Hypercapnia-induced vasoreactivity as evaluated by Vascular-Space-Occupancy (VASO) dependent fMRI

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INTRODUCTION: Hypercapnia is believed to cause vascular changes but no alterations in metabolism, and have been used to evaluate the cerebral vascular reserve and vasoreactivity using various techniques. While these studies have shown clear signal changes based on either CBF or venous oxygenation, the changes in CBV and their characteristics are not fully investigated. In particular, multiple factors can affect vessel caliber and brain perfusion. The chemical factor (CO_2 and the associated changes in $[H^+]$ and $[HCO_3^-]$) is of course the most obvious one and is considered the main factor. In addition, the changes in activities of autonomic nerve systems (sympathetic and parasympathetic systems) can affect the blood pressure, heart rate, cardiac output, etc., which can in turn cause a change in perfusion, i.e. Perfusion=ΔPressure/Vascular Resistance. Furthermore, vascular systems have auto-regulation capacity, which tries to keep blood flow constant by causing vasodilation when perfusion pressure decreases and vasoconstriction when pressure increases. Therefore, these factors need to be considered when evaluating the vasoreactivity under hypercapnia. Here we performed VASO fMRI while simultaneously monitoring the physiologic parameters, including arterial blood pressure, heart rate (HR), arterial oxygenation (sO2), end-tidal CO2 (EtCO2), breathing rate. The hypercapnia were induced by two separate methods, breathing a 5% CO2 gas mixture and breath holding for 24s. The physiologic measures were compared to the MRI measures.

METHODS: MR experiments (3T Philips) were performed on two healthy subjects with informed consent. The VASO fMRI technique is described in literature (1) and the VASO signal will show a signal decrease when CBV increases. The imaging parameters were: FOV=220mm, matrix=80x80, TR/TE/TI=3000/16/889ms, 1 slice, thickness 6mm. After the physiologic monitoring probes were attached to the subjects, the subjects were positioned on the table and were instructed to breathe through mouth via a mouthpiece (nose was blocked by a nose clip). They start by breathing room air and a researcher was inside the magnet room throughout the experiment to switch to/from the gas mixture. The operator was able to communicate with this researcher via a special headset, so that the operator can instruct her when to turn the switch without letting the subject know this (after the scan session, the subjects were interviewed and they reported that they were not aware of the timing of the air switching). The MRI starts with a localizer and immediately followed by the CO2 VASO fMRI scan. The CO2 VASO scan starts with a one minute room-air followed by 3 repetitions of 4 minutes 5% CO2 and 4 minutes of room-air (duration=25 min). After this scan, the subjects continue to breathe the room-air and were instructed to do the breath holding upon a light tap on the leg. Each breath-hold VASO scan had 3 periods of 24s breath-hold interleaved with 48s of regular breathing. Two breath-hold VASO scans were performed on each subject.

Data were processed using in-house MATLAB scripts. Since VASO images have T1-weighting, which can be utilized to segment out gray and white matters, an intensity threshold was applied to find the gray matter mask (Fig. 1). The voxels inside the mask were spatially averaged to obtain the VASO time-courses, which are shown in percentages of the baseline signal. Motion correction was performed on all functional images using SPM2.

