# Characterizing the evolution of the ischemic penumbra using pH–weighted imaging

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## Introduction

The decision to use thrombolytic agents such as rtPA for ischemic stroke treatment hinges on careful characterization of the ischemic penumbra, the still viable tissue under the risk of progression to infarction. The diffusion-perfusion mismatch approach in MRI[1,2] has been very useful in that it identifies tissue that has not experienced cell depolarization but is at risk of infarction. However, areas of hypoperfusion may in some cases only reflect regions of benign oligemia. Because treatment has risks, additional imaging parameters to assess the likelihood of progression to infarction would be helpful. Recently, the possibility to perform pH-weighted (pHw) imaging with MRI was developed[3]. Because reduced tissue pH directly reflects impairment of oxidative metabolism, we hypothesized that the diffusion-pH mismatch may better define the fraction of the ischemic flow penumbra that is at risk of infarction. In this study, pHw imaging was combined with diffusion, perfusion and relaxation imaging to characterize the evolution of acute ischemia in a rat model of permanent middle cerebral artery occlusion (MCAO).

## Methods

Adult male Wister rats (280-320 grams, n = 15) were induced with 5% isoflurane and maintained under anesthesia with 2.5% isoflurane. Permanent MCAO preparation was performed using a suture into the lumen of the Internal Carotid Artery (ICA) that was further progressed toward the split with the MCA. Respiratory rate and blood pressure were monitored online. All image modalities were acquired using single shot EPI on a 4.7 T Bruker Biospec imager, facilitating co-registration. The in-plane resolution was 0.5x0.5 $cm^2$, with the slice thickness of 2 mm. Evolution was followed until 3.5 hrs post-occlusion and a 24 hr follow up was performed to assess T2-hyperintensity, which is known to agree with infarction as assessed by histology.

## Results and Discussion.

In all animals, the maximal MCA area was hypoperfused, but no T1 and T2 changes were found during the first 3.5 hrs of imaging. The rats showed heterogeneous temporal evolution of the pHw and diffusion deficits, as expected based on variability with suture insertion. Based on the results, we were able to assign three groups, namely 1) perfusion deficit = pH deficit = diffusion deficit (n = 5); 2) perfusion deficit = pH-deficit > diffusion deficit (n = 6); 3) perfusion deficit > pH deficit ≥ diffusion deficit (n = 4). In group 1 and 2, all animals evolved to full infarction over the initial area of perfusion deficit. In group 3, the area of pH deficit evolved to the area of perfusion deficit (e.g. see first row in the figure). Even though the pH deficit area was larger than the diffusion area at 3.5 hrs, the animal evolved to full infarction over the remaining period to follow-up, in agreement with our hypothesis. In the animal in the second row of the figure, the pH-diffusion mismatch was small and remained small during the first 3.5 hrs. The 24 hr followup showed an infarcted region in reasonable agreement with the pH deficit at 3.5 hrs and much smaller than the perfusion deficit, again in line with our hypothesis.

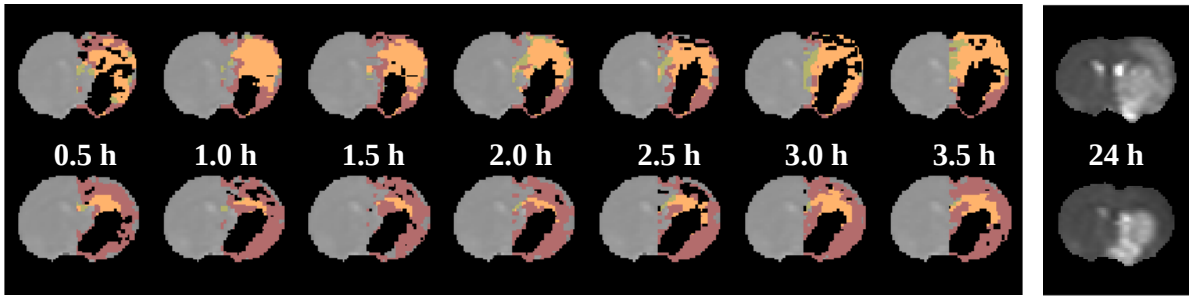


Fig. 1: Evolution of pHw-deficit (orange) and Diffusion deficit (black) with respect to perfusion deficit (purple) as a function of time post-MCAO occlusion. Hyperintensity in the T2 image at 24 hrs shows final infarction area.

## Conclusions

These initial data show that pHw imaging may have the potential to be a useful addition to the acute stroke exam by providing an opportunity to subdivide the area of perfusion deficit into regions of benign oligemia and impaired oxygen metabolism, with the latter having more predictive power for ultimate progression to infarction. Followup studies with models of reversible ischemia are needed to further confirm the hypothesis that a pHw-diffusion mismatch may be a better predictor of treatment risk assessment.

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**References: 1**. Warach S. et al. JCBFM 1996; 16: 53-59. **2**. Schaefer PW et al, AJNR 2002; 23, 1785. **3**. Zhou J. et al. Nature Med. 2003; 9:1085-1090.