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Detection of KCl Induced Cortical Spreading Depolarization (CSD) with Dynamic Ultrafast Doppler

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***Abstract*—Cortical spreading depolarization (CSD) reflects neuronal depolarization slowly propagating in the cortex and is accompanied with vascular response. Dynamic ultrafast Doppler has potential to access the hemodynamic response to CSD, specifically to the penetrating vessels in the cortex. In this study, the CSD was experimentally triggered by topical application of potassium chloride (KCl) on the surface of the brain. The vascular response caused by KCl induced CSD was successfully detected during the dynamic ultrafast Doppler. The propagation of vascular responses from the center of right cortex (stimulated side) to the medial and lateral side was observed. The perfusion change (∆CBV) decreased over 30 % from the baseline at the beginning, and the CBV response subsequently elevated dramatically to over 30% very likely due to vasodilation. At the end of episode, CBV decreased slowly along the time. In this study, we firstly detect the vascular responses caused by KCl induced CSD with the dynamic ultrafast Doppler.**

Keywords—Cortical spreading depolarization (CSD), ultrafast Doppler, functional ultrasound (fUS)

I. INTRODUCTION

Cortical spreading depolarization (CSD) reflects neuronal depolarization slowly propagating (2~8 mm/min) in the brain cortex, which can be induced by noxious stimulation including but not limited to electrical, hyperthermia, or chemical/ionic stimuli, to the brain tissue. In addition, CSD is highly associated with vascular response indicating brain pathology caused by injuries, such as migraine, ischemia, traumatic brain injury, epilepsy etc [1-2]. To date, it is still hard to explain the heterogeneity of CSD and to understand the relationship between benign migraine to the subsequent brain injuries. Hemodynamics of CSD, say vasodilation and constriction through neurovascular coupling, also plays an important role to the brain homeostasis and pathology. In the past years, CSD and its vascular response were studied using multispectral reflectance, near-infrared spectroscopy, light transmission, laser Doppler and intravascular fluorescence imaging [3]. However, most of tools for flow monitoring can only detect flow changes from pial vessels on the surface of the brain. It is hard to recognize and investigate the flow change "in" the cortex or even in the sub-cortical regions.

Ultrafast Doppler, which is also called functional ultrasound (fUS), is a quantitative vasculature imaging able to access hemodynamics in the whole brain. Ultrafast Doppler gained the sensitivity primarily based on the ultrafast imaging [4], which is achieved by the plane wave imaging with reduced transmission time as shown in Fig. 1. The imaging frame rate is up to 2k~10k frames per second (fps). In addition, the spatial resolution and sensitivity can be further improved using multiple plane wave coherent imaging to form a high quality images, and then an advanced spatiotemporal clutter filters can be conducted for differentiating low blood flow from stationary tissues. Therefore, ultrafast Doppler is sensitive to the perfusion in the brain, say cerebral blood volume (CBV) and cerebral blood flow (CBF) in the individual small vessels. This imaging technique can be an important imaging tool to conduct functional neuroimaging and access brain functional connectivity in the small animals [5-9] or even in the behaving primates [10].

Dynamic ultrafast Doppler has potential to access the hemodynamic response to CSD in the whole brain, and also to

quantify flow responses from specific brain area to a single vessel. In this study, ultrafast Doppler, cooperated with ECoG recording, was proposed to dynamically monitor the vascular responses due to potassium chloride (KCl) induced CSD and to verify the CSD induction, respectively.

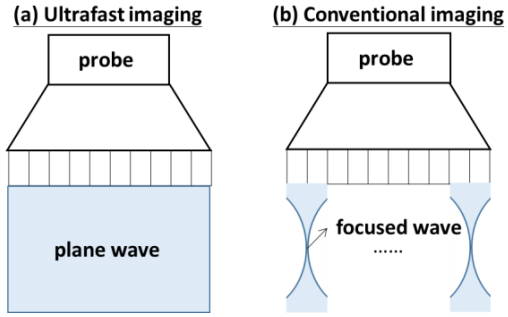

Fig. 1. a). For ultrafast ultrasound, plane ultrasonic waves are emitted, b). For conventional ultrasound, focused ultrasonic waves are used.

