tPA-induced Suppression of Cerebrovascular Parameters in Acute Rat Stroke Model: Dynamic MRI Study

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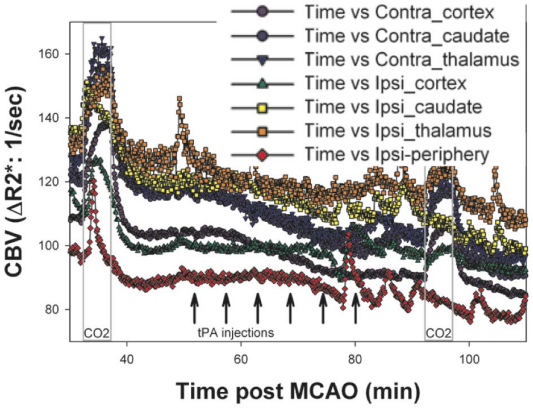

Figure 1. Representative ΔR2*(t) from various ROI's from a rat with a permanent MCAO (ipsi-: stroke).

INTRODUCTION

Tissue plasminogen activator (tPA) has been frequently used for treating acute ischemic stroke based on the "re-canalization hypothesis," i.e., reopening of occluded vessels by lyses of the blood clot improves the clinical outcome via reinstitution of regional blood perfusion. Despite the promising results, exogenous tPA may worsen the ischemia-induced blood brain-barrier disruption, elevate risks of intracranial hemorrhage, and in part consequently reduce the therapeutic time window. Emerging data suggest that exogenous tPA may have pleiotropic actions in the brain, which include abnormal vasoactivity and activation of extracellular proteases for neurovascular injury. Therefore, it is critically important to understand the overall effects of tPA treatment on cerebrohemodynamics. In this study, we investigated the vasoreactivity in response to intravenously administered tPA and to systemic hypercapnia before and after tPA using a permanent focal stroke rat model.

MATERIALS AND METHODS

Two Wistar male rats (~270 g) undergone permanent suture occlusion of middle cerebral artery (MCAO) were used. During MRI sessions (Bruker 9.4T scanner), mechanically ventilated rats were anaesthetized with alpha-chloralose while blood pressure, body temperature, and pulse/oxygen saturation were continuously monitored. For measuring dynamic vasoreactivity, we quantified vascular reponses to IV injections of tPA (10 mg/kg for 30 min) and CO_2 (5% CO_2, Air/Oxy: 47.5/47.5% for 5 min) before and after the tPA administration (see Fig 1 and 2 top). T2- and T2*- weighted images were acquired before and after administering a blood pool superparamagnetic iron oxide nanoparticles (SPION: 36 mg/kg) using single shot EPI. Specifically, time courses of $\Delta R2^*(t)$ ($= 1/T_2^*(t)_{(post\text{-}SPION)} - 1/T_2^*_{(pre\text{-}SPION)}$) and $\Delta R2(t)$ ($= 1/T_2(t)_{(post\text{-}SPION)} - 1/T_{2\,(pre\text{-}SPION)}$) maps were created using alternating gradient and spin echo (GE, SE) EPI acquisitions (TR/TE = 3000/12 and 3000/25 ms for GE and SE, respectively). Cerebral blood volume (CBV(t) ~ $\Delta R2^*(t)$) and microvascular volume (MVV(t) ~ $\Delta R2(t)$) were calculated, from which vessel size index (VSI(t)) maps (~$\Delta R2^*(t)$ / $\Delta R2(t)$) were quantified assuming one GE SE epoch as a time point.[1,2]

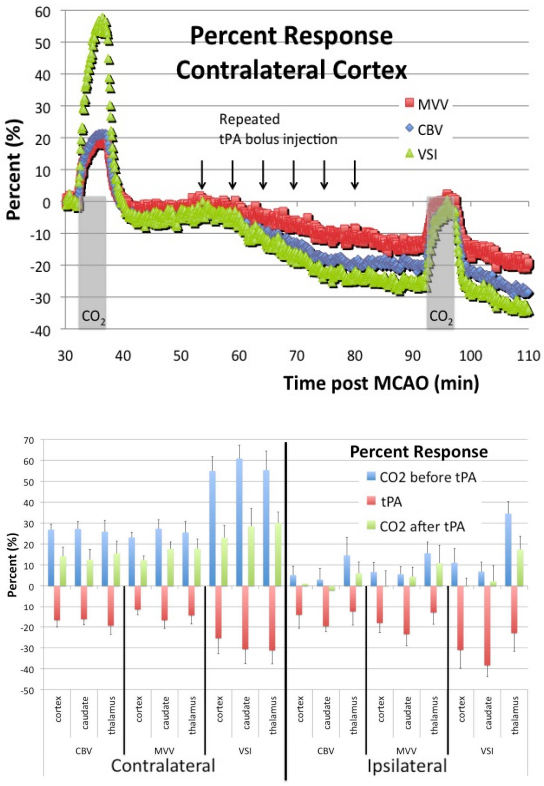

Figure 2. Top – representative % changes in CBV, MVV, and VSI in response to tPA and CO_2 in contralateral cortex. Bottom – % responses from cortex, caudate and thalamus in contralateral and ipsilateral (stroke) hemispheres.

RESULTS AND DISCUSSION

For continuously monitoring VSI, we alternated gradient echo and spin echo EPI acquisitions. During the 1st CO_2 episode before tPA injections, CBV, MVV, and VSI all increased significantly (Fig 2 top). However, temporal profile (i.e., delay and shape) and response magnitude of these vascular parameters were largely different between the ipsi- (stroke) and the contralateral brain regions (Fig 1 and 2 bottom). We also demonstrated that both CBV and MVV quickly decreased after the tPA injection and continuously decreased for the rest of experiment, in which VSI also decreased (Fig 2 top). This strongly suggests the prolonged effect of tPA-induced cerebral vasoconstriction. After tPA injections, CBV, MVV, and VSI still responded to the 2nd hypercapnia (Fig 2); however, the response magnitudes were consistently lower than those measured in the 1st hypercapnia. Surprisingly, despite the reduced response to CO_2 in the ipsilateral hemisphere compared to the contralateral counterpart, tPA-induced vaso-suppression near equally and significantly affected both ipsi- and contra-lateral hemispheres (Fig 2 bottom). Although dose-dependent effects of tPA vasoactivity and interaction with tPA thrombolytic activity need to be further investigated, the data suggest that tPA may cause cerebral vasoconstriction and impair vasodilatation, contributing to altered cerebrohemodynamics of tPA-treated ischemic brains.

REFERENCES **1.** Dennie J, *et al. Magn Reson Med* 40(6):793-799. **2.** Kim YR, *et al. J Cereb Blood Flow Metab.* 25(7):820-829.