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Monitoring of Vascular Response to Peri-Infarct Depolarization (PID) in Photothrombotic Stroke Animal Model

Yu-Chieh Jill Kao
Neuroscience Research Center;
Department of Radiology,
College of Medicine
Taipei Medical University
Taipei, Taiwan
ykao@tmu.edu.tw

Bao-Yu Hsieh
Department of Biomedical Imaging and Radiological Science,
China Medical University,
Taichung, Taiwan
byhsieh@mail.cmu.edu.tw

***Abstract*—Peri-infarct depolarization (PID) is abnormal transient depolarization waves slowly propagating in the cortex and confined in the ipsi-lesional cortex in accompanied with dramatic cerebral blood flow change. Ultrafast Doppler is a quantitative imaging method to investigate both CBF and CBV in a high spatiotemporal resolution and to measure the hemodynamic response of penetrating vessels in the cortex. In this study, the hemodynamics of cortical vessels during stroke-induced PID was monitored by the dynamic ultrafast Doppler under the animal model of photothrombotic stroke. The propagating PID-induced blood flow change (△CBV) initiated from the center of the stoke induction site and propagated outward in the right cortex. This study, for the first time, introduces a novel platform to demonstrate that dynamic ultrafast Doppler is feasible to monitor PID during acute stroke.**

Keywords—peri-infarct depolarization (PID), stroke, functional ultrasound (fUS), ultrafast Doppler

I. Introduction

Peri-infarct depolarization (PID) induced by ischemic stroke is a transient depolarization wave slowly propagating in the cortex in accompanied with dramatic cerebral blood volume (CBV) change in the acute phase of insult [1-3]. PID may exacerbate ischemic injury, as the number of PID correlates with the penumbral volume, final infarct volume and functional deficit outcome [4].

Ultrafast Doppler has potential to quantitatively measure both CBF and CBV in a high frame rate and to specifically focus on the hemodynamic response of penetrating vessels in the cortex [5-7]. In this study, we will probe the hemodynamics of cortical vessels during stroke-induced PID with dynamic ultrafast Doppler to monitor the event of PID in advance.

Photothrombosis has been used to induce ischemic stroke lesion by illuminating the brain after injection the photosensitive dye, rose Bengal, which produces highly reproducible ischemic lesions [8]. The location and even the size can be easily controlled by the alignment and laser power, duration etc. [4]. In addition, the stroke lesion can be induced in parallel with MRI acquisition.

In this study, we aimed to track the dynamic vascular response caused by cortical spreading depolarization (CSD)/peri-infarct depolarization (PID) under the acute stroke progression with ultrafast Doppler.

II. Materials and Methods

A. Animal preparation

The adult male Sprague-Dawley (SD) rat weighting ~250g was anesthetized with isoflurane, and the head was fixed at the stereotaxic during the ultrafast Doppler imaging. Before imaging and stroke induction, the craniotomy was performed to remove the skull on the top of the brain. For photothrombotic (PT) stroke, the brain surface (5.3 mm posterior to the bregma) was exposed by 20 mW green laser (532 nm, 1 mm spot size in diameter) for 15 minutes [Fig. 1]. The laser was turned on at the beginning during the imaging acquisition. The rose bengal (10 mg/ml, i.v.) was administered 5 minutes after the laser was on. The imaging plane was at bregma, not at the location of induced stroke. The total imaging acquisition time is 25 min. The whole brain synthetic aperture (SA) B-mode and ultrafast Doppler images were acquired before and after the stroke induction, respectively. Two control animal experiments were performed under the reference condition of (1) laser irradiation only, without rose bengal injection, and (2) rose bengal injection only, without laser irradiation, to compare with PT animals.

B. Ultrafast Doppler imaging and data analysis

For ultrafast Doppler imaging, a 16.4-MHz linear array transducer and a programmable ultrasonic system (Prodigy, S-Sharp, Taiwan) was used in this study. 12-angle (-11°, -9°, -7°, -5°, -3°, -1°, 1°, 3°, 5°, 7°, 9°, 11°) coherent compounding plane-wave images at pulse repetition frequency (PRF) of 5k Hz was conducted for imaging acquisition. 64 compounding images as 768 firings in total were acquired for one Doppler frame. The compounding frame rate is 416 fps to track Doppler signals in

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the brain. The imaging processing is based on the ultrafast compound Doppler imaging technique followed a singular value decomposition (SVD) filter [9] was applied. For monitoring vascular responses, multiple Doppler frames were recorded for 23 minutes and the interval between frames is 15 seconds. The 100 Doppler frames were recorded to dynamically monitor the perfusion in the brain.

