A multimodality investigation of cerebral haemodynamics and autoregulation in phMRI

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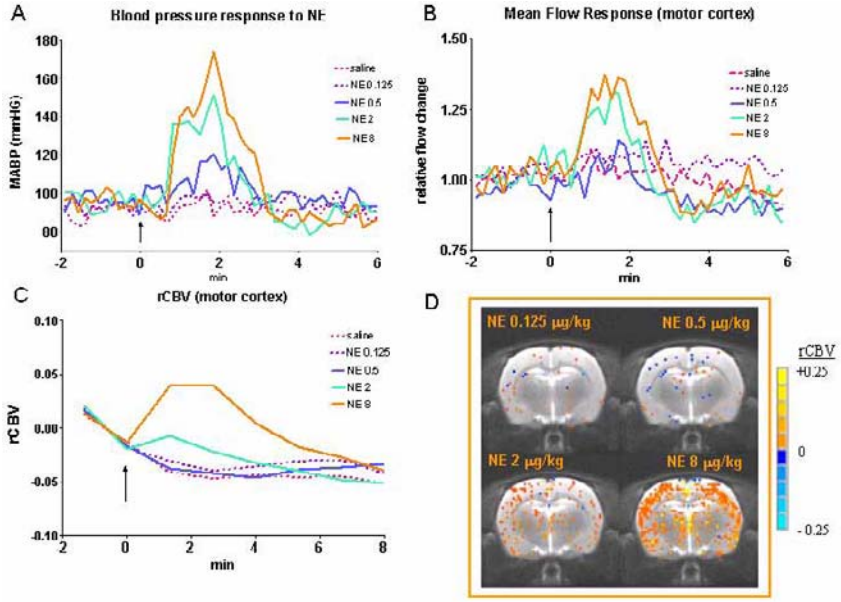
Introduction: Pharmacological MRI methods (phMRI) can be applied to assess the effects of acute drug challenge on cerebral haemodynamics as a surrogate for changes in the underlying neuronal activity. However, many psychoactive drugs can induce a variety of peripheral effects, including significantly alterations of arterial blood pressure. Rapid changes in blood pressure can affect haemodynamic parameters in the brain, particularly when autoregulatory mechanisms are compromised, thus potentially introducing confounds [1,2]. It is therefore critically important to assess the extent of the autoregulatory range under the specific experimental conditions used in phMRI experiments. Here, we have applied both MR and optical (Laser Doppler Flow, LDF) methods to measure changes in cerebral blood flow (CBF) and blood volume (CBV) induced by an intravenous norepinephrine (NE) challenge in the halothane-anaesthetised rat. NE is a potent non-brain penetrant vasopressor that elicits dose-dependent increases in mean arterial blood pressure (MABP) [3]. We explored four different doses in order to correlate the magnitude of the cardiovascular response with the corresponding changes in brain haemodynamic parameters.

Methods: All experiments were carried out in accordance with Italian regulations governing animal welfare and protection. Protocols were also reviewed and consented to by a local animal care committee, in accordance with the guidelines of the Principles of Laboratory Animal Care (NIH publication 86-23, revised 1985).
LDF measurements: Male Sprague-Dawley rats (250-350g) were anaesthetised with 3% halothane in O_2:N_2 1:2, tracheotomised and mechanically ventilated under infusion of the neuromuscular blocker D-tubocurarine. The femoral artery was cannulated to monitor arterial blood pressure and blood gas levels. Subsequently, the animals were placed in a stereotaxic frame and implanted with a Laser-Doppler-Flow (LDF) probe (Oxylite, Optronix) in the motor cortex (M1, n=8; AP +2.2 mm, ML +2.8 mm, DV -2.5 mm) as previously described [4]. After surgery, the anaesthesia was decreased to 1% halothane for maintenance. After 2h stabilisation, animals were challenged with NE (0.125, 0.5, 2, 8 µg/kg i.v.) or vehicle (saline).
rCBV measurements: MRI experiments were performed on 7 male Sprague-Dawley rats, prepared as described elsewhere [5,6]. The data were acquired using a Bruker Biospec 4.7T system, a 72mm birdcage resonator for RF transmit and a quadrature surface receive coil (Bruker, Ettlingen, Germany). The time series data were acquired using the RARE sequence: matrix 128x128; FOV 40mm; slice thickness 2mm; 8 contiguous coronal slices; RARE factor 32; TE_{eff}=110ms; TR=2700ms; δt=80s. A 2.67 ml/kg dose of Endorem blood pool contrast agent (Guerbet, France) was administered i.v. following 5 reference image frames, to sensitise the acquisition to changes in CBV as described in [7]. After 20 min stabilisation, animals were challenged with NE (0.125, 0.5, 2, 8 µg/kg i.v.) or its vehicle (saline).

