Effects of Hypercapnia on DTI Quantification

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Introduction

Diffusion Tensor Imaging (DTI) offers a valuable *in vivo* tool to characterize water diffusion behavior in biological tissues, particularly brain tissues. To such principle, it can be predicted that quantification of diffusivity might be interfered by the presence of cerebral vasculature. However, knowledge about the degree of influencing of vasculature effects towards diffusion indices is limited. In this study, we employed a hypercapnia model which will cause passive dilation of blood vessels and increase blood flow by inhaling 5% carbon dioxide (CO_2) [1]. *In vivo* DTI experiment was performed and cerebrovascular response was confirmed by BOLD [2]. Thus, the correlation of blood flow and diffusivity values were investigated to provide substantial information on applying *in vivo* DTI for evaluating brain tissue as well as exogenic vascular regulations.

Methods

Stimulation Paradigms: Normal adult Sprague-Dawley rats (N=7) were kept warm at normal temperature and inhaled isoflurane anesthesia (3% induction and 1.5-2% maintenance). Each scan included 48 continuous DTI acquisitions which were segmented into 6 couples of OFF/ON periods by manually switching room air (OFF) or 5% CO_2 (ON) circulation into the animal mouth cone at certain time points. Each couple of OFF/ON period included 5 DTI acquisitions for normocapnia (OFF) with room air inhalation and 3 DTI acquisitions for hypercapnia (ON) with 5% CO_2/air inhalation.

MRI Protocols: All MRI measurements were acquired using a 7T Bruker scanner. In vivo Diffusion-weighted (DW) images were acquired with a spin echo 2-shot EPI readout sequence with encoding scheme of 6 gradient directions. 5 additional Images with b-value = 0 (B_0 images) were also acquired [3, 4], yielding a scan time of 81.4 seconds per DTI acquisition. The imaging parameters were: TR/TE=3700/29.97ms, δ/Δ=5/17ms, FOV=5 x 5cm^2, acq matrix = 96 x 96, slice thickness = 1mm (0.5mm gap), b-value of 1000s/mm^2. Monitoring of respiration rate, heart rate, arterial oxygen saturation and rectal temperature were performed by animal probe (SA-Instruments, Stony Brook, NY) throughout the experiments and were shown in Fig.1.

Data Analysis: All the DTI derived parametric maps were analyzed using the STIMULATE software package (STIMULATE, Center for Magnetic Resonance Research, University of Minnesota). Percentage changes of mean diffusivity, axial diffusivity, radial diffusivity and FA were calculated from activated voxels generated by fixing the correlation threshold at 0.2 and were averaged across stimulations and animals. The activated voxels in whole brain included for each parametric map analysis were shown in percentage in Table 1. When averaging the DTI derived values for normocapnia and hypercapnia conditions, the first 3 trials of each OFF period were considered to be recovery time, and the first trial of each ON period was considered to be activation rise time [5, 6]. Therefore 2 trials of OFF periods and 2 trials of ON periods were used to evaluate the signal changes between normocapnia and hypercapnia as shown in Table 1. Voxel-based two-sample t-test analysis was also performed on mean diffusivity and B_0 with threshold of $p<0.05$ using SPM5 (FIL, UCL, London, UK).