Dynamic perfusion change in the region of interest (ROI) can be calculated through time frames by a custom-written program in Matlab [Fig. 3(a)]. Power Doppler enhancement (%) or cerebral blood volume change (ΔCBV) to the baseline can be calculated as the following equation (1).

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

The ΔCBV before the stroke induction in the right (stroke induction) and the left cortex as reference were estimated, and the CBV change image with time were co-registered to the B-mode images.

In addition, the whole brain scans with 0.5 mm step size were performed before and after PT treatment as well to confirm the stroke ischemic core formation. After the US imaging, the imaging window on the skull was covered by dental cement. The stroke lesion was further confirmed by MRI ADC image at acute phase and T_2-weighted images in 48 hours after stroke.

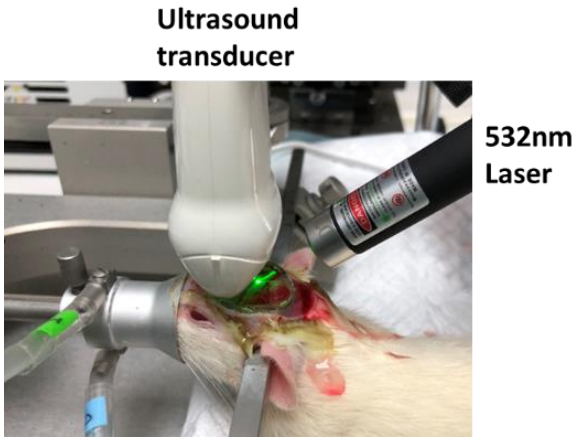

Fig. 1. Experimental setup for animal preparation.

III. Results

A. B-mode and ultrafast Doppler imaging of the infarct lesion

Fig. 2 shows the synthetic aperture (SA) B-mode structural image and ultrafast Doppler images before and after PT stroke. In the B-mode images at bregma -3.96 mm, there is no difference before and 25 min after PT stroke. However, the loss of vasculature on the right cortex (red arrow) validates the success in stroke induction of this animal model in the ultrafast Doppler images. The lesion can be identified in multiple slices. The location and stroke lesion were also confirmed by MRI ADC and T_2-weighted images in the acute and chronic phase, respectively. The lesion size and the location of stroke shown in MRI matched the ultrafast Doppler image shown in Fig. 2, which suggested that the ultrafast Doppler imaging can be used to visualize the infarct lesion of the stroke in the acute phase.

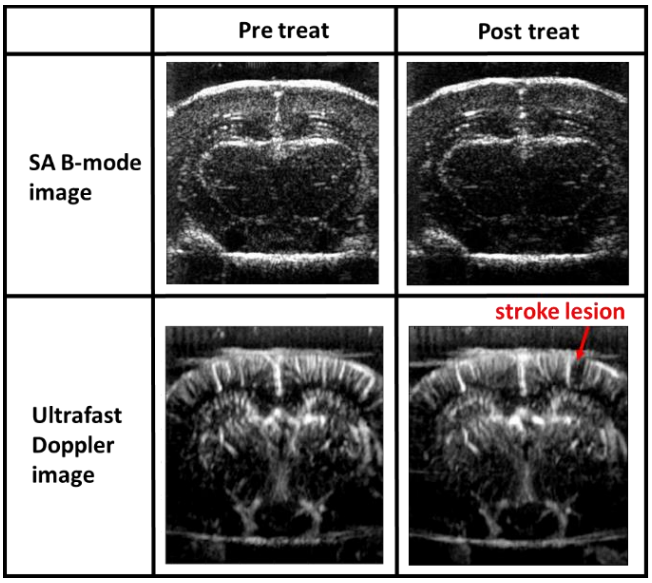

Fig. 2. Synthetic aperture B-mode and ultrafast Doppler vasculature images before and after PT treatment.

B. Time-intensity curve of ΔCBV

In the time-intensity curve (TIC) within the right cortex, there is no apparent change at the beginning when only the laser was illuminating the brain tissue (w/o the drug). The PID was detected with a short delay after the rose bengal injection, which is correlated with stroke induction. PID was initiated in the infarct lesion and then propagated to the site of imaging. This is in line with that the PID was presumed to be generated at the ischemic region where was illuminated by the laser spot, then propagated outward. In the series of sequential ultrafast Doppler images, we can investigate that the PID-induced perfusion change appeared from the center of the right cortex, propagated outward and confined in the ipsi-lesional cortex.

