Assessment of Cerebral Autoregulation by Inducing Acute Hypertension in Rats

Guang Li1,2, Yen-Yu L Shih1, Bryan H. De La Garza3, Jeffrey W. Kiel4,5, and Timothy Q. Duong2,6
1Radiology, University of Texas Health Science Center at San Antonio, San Antonio, TX, United States, 2Research Imaging Institute, University of Texas Health Science Center at San Antonio, San Antonio, TX, United States, 3Ophthalmology, University of Texas Health Science Center at San Antonio, San Antonio, TX, United States, 4Physiology, University of Texas Health Science Center at San Antonio, San Antonio, TX, United States

Background: Static cerebral autoregulation (CA) describes the capability of the vasculature to maintain relatively stable cerebral blood flow (CBF) over a wide range of blood pressure (BP), e.g. 60-150 mmHg BP in human. Dynamic CA describes the capability of the vasculature (BF) to respond to sudden BP changes [1]. CA has been studied using PET for measuring CBF, ultrasound and Laser Doppler techniques for measuring flow in large (carotid) arteries.

In this study, we developed a rat model of acute hypertension by occluding the descending aorta and used CBF MRI to evaluate CA under normocapnia and hypercapnia. Occlusion of the descending aorta avoids potential pharmaceutical complications and it can be repeatedly applied in the scanner. The long term goal is to apply this approach to study CA in rat models of chronic hypertension, stroke and diabetes.

Method: In this study, 6 Long-Evans rats were used for MRI and 3 for blood-gas measurements. Anesthesia was maintained at 1.1% isoflurane. The rats were paralyzed with pancuronium bromide (4 mg/kg first dose, 4 mg/kg/hr, i.p.) and mechanically ventilated under normocapnia (house air: n=2; 30% O2; n=3), and then under hypercapnia (7.5% CO2: n=1; 5% CO2: n=3, mixed with 30% O2). Systemic BP was continuously monitored through a PE-50 tube cannulating the right axillary artery. Arterial blood was sampled through the same PE50 for blood gas measurement. End-tidal CO2, SO2, heart rate (HR), and rectal temperature were maintained within normal ranges. BP was modulated by a balloon catheter placed in the descending aorta (placed near diaphragm), inserted via the right femoral artery. The BP was elevated by 10-60 mmHg from baseline by partially or completely redirecting blood from lower body to upper body.

Magnetic Resonance Imaging (MRI) studies were performed on an 11.7 T Bruker Biospec using a surface coil with active decoupling (ID=2 cm) and a separated butterfly neck coil for continuous arterial spin labeling (cASL). CBF MRI was acquired using 5-slice EPI-cASL with FOV=22×22.4 mm², TR/TE/LD=3000/10.2/2900 ms, resolution=175×175×1500 μm³. Modulation paradigm was OFF-OFF. The first off period (2min, 20-pair non- and labeled images) was baseline and the ON period (1 min, 10-pair images) was BP elevation period. ROIs were manually drawn to segment cerebrum in each set of 5-slice CBF images. The mean CBF value within these ROIs was reported. BOLD data were extracted from non-labeled images. Multiple trials were performed on each rat and 10–15 minutes break was given between consecutive trials. Total 23 trials under normocapnia and 21 trials under hypercapnia were performed on 6 rats.

Results: Arterial pO2 and pH increased significantly during BP elevation under both hypercapnia and normocapnia. pCO2 decreased significantly under normocapnia but not under hypercapnia (Table 1). Fig 1 shows the typical traces of BP, HR, CBF and BOLD changes associated with the balloon occlusion under normocapnia. CBF signals declined slowly toward baseline after its initial increase during sustained BP elevation. BP, CBF and BOLD (but not HR) undershot immediately after the deflating the balloon occluder. Under normocapnia (Fig 2A), the slope of ΔCBF vs. ΔBP was not different from 0 (p=0.53) and there was a small offset of 0.18 ml/g/min (p<0.001). By contrast, under hypercapnia (Fig 2B), ΔCBF increased linearly with ΔBP, which indicates autoregulation impairment. %CBF vs. %BOLD remained linearly correlated under both hypercapnia and normocapnia (Fig 3).

Discussion & Conclusion: Normal CA was detected under normocapnia as indicated by the absence of correlation between ΔCBF vs. ΔBP (Fig 2A). The offset of 0.18 ml/g/min on ΔCBF vs. ΔBP plot was because the reported CBF was averaged over the duration of BP elevation where CBF transiently increased and slowly returned toward baseline. It is also possible that CA established a new and higher CBF during elevated BP period. The offset in Fig 2A and the slow return toward baseline in Fig 1 could be due to isoflurane, which is a vasodilator and has a dose-dependent effect on CA [4]. Our results are consistent with similar transient CBF increases that had also been observed in dogs [5] and monkeys [6] under pentobarbital after the aorta occlusion. By contrast, CA was markedly impaired under hypercapnia as indicated by the linear correlation between ΔCBF vs. ΔBP (Fig 2B) because the added CO2 acts as a strong vasodilator. This is consistent with a previous report [7].

BOLD vs. CBF remained linearly correlated under normocapnia and hypercapnia. The increased BOLD signal with increasing CBF could be because of decreased oxygen extraction fraction and/or increased blood pO2 during elevated BP. Blood gases showed increased arterial pO2 which is likely due to the increased pulmonary perfusion caused by elevated BP.

In conclusion, we developed a model of acute hypertension in rat for use in the MRI scanner. CBF MRI results indicated that there were apparent CA under isoflurane anesthesia but was markedly impaired during hypercapnia. This approach sets the stage for study of CA in rat models of chronic hypertension, stroke and diabetes.

References

Table 1. Blood gases under hyper- and normocapnia conditions during normal and elevated BP (* indicates statistical significant from baseline, Wilcoxon rank-sum test)

<table>
<thead>
<tr>
<th>Condition</th>
<th>pCO2 (mm Hg)</th>
<th>pO2 (mm Hg)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normocapnia</td>
<td>32.6±3.9</td>
<td>157±19.5</td>
<td>7.49±0.039*</td>
</tr>
<tr>
<td>Hypercapnia</td>
<td>63.3±7.4</td>
<td>135±16.8</td>
<td>7.22±0.036</td>
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</tbody>
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Fig1. BP, HR, CBF and BOLD changes during acute hypertension under normocapnia. Occlusion duration is indicated by the shaded area.

Fig2 A) Normocapnia: ΔBOLD only increases by a constant of 0.18 ml/g/min and is not correlated to Δ BP (p_{slope}=0.53 \& p_{offset}<0.001), which indicates existence of CA. B) Hypercapnia: ΔCBF linearly increases with ΔBP (p_{slope}=0.002 \& p_{offset}=0.07), which indicates CA impairment.

Fig3 A) & B) BOLD increases linearly with CBF under both hypercapnia and normocapnia (A includes only trials under 30% O2)}