Results: Baseline MABP levels were equivalent in all treatment groups (overall mean 94.0±12 mmHg). Increasing doses of NE (0.125, 0.5, 2 and 8 µg/ml) produced transient, dose-dependent rises in MABP (96±14, 121±13, 152±27 and 174±17 mmHg at peak, respectively, Fig 1A). At the three highest doses the effect reached statistical significance ($p<0.01$, $p<0.05$ and $p<0.001$ at peak vs. saline, respectively). No significant changes in LDF were observed with MABP increases up to 130 mmHg (NE 0.5 ug/kg, Fig 1B). Larger MABP increases (NE 2 and 8 ug/kg) gave rise to a marked increase in LDF (+30% and +37%, respectively), thus indicating a breakdown in blood flow autoregulation for large MABP responses ($p<0.001$ and $p<0.01$ at peak, respectively, Fig 1B). The two highest doses of NE also induced a transient increase in rCBV ($p<0.05$, Fig 1C). Interestingly, the concomitant changes in rCBV were mainly localised in cortical structures of the brain (Fig 1D).

Discussion: Whether autoregulation is preserved under anaesthesia has been a contentious matter in recent literature with often inconsistent results, possibly because autoregulation is sensitive to the specific experimental conditions [8,9]. Here we have measured independently MABP, CBF and CBV changes induced by acute challenge with a drug that does not cross the BBB, and therefore is not expected to elicit changes in neuronal activity. The challenge was administered intravenously, thus inducing a rapid cardiovascular response that closely mimics the profile of MABP changes observed in phMRI experiments using this route of administration. The LDF data demonstrated that CBF autoregulation was preserved under our experimental conditions over a wide range of pressure changes. Moreover, our data suggest that with MABP changes within the CBF autoregulatory range, the concomitant CBV changes are smaller than previously reported [10]. This finding is in good agreement with the results of Zaharchuk et al. [11], which observed small and non-significant CBV changes when the MABP was decreased from 140 down to 50 mmHg under experimental conditions very similar to those of our study. Above a certain MABP threshold, autoregulation breaks down, and measurable changes in both rCBF and rCBV were observed. Interestingly, in this regime, changes in rCBV were not uniformly widespread in the brain, but showed a certain degree of regionalisation particularly in cortical structures, possibly reflecting higher vascular density.



Conclusion: We have demonstrated that, in our phMRI model of the halothane anaesthetised rat, autoregulation is maintained over a MABP range of 80-140 mmHg. However, larger changes violating this range might confound the interpretation of the phMRI activation maps. The autoregulatory range depends on experimental conditions, and should be assessed in the specific anaesthetic protocol used in the phMRI experiment.

Figure 1: A: Blood pressure response to IV challenge with NE. B: LDF response to NE challenge in the motor cortex. C: Time evolution of the rCBV changes produced by NE. D: Maps of rCBV changes produced by increasing doses of NE in a representative brain slice. Yellow/orange areas indicate *increased* rCBV vs. saline ($p<0.05$). The time of injection is indicated by a vertical arrow. Doses are expressed in µg/kg.

References:
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