

INTRODUCTION

Recent progress in the field of ischemic stroke has shown that thrombolysis treatment increases survival and reduces disability, but that early intervention is the key to successful therapeutic outcome.¹ The classical definition of ischemic penumbra is that of a region of hypoperfusion that is still viable but at risk of infarction, restricted to an area in which metabolism is impaired, but still sufficient to maintain cellular polarization. Modern MRI technologies, such as perfusion and diffusion weighted imaging (PWI, DWI), can identify regions of reduced perfusion and cellular depolarization, respectively, but it may be unclear whether reduced perfusion corresponds to benign oligoemia or a true penumbra. Recently, amide proton transfer (APT) imaging² has been shown to be able to monitor tissue pH and protein content through indirect detection of exchangeable amide protons via magnetization transfer asymmetry analysis (MTR_{asym}). We hypothesized that the pH-weighted imaging (pHWI) acquired using the APT technique may be able to subdivide the PWI-DWI mismatch into the penumbra and the region of oligoemia.

MATERIALS AND METHODS

Adult male Wister rats (n = 31) underwent middle cerebral artery occlusion (MCAO) and were imaged on a 4.7 T animal scanner during the hyperacute period every half hour from 0.5 or 1 hr up to 3.5hr post MCAO as well as at 24 hr for follow-up T₂ MRI. Multi-parametric MRI including pHWI, perfusion-weighted (PWI), diffusion-weighted (DWI), and T₁ and T₂ images were acquired using single shot EPI. In two rats only minimal hypoperfusion, and no pH and ADC abnormalities were detected during either the hyperacute stage or at 24 hr follow-up MRI. For three additional animals (n = 3) high signal

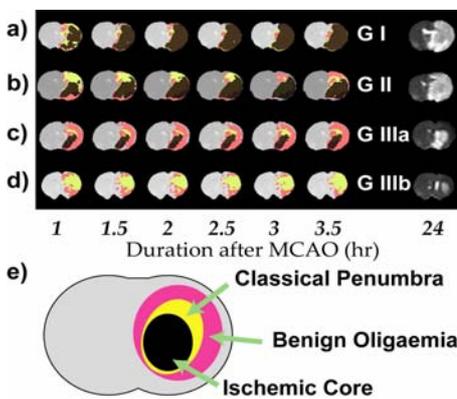


Fig.1, Ischemia evolution for four representative animals shown in a-d. Pink, yellow and black colors represent PWI, pHWI and ADC deficits, respectively.

fluctuations were measured, which could be traced to a malfunction of the active coil decoupler. These five animals were excluded from the data analysis. In addition, six animals (n = 6, mainly group I and group II to be defined below) died within 24 hr and no follow-up MRI study performed, but the evolution in the first hours was included in the group study.

RESULTS

All 26 animals included in the analysis showed the expected maximum perfusion deficit on PWI, but, due to the variability of the model, different animals showed different deficits on pHWI and ADC_{ave} [(1/3)trace(ADC)] images. CBF, ADC and MTR_{asym} from the contralateral brains of eight animals (n = 8) were used as the reference values. CBF, pH (i.e., MTR_{asym}), and ADC deficits were defined as values falling outside two standard deviations from the mean value. To reflect the different types of evolutions in the pHWI and ADC_{ave} maps, animals were assigned to three groups based on the correspondence of the deficits on these image types during the initial 3.5 hr of ischemia:

Group I (n = 8, severe ischemia): the spatial pHWI and ADC_{ave} deficits are within 20% at the start of the first MRI scans.

Group II (n = 11, severe ischemia at 3-3.5 hr): spatial difference between the pHWI and ADC_{ave} deficits evolved to within 20% up to 3.5 hr.

Group III (n = 7): PWI deficit > pHWI deficit >> ADC_{ave} deficit during the 0.5-3.5 hr initial period.

Fig. 1 shows results of processed images (Fig. 1a-d) and a schematic drawing of the principles of subdivision (Fig. 1e). Deficits: ADC_{ave} (black); pHWI (yellow); CBF(pink), with black dominant over yellow over pink. In the classical definition, the outer boundary of the penumbra would be the border between pink and yellow, and oligoemia would be represented by the pink-yellow mismatch (Fig. 1). The black/yellow boundary is between areas of abnormal diffusion and pH changes. This may coincide with the inner boundary of the penumbra, but due to possible heterogeneity of this core (diffusion deficit) area³⁻⁵, this is difficult to assess. Areas of reduced pH were always larger than or equal to regions of cellular depolarization as outlined by DWI and smaller than or equal to areas outlined by PWI (Fig. 2). Although there was some individual variability, group analysis showed that the resulting pHWI deficits at 3.5 hr predicted well the resulting infarct at the 24 hr endpoint. On the contrary, the final infarcts were smaller than the PWI deficits, in a range from 65-90% depending on the severity of the occlusion, and, in most cases, much larger than the initial DWI deficits.

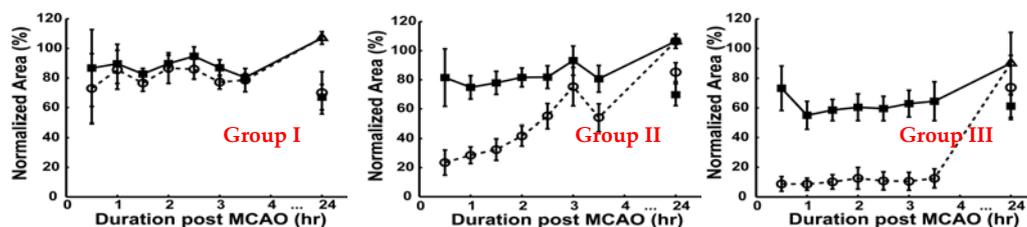


Fig. 2. Temporal evolutions of pHWI (filled squares) and ADC_{ave} deficits (circles) normalized by the PWI deficit for the three ischemic groups. The final infarct volume is indicated by a triangle. The mean \diamond standard error over the group is displayed. It can be seen that, for this permanent occlusion model, pHWI predicts well the final T₂ deficit, which is smaller than the initial perfusion deficit.

REFERENCES

1)Brott N. Engl. J. Med. 2000;43:710. 2) Zhou, Nat. Med. 2003;9:1085. 3) Kidwell, Ann. Neur. 2000; 47:462. 4) Nicoli, Stroke 2003;3:e82. 5) Guadagno, Cerebrov. Dis. 2005;19:239.