Longitudinal MRI for the detection of a typical pattern of cerebral blood flow (CBF) and tissue integrity changes after stroke in ischemia tolerant rats

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Introduction: The individual vulnerability to ischemia has a significant impact on tissue damage and outcome in stroke patients. Tolerance to ischemia can be induced experimentally by "preconditioning". One preconditioning model that has been used to render the brain more tolerant to ischemia is the injection of 3-nitroproprionic acid (3NPA), a respiratory chain inhibitor. We used longitudinal MRI in adult rats to characterize how preconditioning with 3NPA affects the development of a stroke lesion, and if a typical "MRI signature" of preconditioned tissue can be extracted from these data.

Methods: 14 adult Wistar rats received i.p. injections of 20mg/kg 3NPA or saline and were subjected to transient (60min) middle cerebral artery occlusion (MCAO) three days later. MR images were acquired during the occlusion (day 0) and after reperfusion (days 1, 4, 14). Quantitative CBF maps were obtained using Flow-sensitive alternating inversion recovery (FAIR) with the QUIPSSII modification. ASL imaging parameters were: slice thickness=2mm (3slices), gap=1mm, gap between tagging and imaging plane: 5mm, FOV=4x4cm, matrix: 64x64, flip angle=90°, number of interleaves=8, number of repetitions=12, TE= 4.3ms, TI1=700ms, TI2=1250ms. In addition, diffusion weighted (DWI) images, T1 and T2 maps and anatomical T2w images (matrix 256x256) were obtained. Functional deficits were assessed at each time point using a modified neurologic deficit scale.

Results: During MCAO, preconditioned animals had fewer voxels with severely compromised CBF than controls (Figure 1). However, CBF on the unaffected side was lower in the 3NPA group during ischemia. A similarly low CBF was also found in 3NPA preconditioned animals without stroke (data not shown). Although the extend of the initial lesion on apparent diffusion coefficient (ADC) maps was similar at 15min after insertion of the occluding device, there was a remarkable ADC recovery within the next 30min of MCAO in the 3NPA group (Figure 2). Over two weeks, CBF increased within the area of the initial perfusion deficit in both groups (Figure 1D). An area of hyperperfusion could be observed in controls between 4 and 14 days after stroke, with a maximum in the infarct border zone. Such hyperperfusion was much less pronounced, infarcts were smaller and functional deficits less severe in the 3NPA group (Figure 3).

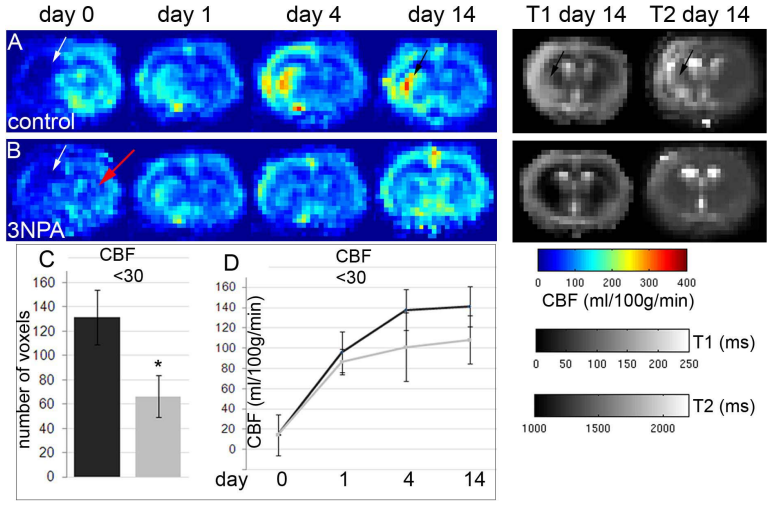

Figure 1: Averaged CBF maps from control (A) and 3NPA (B) animals over time, compared to averaged T1 and T2 maps on day 14. White arrows point to the area of CBF reduction during MCAO, black arrows indicate hyperperfusion at later time points and the corresponding anatomical location with respect to the lesion on day 14 (infarct border). CBF is lower on the unaffected side in 3NPA animals during ischemia (red arrow). 1C: Mean number of voxels (± SD) with CBF reduction below 30 ml/100g/min in controls (dark gray) and 3NPA animals (light gray). * indicates significance ($p < 0.05$). 1D: CBF values within the masks generated on day 0 from voxels with CBF < 30ml/100g/min over time.

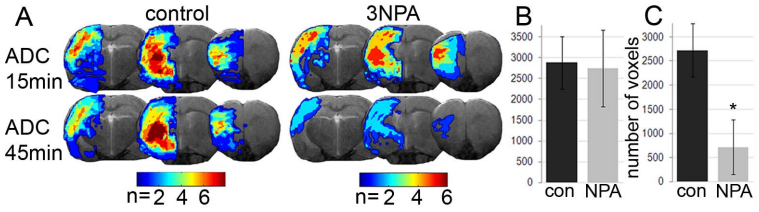

Figure 2A: Areas with reduced ADC 15min (upper panel) or 45min (lower panel) after onset of ischemia from individual animals of the control (n=8) or 3NPA (n=6) group overlaid onto a T2w image. 2B and 2C: averaged size of the regions with reduced ADC 15min (2B) or 45min (2C) after onset of ischemia in both groups. * indicates $p < 0.05$.

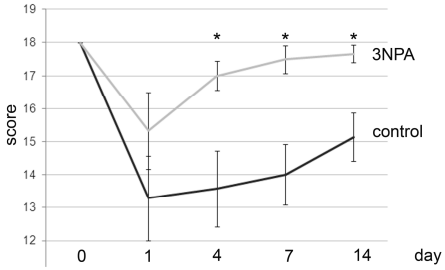

Figure 3: Functional test scores in controls and 3NPA animals over time. * indicates significance in repeated measures ANOVA followed by independent t-test ($p < 0.05$).

Conclusions: Even with a large initial lesion on ADC maps, tissue recovery was substantial in 3NPA preconditioned animals, most likely due to better residual perfusion in the ischemic area and was associated with a better functional outcome. Lower CBF values on the unaffected hemisphere were observed after 3NPA preconditioning and could indicate vascular/metabolic adjustments of ischemia tolerance. Thus, MRI might have the potential to discriminate ischemia tolerant from vulnerable brains.