How Long Does It Take Before ADC Reduction Becomes Irreversible?

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INTRODUCTION Ischemic stroke occurs when basal cerebral blood flow (CBF) falls below a critical threshold (1-4), resulting in energy failure which subsequently manifests into a reduction in the water apparent diffusion coefficient (ADC) in the brain (5). A single, operationally defined critical ADC threshold, often derived by correlation with endpoint imaging or histology, has been widely used to characterize lesion volumes and predict ischemic tissue outcome in both research and clinical settings. While this approach is simple and has some predictive values under certain conditions, it has many drawbacks. A single ADC threshold does not account for the duration that the tissue experiences an ADC below a critical threshold. It also does not take into the account the types of ischemic injury (i.e., whether the occlusion was permanent or transient). In this study, we investigated the temporal dependence of the critical ADC thresholds under four different occlusion durations in a rat stroke model in attempt to address the question of "How long does it take before the ADC reduction becomes irreversible?"

METHODS Four different occlusion durations were studied on male SD rats (300-350g): 30-min MCAO (n = 12), 60-min MCAO (n = 12), 90-min MCAO (n = 12) and permanent MCAO (n = 12) using the intraluminal suture occlusion model. MRI data at 4.7T were acquired at 30, 60, 90, 120, 180 mins and TTC histology was obtained 24 hours after stroke. ADC_{ave} was measured using spin-echo EPI with matrix = 64x64, FOV = 2.56x2.56cm, eight 1.5-mm slices, TE = 37ms, TR = 2s, 16 averages, b = 10, 1270 s/mm^2 along each of the 3 principle axes. ADC thresholds were determined by setting the CBF and ADC-derived lesion volume at different time points equal to the TTC infarct volume at 24 hours.

RESULTS **Fig 1** shows the infarct volumes increased with increasing occlusion durations as expected. **Fig 2** shows the ADC thresholds for different occlusion groups up to 180 minutes after the onset of occlusion. For the permanent and 90-min MCAO, ADC thresholds decreased monotonically as expected. In contrast, the ADC critical thresholds of the 30-min and 60-min MCAO group started out lower than the permanent MCAO group, transiently increased after reperfusion and then decreased monotonically with time. Surprisingly, the 90-min MCAO group did not show a transient increase in ADC thresholds and the pattern is similar to the permanent MCAO except the ADC thresholds were lower at all time points.

DISCUSSION & CONCLUSION We quantified the critical ADC thresholds under different conditions and showed that they were strongly dependent the durations of occlusion and the time after occlusion. It is surprising that the 90-MCAO group did not show a transient increase in ADC threshold. The critical ADC thresholds of the 90-MCAO group were significantly and consistently below those of the permanent MCAO group at all time points. The final infarct volumes by histology of the 90-MCAO group were clearly smaller than those of the permanent MCAO group, suggesting that some tissues were indeed salvaged compared to the permanent MCAO group. A possible explanation is that ADC decrease was no longer reversible after 90-min of exposure to ADC reduction despite reperfusion. Those tissues with reduced ADC likely became infarct and the tissues that were salvaged in the 90-MCAO group likely came from mismatch pixels predominantly at the time of reperfusion.

A limitation of diffusion imaging in stroke is that is not possible to distinguish salvageable and non-salvageable tissues. ADC reduction has been shown to be reversible under many conditions (such as ischemia and seizure). While the importance of the duration of exposure to ADC reduction is well appreciated, the critical duration of exposure to ADC reduction that ultimately results in irreversibility is unknown. Our data suggest that an upper limit of a critical duration of exposure, a point of no return, to be 90 mins for majority of the pixels. That is if the ADC reduction lasts $\geq$ 90 mins, the ADC reduction from essentially all pixels is irreversible, whereas if the ADC reduction lasts 30 or 60 mins, ADC reduction may still reversible. Individual pixels may have slightly different critical exposure times which may depend on the severity of CBF reduction. Future studies will track individual pixels by using independent component analysis to cluster pixels with similar "ADC thresholds *vs* time after occlusion" patterns. By cross validating these findings with endpoint imaging and histology, we have the opportunity to get better estimates of the upper limit of the exposure duration for irreversible ADC reduction in ischemic brain injury on a pixel by pixel basis.

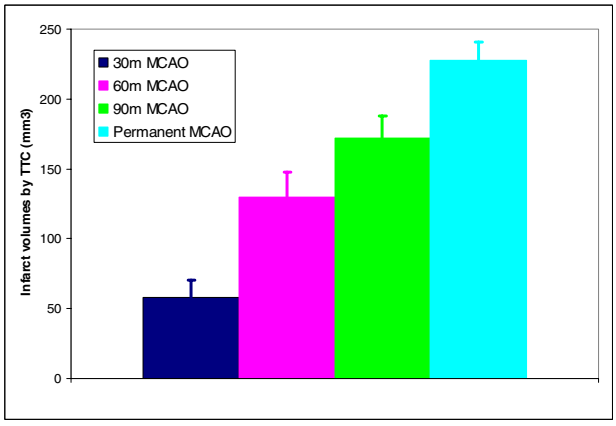

Figure 1. TTC infarct volumes for four different occlusion durations in a rat stroke model.

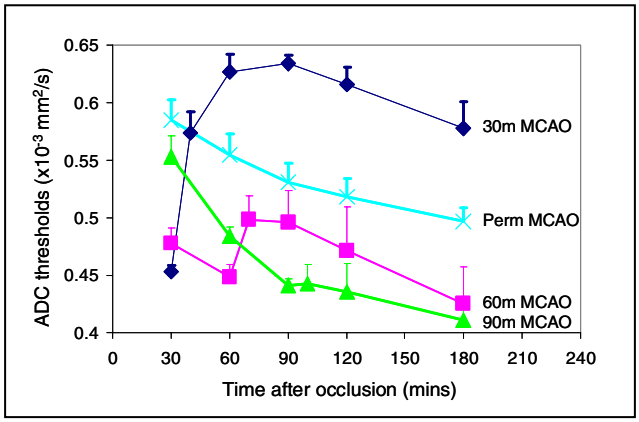

Figure 2. Critical ADC thresholds at different times after occlusion from a rat stroke model subjected to 4 different occlusion durations. Mean ± SEM.

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