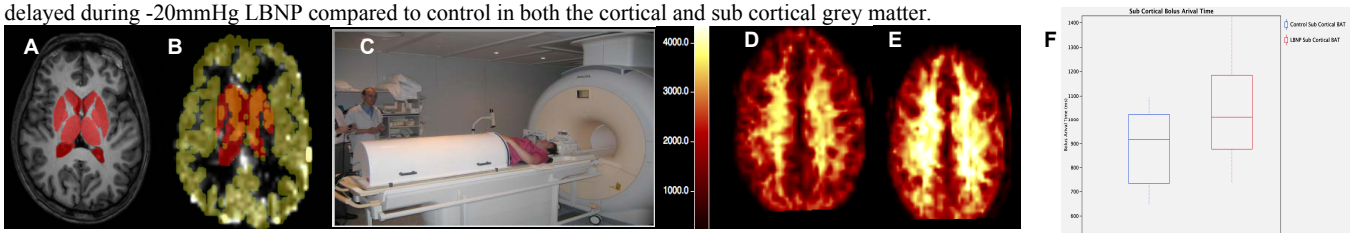
Introduction: Cerebral autoregulation is a complex homeostatic mechanism that maintains constant cerebral blood flow (CBF) throughout a wide range of cardiac outputs. Disease processes such as diabetic autonomic neuropathy may affect the mechanism leading to postural hypotension[1]. We present the first MRI perfusion data demonstrating active cerebral autoregulation in healthy volunteers. Investigation of cerebral autoregulation using MRI is challenging because orthostatic challenges, which elicit an autoregulatory response such as tilt table tests are incompatible with MRI. Lower body negative pressure (LBNP) of -20mmHg, created by applying an external vacuum to the lower limbs and torso has been shown to be an equivalent stimulus to 70^0 tilt table test[2]. We have constructed a LBNP chamber which is MRI compatible and investigated the effects of LBNP on cerebral perfusion and bolus arrival time using arterial spin labeling (ASL) and phase contrast angiography (PCA).

Materials & Methods: Ten healthy volunteers (aged 24-31 years 3 female - 7 male) underwent imaging with a 3T Achieva MR scanner (Phillips, The Netherlands) with their legs and lower torso within the Manchester MRI compatible LBNP chamber. The negative pressure was controlled via a controllable vacuum pump in the scan control room.

Imaging consisted of a high resolution anatomical 3D T1 inversion recovery (T1 IR) sequence, and an ASL sequence followed by a PCA acquisition in both the rest (control state) and under -20mmHg LBNP. ASL imaging used STAR labeling and EPI collection (20 slices; 5mm slice thickness with 1mm slice gap; TR: 3000ms; TE: 21ms; FOV: 224 x 224 mm; Voxel size: 3.5mm x 3.5mm; Matrix size: 64 x 64, Label thickness: 150mm; 10mm label gap; 20 dynamic scans) collected at 4 inversion times: 800ms, 1200ms, 1600ms and 2000ms. PCA acquisition was collected using sagittal 2D cine phase-contrast images. ECG cardiac gating was used to cover the entire cardiac cycle. 16 phase images were calculated over the cardiac cycle from 256 acquisitions. The imaging parameters were as follows: TE 4.43 msec; TR dependant on heart rate ranging between 7.4 – 14.1 msec; flip angle 10°; number of averages 3; matrix 256 x 256; pixel size 1.17 x 1.17 mm; slice thickness 6 mm; and velocity encoding 200 cm/s.) For each subject a 2D PCA slice was collected at a level of skull base containing both internal carotid arteries and basilar artery. PCA imaging was also acquired at rest and under -20mmHg at the level of the aortic arch. Throughout scanning the subjects pulse and blood pressure were monitored using Precess 3160 MRI patient monitoring system (Invivo, Florida, USA).

PCA results were analysed using Q flow software (Philips, Best, the Netherlands) CBF was calculated from the sum of the average flow over the cardiac cycle in each vessel producing a flow result in ml/s. Cardiac output was calculated form flow volumes in the ascending and descending aorta. ASL images were analysed using in-house code written in MATLAB (Mathworks, Boston, USA), assuming a single blood compartment model[3]. The model accounted for the differences in individual slice acquisition times. M_0 and T1 maps were calculated by fitting the control data at the four inversion times to a recovery curve. A global value for M_0 was calculated and used in the model to quantify perfusion. Control and labeled images were subtracted and a two-parameter fit for bolus arrival time (BAT) and CBF was performed on a voxel by voxel basis, producing CBF and tA maps. Perfusion was calculated with units ml/100ml/min. Tissue segmentation masks were created for both cortical and sub cortical grey matter structures form the aligned high resolution T1 IR images and then applied to co registered perfusion and arrival time maps using a combination of FSL (Oxford, UK) and in house code.

Results: During -20mmHg LBNP cardiac output was reduced on average by 0.5l/min, blood pressure remained constant and pulse was raised by 7 bmp. This represents a normotensive hypovolemic stimulus. There was no difference between ASL grey matter perfusion values (mean 39.2 ml/100ml/min and 42.3ml/100ml/min respectively) or PCA cerebral blood flow values between control and -20mmHg. The arrival time of the labeled bolus was delayed during -20mmHg LBNP compared to control in both the cortical and sub cortical grey matter.



Measurement	Units	Mean	SD	Difference
Cortical GM perfusion Control	ml/100ml/min	39.2	7.3	
Cortical GM perfusion -20mmHG LBNP	ml/100ml/min	42.3	10.1	0.09
Cortical GM BAT control	ms	782	140	
Cortical GM BAT -20mmHg LBNP	ms	831	139	0.039
Sub cortical GM perfusion Control	ml/100ml/min	31.3	5.7	
Sub cortical GM perfusion -20mmHg LBNP	ml/100ml/min	33.1	6.8	0.17
Sub cortical GM BAT Control	ms	896	150	
Sub cortical GM BAT -20mmHg LBNP	ms	1033	205	0.034

Table 1: STAR ASL results for perfusion and BAT (Difference = t-test p value)

A: Example T1 IR image with sub cortical structures segmented.
B: Calculated ASL Perfusion map with applied sub cortical (orange) and cortical (yellow) masks applied.
C: Subject inside Manchester LBMP chamber undergoing MRI scan.
D: Example bolus Arrival time map under control conditions. (Yellows indicate areas with longer arrival.
E: The same subjects bolus arrival time map during -20mmHg LBNP.
F: Box plots of mean arrival times in sub cortical grey matter structures under control (blue) and -20mmHg LBNP (red).

Conclusion: LBNP is capable of producing a normotensive hypovolemic challenge in the MRI environment [4-5]. In young healthy individuals cerebral autoregulation is able to compensate for -20mmHg LBNP and maintain constant perfusion. Sub cortical grey matter perfusion was lower than cortical perfusion but neither was affected by the LBNP stimulus. The observed significant delay in bolus arrival time suggests that the -20mmHg LBNP stimulus causes dilation of pial vessels possibly affecting white matter perfusion but autoregulatory mechanisms are maintaining grey matter blood flow. Arrival time may prove to be an important biomarker in detecting cerebral autoregulation [6]. This experiment demonstrates that normal cerebral autoregulation is observable using MRI, giving promise for future studies of subjects with abnormal cerebral autoregulation.

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