RESULTS and DISCUSSION: Fig. 2a summarizes the temporal dynamics of the physiologic parameters and the VASO MRI signals. Breathing 5% CO2 induced an EtCO2 increase from 36mmHg to 46mmHg, similar to literature values (2). The VASO signal shows a decrease by about 1.5%, corresponding to a CBV increase of 31% when assuming a baseline CBV of 0.047ml blood/100ml (1). This overall trend is consistent with previous reports of BOLD and CBF increases during hypercapnia, as CBV increase is probably the most direct effect of vasodilation due to CO2 acting on the vascular smooth vessels. In addition, there are several notable changes in the physiologic parameters that may also affect brain perfusion. The blood pressures (systolic, diastolic and mean arterial pressure) showed an increase by about 15mmHg. Since the blood flow is proportional to perfusion pressure, which is the difference between arterial pressure and intracranial pressure, this increase in MAP might have contributed to the blood flow increases observed in literature. For breath holding, it appears that a 24s of breath holding can result in similar changes in EtCO2 (10mmHg). However, since CO2 breathing is involuntary and breath hold is voluntary, these two hypercapnia challenges may have different autonomic nerve system activities and thereby differences in other physiologic parameters. This might explain the specific HR pattern observed during the breath-hold (Fig. 1a). Specifically, the HR shows a transient decrease upon holding the breath, then a return (perhaps even an overshoot) upon resuming breath. Moreover, in this subject, there also appears to be a transient drop in arterial oxygenation at the end of breath holding. Breath holding also causes a VASO signal decrease, consistent with a previous report (1). The possible blood pressure change associated with breath holding could not be evaluated, as our blood pressure measurement only has a temporal resolution of 2 min. Fig. 2b shows the results from another subject. Similar patterns in the physiologic parameters are observed. However, in the VASO signal, the pattern is slightly different in that the signal change adapts considerably after an initial signal jump. Specifically, when switching from room-air to 5% CO2, the VASO signal decreases in the initial period, then slowly return back to baseline level. Similarly, when switching from CO2 to room-air, the signal increases first then slowly reduce back to baseline. Therefore, the signals at the end of each breathing period are actually very similar, regardless what kind of air the subject is breathing. The differences in VASO signal behavior between these two subjects may have the origin from their EtCO2 time-courses, in which subject 1 showed a slow change and subject 2 showed a rapid change accompanied by an undershoot. A more thorough investigation is needed to understand the precise mechanism for these differential responses. We should note that subject 1 is a hypertensive 60 yo female and subject 2 is a 46 yo female, and it is possible that the difference is age-related. Nonetheless, it is evident from our data that high temporal resolution dynamic scans are important for studies of vascular reactivity, as the vascular systems are not always at a steady state, and single point measurement may not catch important features of the vascular responses. It also appears that CO2 breathing is a more useful challenge in comparison with breath holding because 1) breath holding may involve many other mechanisms related to voluntary stop of breathing; 2) the duration of breath holding is limited by physiology and may vary among subjects. In summary, fMRI techniques (not only VASO fMRI, but also BOLD and ASL) have great potentials for studies of cerebral vascular reserve, and may become a useful tool for clinical evaluations of vascular risk factors.

REFERENCES: 1) Lu et al. MRM 50: 263, (2003); 2) Cohen et al. JCBF&M 22:1042 (2002);

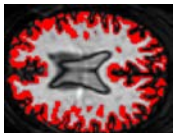

Fig. 1: Gray matter mask that was used for spatial averaging of VASO signals.

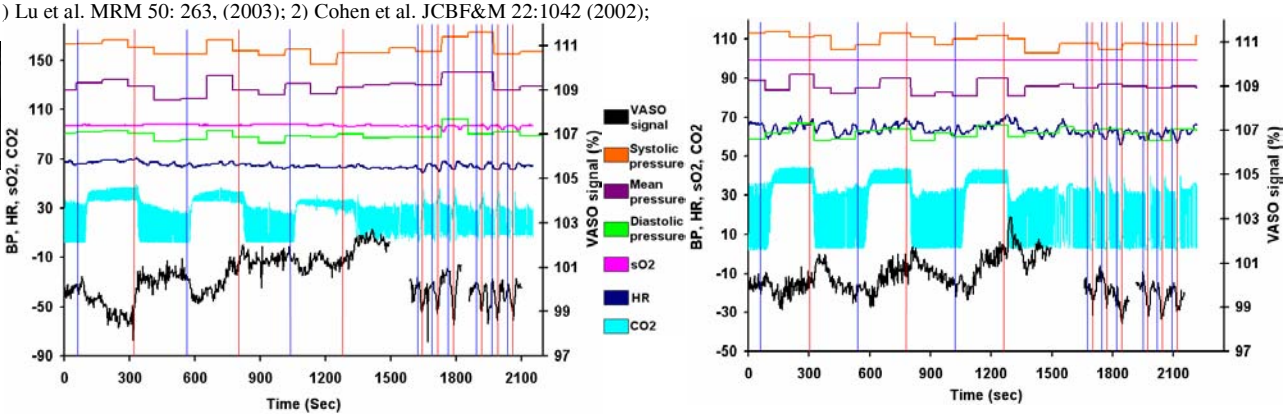

Fig. 2: VASO MRI signal and physiologic parameters from (a) subject 1 and (b) subject 2. The blue and red vertical lines indicate the start and end of the hypercapnia, respectively. Three VASO MRI scans were performed: 1 CO2 scan followed by 2 breath-hold scans.