II. Method

A. Animal Preparation and Experimental Setup

The Sprague-Dawley rats weighting ~250g were used in this study. The animals was anesthetized under zoletil at the beginning. During the experiment, isoflurane (0.5-1%) was applied for anesthesia. Before imaging, the craniotomy was performed to remove the skull on the top at the bregma. The size of imaging window is 10 mm (width)× 3 mm (length). The high-frequency transducer was fixed on the three-dimensional translation stage. The space between the transducer and the brain was filled with ultrasonic gel for acoustic coupling. The imaging plane was placed on the bragma to sequentially acquire the coronal section image in the rat brain. In addition, two bur holes, one for KCl stimulation and the other for ECoG recording, were prepared as shown in Fig. 2(a). During the imaging, the CSD was experimentally triggered by topical application of K^+ (2M KCl) on the surface of the right brain. The recording ECoG electrode was placed between stimulation spot and the imaging plane.

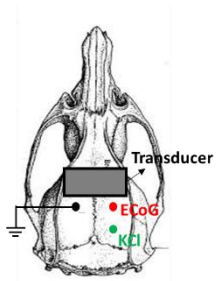

Fig. 2. Experimental preparation (imaging window is at bregma, red dot is for EcoG recording and green dot is for KCl stimulation)

B. Ultrafast DolpperImaging Sequence

An imaging system (Prodigy, S-Sharp, Taiwan) cooperated with a 16.4 MHz transducer was used for ultrafast Doppler imaging. The imaging sequence which is a 12 angles (from -11° to +11° with a 2° interval) plane wave imaging was conducted at the imaging frame rate of 5,000 fps, and 64 compounding images were acquired for one Doppler frame. The compounding frame rate is 416 fps. The imaging processing is based on the ultrafast Doppler technique followed a singular value decomposition (SVD) filter. The energy distribution of Doppler blood flow can be analyzed by the incoherent correlation matrix of spatial singular vectors obtained by SVD filter [8]. The blood flow signal can be extracted in an adjustable SVD filter, and the stationary tissue signal can be filtered out to obtain an ultrafast Doppler cerebral blood flow image. The use of the filter can effectively differentiate the static signal of tissue and micro-blood flow. For monitoring vascular responses, multiple Doppler frames were recorded and the interval between frames is 15 seconds. The electrophysiological signal was recorded as well. The diagram of imaging acquisition is shown in Fig. 3. 120 frames in total were recorded as the recording time was 30 minutes to monitor the cerebral blood volume change caused by CSD. The CBV changes (△CBV) were estimated by the equation (1).Let avg.=$\sum_{i=1}^{n}\frac{X_i}{n}$.

$$\mathbf{\Delta CBV = 100 \times [avg.(\frac{I_{1,2,3,\ldots\ldots,n} - I_{1-15}}{I_{1-15}})_{ROI}]} \quad (1)$$

The difference between the mean values within the ROI in the sequential Doppler images and that in the CBV baseline, say the first to the 15th images before the stimulation were calculated, then were normalized to the first image, and were multiplied by 100. The ΔCBV can be calculated and tracked in both right (stimulated side) and left (reference) side.

In addition, we further investigated the time-intensity curves (TIC) affected by the selection of (1) ROI size (1.24×1.24 mm, 0.62×0.63 mm, 0.31×0.31 mm), (2) rank of the singular value (25~60, 15~60, 15~50), and (3) the positions of the ROI (the middle to the periphery of the cortex).

III. Results

A. Detection of cerebral blood volume change (ΔCBV) caused by CSD

The vascular response caused by KCl induced CSD was successfully detected by the dynamic ultrafast Doppler. The single ultrafast power Doppler [Fig. 4(a)] shows the vasculature and hemodynamics of the brain. In the right cortex, the vascular response shows the triphase response [Fig. 4(b)]. The decreased CBV (over 30 % from the baseline) was observed at the beginning due to vasoconstriction. Subsequently, the CBV response elevated dramatically to over 30% very likely due to vasodilation. At the end of the episode, CBV decreased slowly along the time. The drop of electrophysiology signal by simultaneous ECoG recording substantiated the appearance of CSD.

