

Blood Volume in response to Hypercapnia: MRI Study Using Spontaneously Breathing Mice

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INTRODUCTION: The elevated arterial CO₂ (pCO₂) is a strong vasodilator under the normal brain condition, leading to a significant increase in cerebral blood flow (CBF) and cerebral blood volume (CBV)^[1]. In a number of brain diseases (e.g. brain stroke, Alzheimer's disease, atherosclerosis, etc), impaired vasoreactivity in response to systemic hypercapnia has been observed. Despite the promising potential for evaluating neurovascular diseases, the method has not been used in mouse models mainly due to the difficulty in the quantification of vasoreactivity. In the current study, using an alternating gradient and spin echo (GE/SE) EPI and superparamagnetic intravascular contrast agent (Superparamagnetic iron oxide nanoparticles: SPION), we monitored multiple MRI-derived hemodynamic parameters during the graded hypercapnic episodes in normal healthy mice.

MATERIALS & METHODS: CBV (i.e., $\Delta R2^*$), microvascular volume (MVV; $\Delta R2$), and vascular size index (VSI; CBV/MVV) were quantified from three ROIs drawn in cortex, thalamus, and caudate regions of the C57BL/6 mice brain. For the simultaneous monitoring of these parameters, mice anesthetized with 1% isoflurane were allowed for spontaneous respiration while exposed to four different CO₂ gases (2.5%, 5%, 7.5%, and 10% CO₂ in the 50/50 air/oxygen gas mixture) for three minutes per each dose. T₂- and T₂*-weighted images were acquired alternatively using GE/SE EPI sequence with TR/TE = 3000/15.16 ms for GE and 3000/27.73 ms for SE before and after administering SPION.

RESULTS & DISCUSSION: Spontaneous inhalation of CO₂ gas resulted in the significantly increased CBV, MVV and VSI, exhibiting the general trend of cerebral vasodilation. Spatially heterogeneous responses as well as the CO₂ dose-dependent response magnitude were observed for both the CBV and MVV responses (Figure 1). In particular, the CBV response was more localized than the MVV response, in which the CBV responses were spatially concentrated in the cortex and thalamus across the CO₂ dose (Figure 2). Moreover, for the CBV response, the rise time to the peak decreased with the increasing CO₂ concentration whereas such trend was not observed in MVV. On the other hand, the recovery from the peak to baseline following the cessation of CO₂ gas was increasingly delayed as the CO₂ concentration increased for both the CBV and MVV. The peak-to-peak response magnitude was proportional to the CO₂ gas concentration for both

the CBV and MVV at low doses (< 5%), which reached a plateau at high doses. Dynamic features of the CO₂-evoked VSI change were distinct from the volume-related responses, in which the rise time increased as the CO₂ dose increased while the peak VSI values were reached a few minutes after turning off the CO₂ gas for the dose greater than 5%. Our results demonstrate significant changes of hemodynamic MRI parameters during systemic hypercapnia in spontaneously breathing mice under the isoflurane anesthesia. The current experimental setting, the use of GE/SE EPI sequence and SPION with the non-invasive subject preparation, produced consistent vasoreactive responses, thus validating the hypercapnic method for evaluating hemodynamic changes altered by numerous pharmacologic agents and pathophysiological states in the different disease models.

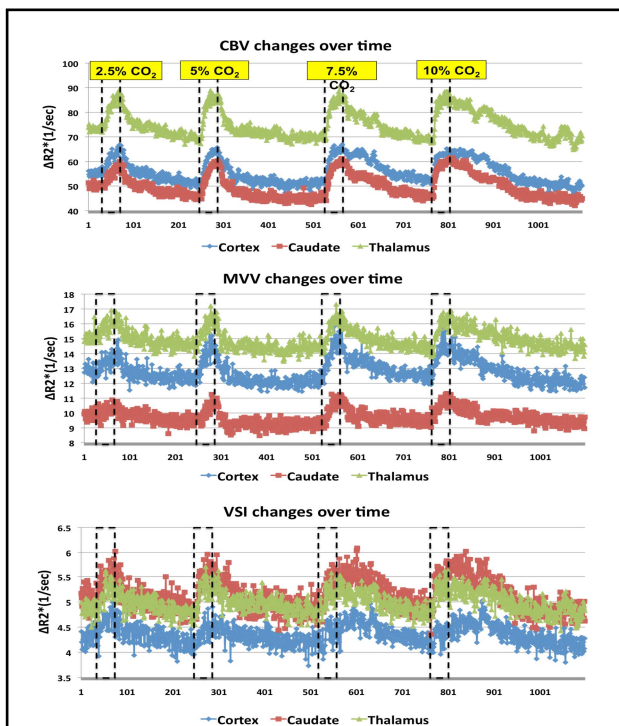


Fig. 1. Representative hemodynamic changes over time in response to the different CO₂ gas inspiration.

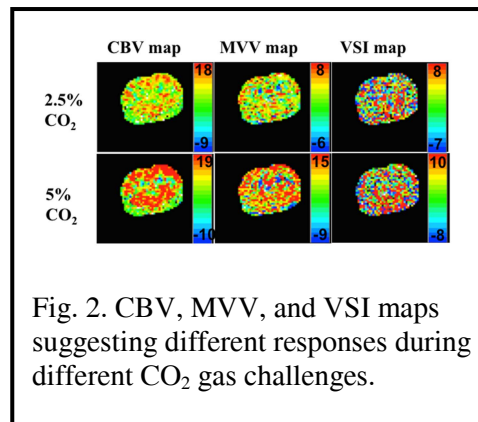


Fig. 2. CBV, MVV, and VSI maps suggesting different responses during different CO₂ gas challenges.

REFERENCE [1]
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