Results and Discussions

The statistical dependence of trace (Fig.2A) and B_0 value (Fig.2B) between normoxia/hypercapnia has shown strong evidence of diffusivity change accompanied with BOLD effect which indicated the elevation of both CBV and CBF caused by hemodynamic activation under hypercapnic challenge [5]. And the statistical significance concentrated on the cortex and subcortical grey matter in brain also suggested that typical regions which contained abundant vasculatures might be more susceptible to hemodynamic changes [7]. Furthermore, the averaged stimulus-induced diffusivity changes shown in Fig.3 demonstrated that axial diffusivity, which was used to interpret the principal diffusion direction in microstructures, had a further increase up to 10% when compared with radial and mean diffusivity. As illustrated in Table 1, the activated voxels, which exhibited high correlation between hypercapnic challenges and diffusion quantification changes, accounted for about one third of the whole brain area. In addition, different trends but substantial FA value changes were observed in different parts of brain. These quantification alterations correlated with CO_2 manipulations significantly, hence might be contributed by the cerebral vascular smooth muscle response to the increased partial pressure of CO_2 which would enhance the ion exchange in local acidic environment and resulted in passive vessel dilation as well as decreased resistance of cerebral arterial smooth muscle [5]. It is also noteworthy that isoflurane, which was used for anesthesia in this study, is a potent cerebrovasodilator that increases basal CBF. Thus it may reduce the hypercapnia-evoked hemodynamic effects as well as diffusivity changes [6].

Conclusions

As observed from this *in vivo* study, changes occur in all parametric DTI maps at activated voxels in response to hypercapnia induced cerebrovascular changes, suggesting that vascular factors may interfere with *in vivo* DTI characterization of neural tissues in normal anesthetized animals. Our data implied that these alterations could lead to change in different diffusivity index to a variable extent, but more apparent changes may be observed in axial direction. Different activated voxel localizations in brain exhibited opposite trends in FA quantification corresponding to hypercapnic stimulation. Consequently, hemodynamic challenges can potentially affect the DTI quantification of tissue microscopic diffusivities and possibly lead to contamination towards pathological alterations. When exogenic vascular regulations happened and small voxel size evaluations were performed for *in vivo* DTI, these quantification interferences would become more complicated and problematic. Therefore, cautions must be taken when interpreting DTI parameters *in vivo.*

References

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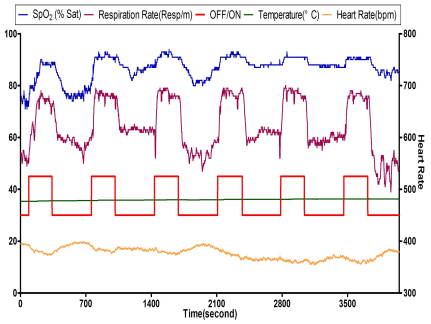

Fig.1. Continuous physiology records of heart rate, respiration rate, rectal temperature, and SpO_2 during six couples of OFF/ON periods.

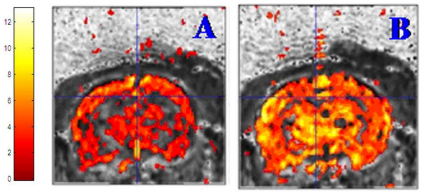

Fig.2. Statistical map overlaid on FA map of an animal. Voxel-based two-sample t-test was perform respectively on trace (**A**) and B_0 (**B**) from 48 time points of normocapnia (OFF) and hypercapnia (ON) with threshold of $p<0.05$.

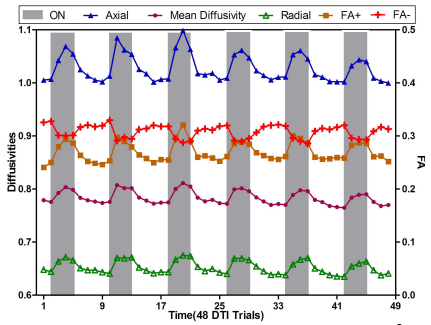

Fig.3. Axial, radial, mean diffusivity (in mm^2/s) and FA values measured from activated voxels of a representative animal during 48 continuous DTI acquisitions. Gray swathes indicate hypercapnia stimulation periods.

	Diffusivity change %	Activated voxels %
MD	5.5±2.4%	38.6±16.4%
Axial	8.1±5.2%	28.5±11.8%
Radial	6.3±2.9%	28.3±12.9%
FA	16.3±13.8%	14.9±9.9%
	-10.6±5.3%	11.5±3.5%

Table 1. Percentage changes in DT-derived parameters and the percentage of measured activated voxels in whole brain for each map are presented as inter-animal mean±inter-animal standard deviation.