The dynamic results showed the consistent trend as that the CBV decreased at the beginning of the first PID, which corresponding to hypoperfusion due to vasoconstriction. The CBV elevation greater than 20% of the basal flow along with the draw back or even overshot was observed during the following PIDs [Fig. 3(b)]. Multiple CBV changes were shown in this representative animal in the ipsi-lesional hemisphere, suggesting multiple PIDs were appeared in the acute phase of PT stroke. In contrast, the left cortex has no change in the perfusion.

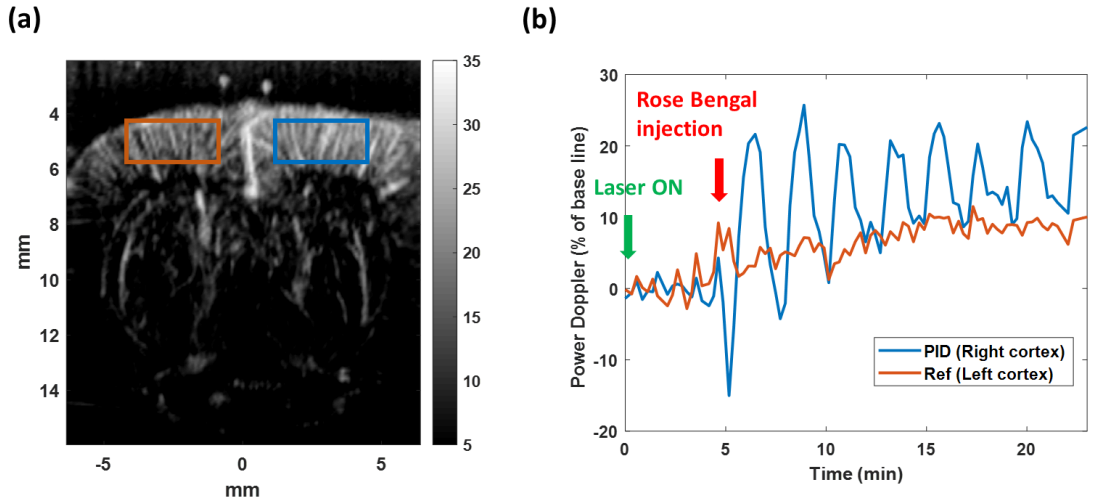

Fig. 3. (a) Ultrafast Doppler image and region of interest (blue rectangular: stimulated side; orange rectangular: reference side), (b) Dynamic ultrafast Doppler signals within the right (PID induction) and left (Ref) cortex.

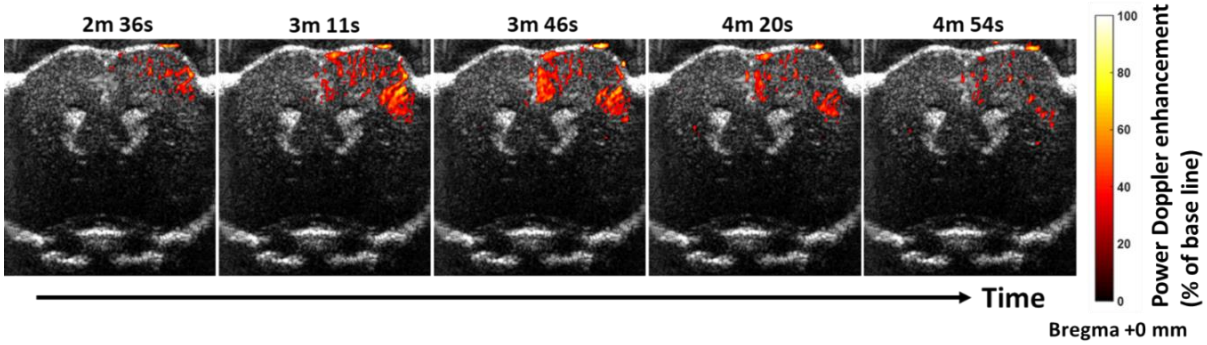

Fig. 4. Vascular response wave propagation images.

In addition, we can observe the propagating CBV enhancement during single episode of CSD confined in the ipsi-lesional cortex at the imaging plane [Fig. 4].

IV. Discussion and Conclusion

This study, for the first time, introduces a novel platform to monitor PID associated vascular response with dynamic ultrafast Doppler in the PT stroke animal model. This is a pioneer study, and more animal data need to be collected in the near future. With this imaging tool, the number of PID correlates with the final infarct volume and functional deficit outcome can be further investigated to understand the mechanism of PID in advance and to predict the outcome after stroke.

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