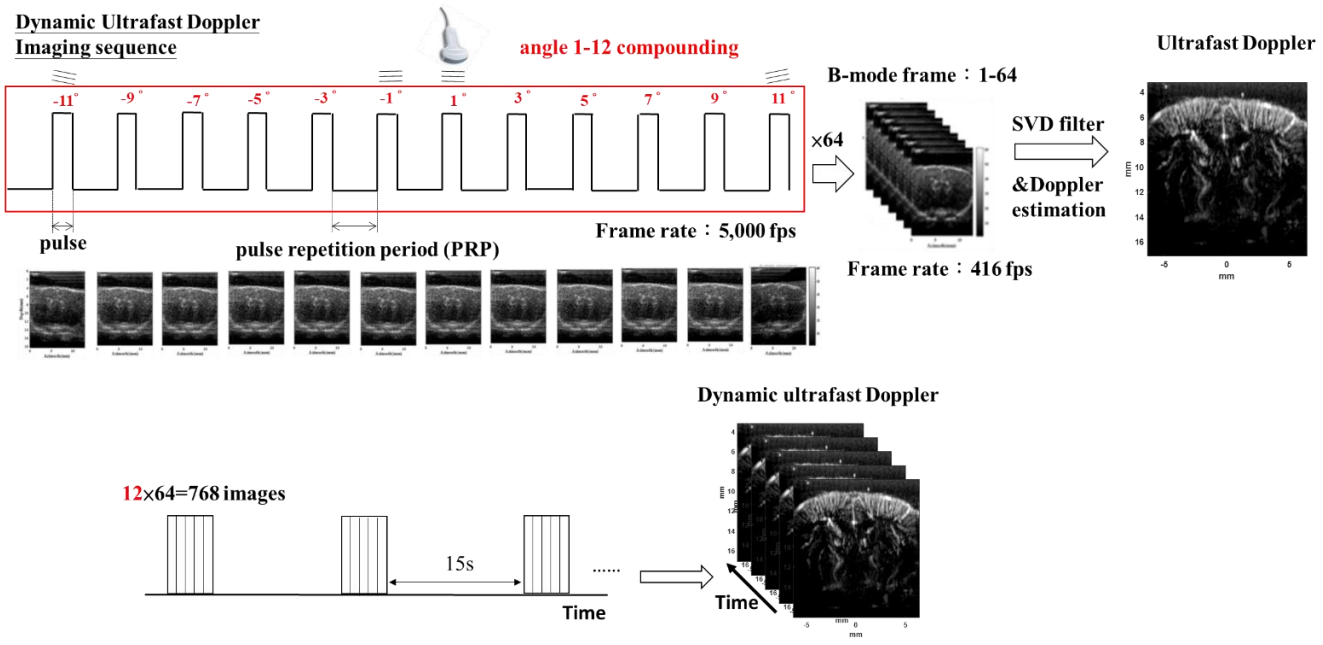

Fig. 3. Dynamic ultrafast Doppler imaging sequence: a 12 angles (from -11° to +11° with a 2° interval) plane wave imaging was conducted at the imaging frame rate of 5k fps, and 64 compounding images were acquired for one Doppler frame. 100 Doppler frames were recorded and the interval between frames is 15 seconds.

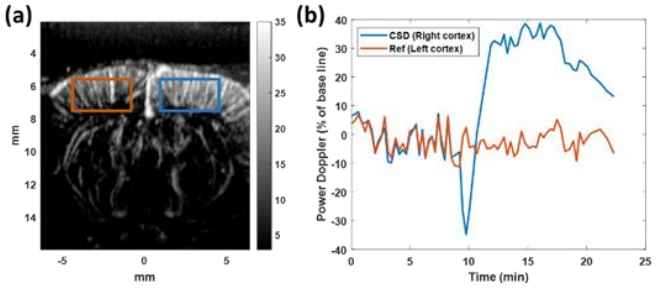

Fig. 4. a) Ultrafast Doppler image of the rat's brain at bregma +0.00 mm, b) dynamic ultrafast power Doppler signal within the right (CSD) and left (Ref) cortex.

B. *Time-intensity curve under the different SVD rank selection*

In the ultrafast Doppler, the main component of flow need to be extracted from the stationary tissue signals by an optimized SVD filter. The lower rank and the high rank of vectors show the stationary tissue and high speed flow, respectively. When using the SVD filter, we need to decide the different SVD rank to filter out non-moving tissues and noise. Fig. 5(a) shows the TIC curves under the different SVD rank (25~60, 15~60, 15~50). We found that the level with the rank between 25~60 is slightly higher than that between 15~60, suggesting that the lower rank is the key factor to remove the signals from the stationary tissue and keep the flow signals. On the other hand, the TIC curves under the rank 15~60 and 15~50 were almost the same, which means both of them can be used to remove the noise and tissue motion in these cases. Based on these results, the rank 15~60 was applied to the all images of the dynamic ultrafast Doppler frames.

C. *Time-intensity curve under the different size of the ROI*

Since CSD occurs in the cortical area rather than the whole brain, we have to analyze the CBV change within the selected ROI. Fig. 5(b) shows the TIC curves in the different size (1.24×1.24 mm2, 0.62×0.63 mm2, 0.31×0.31 mm2) but with the same center position. In this result, the vascular responses have the same phenomena, including the amplitude of ΔCBV and the timing of the vasoconstriction and vasodilation as shown in Fig. 5(a). It was suggested that the size of ROI is not a factor to dramatically change the TIC curve in the dynamic ultrafast Doppler images.

D. *Observation of CSD induced ΔCBV propagation*

The propagation of CSD-induced CBV response was obviously observed in the time-series Doppler images. The propagation of vascular responses from the center of right cortex to the medial and lateral side was observed. Fig. 5(c) shows the TIC calculated from the ROI at 3 different locations in the right cortex. The time delays were found in these three curve, which means the vascular response propagate from the center to outward.

IV. Discussion and Conclusion

Ultrafast Doppler imaging is a quantitative vasculature imaging to map hemodynamics in preclinical small animal brains. It is a powerful tool to monitor the cerebral vascular responses caused by CSD .

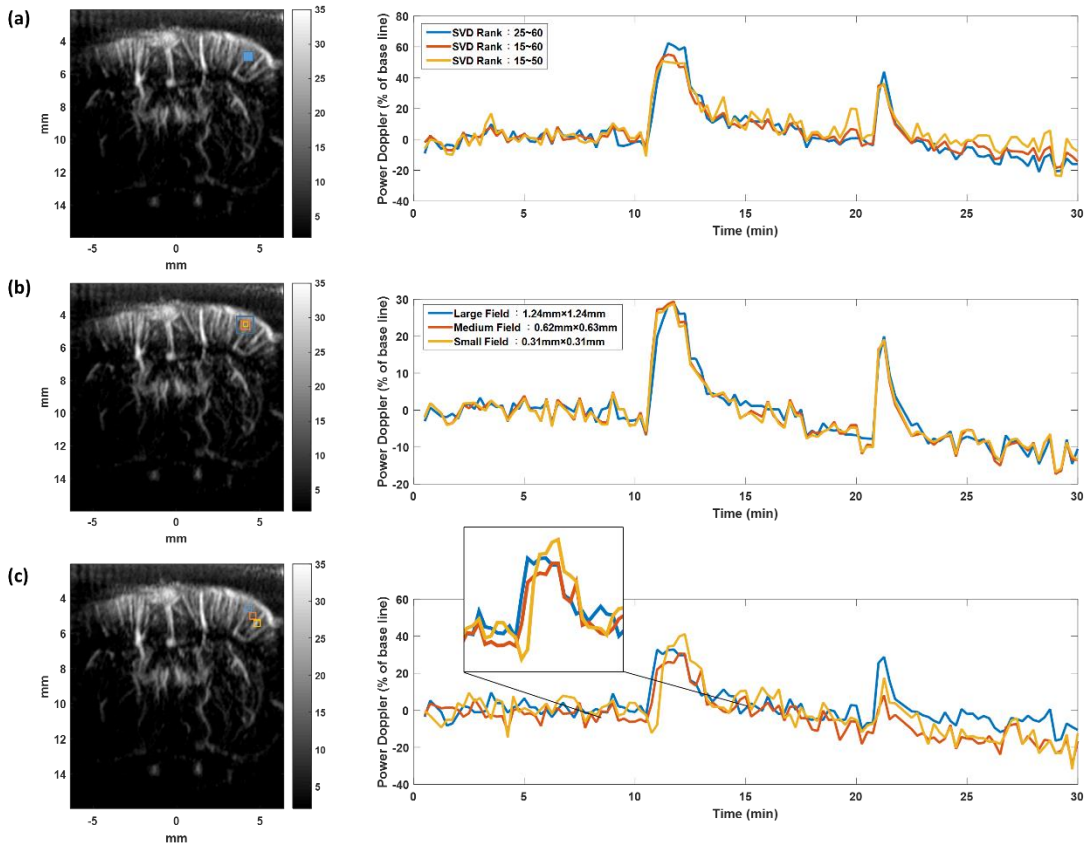

Fig.5. Ultrafast Doppler image are shown on the left and the ROI for TIC calculation are labeled in the images. a) Three different size (1.24mm×1.24 mm, 0.62mm×0.63 mm, 0.31mm×0.31 mm) ROIs were selected for analysis under SVD rank 15~60. b) Three different SVD rank (25-60, 15-60, 15-50) were selected for analysis. C) Three different positions were selected for analysis.

From this result, we firstly detect the vascular responses caused by KCl induced CSD with the dynamic ultrafast Doppler. It has potential to access the hemodynamics of cortical vessels during brain injuries with dynamic ultrafast Doppler to understand the mechanism of CSD in advance.

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