Multimodal monitoring of the dynamic development of brain injury

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Introduction

Most cases of brain injury stem from an abrupt reduction in cerebral blood flow, depriving tissue of oxygen and glucose, which rapidly leads to failure of cell function and death. Directly surrounding the initial lesion, a still viable border zone is supplied by residual flow from collateral blood vessels. This "at risk" tissue, known as ischemic penumbra, is susceptible to secondary necrotic and apoptotic damage occurring over hours and days after the primary insult. The penumbra is characterised by significantly reduced blood flow but preserved metabolic demand as measured by an increased oxygen extraction fraction (OEF) [1]. With time, the penumbra will become irreversibly infarcted. Spreading depolarisation (SD), occur with a high incidence in brain injury patients [2] and could contribute to this secondary damage. SDs are slowly propagating waves of tissue depolarisation that are associated with complex hemodynamic and metabolic coupling. To understand their role in the development brain injury, we have simultaneously measured:

- cortical blood flow with laser speckle flowmetry (LSF)
- oxygen consumption with multispectral reflectometry (RGBR)
- glucose utilization with positron emission tomography of \([^{18}F]\)-fluoro-deoxy-glucose (FDG-PET)
- extracellular glucose and lactate concentrations with online microdialysis (rsMD)

Methods

**Group 1 – MCAo:** in 5 male Wistar rats, left frontal, parietal, temporal bones were thinned out to yield a large imaging field of view centered on the middle cerebral artery (MCA). After positioning the rats onto a specially designed holder for optical imaging in the PET scanner, baseline measurement of LSF and RGBR was started. The MCA was then occluded by lifting a hook positioned below the exposed artery. One hour following MCAo, FDG-PET data were acquired. Imaging was pursued for two additional hours.

**Group 2 – induced SD:** LSF and RGBR were continuously acquired in male Wistar rats through bilaterally thinned skull. A microdialysis probe was implanted via a small craniotomy and the dialysate was analysed for glucose and lactate concentrations every minute by rsMD [3]. After recovery from implantation and baseline measurement, FDG was injected. At 20 minutes post-injection, SDs were elicited either by needle prick (single SD, n=5) or KCl infusion (multiple SDs). The responses to SDs were observed for 70 minutes.

**Analysis:** All images were analyzed using VINCI imaging software (Volume Imaging in Neurological Research, MPI for neurological research, Cologne). PET
and optical images were co-registered using a custom-made fiduciary marker and regions of interest (ROIs) extracted to yield local time courses of all variables [4]. Real-time CBF changes were estimated as the inverse correlation time calculated from the speckle contrast [5]. Concentrations of oxy- and deoxy-haemoglobin (oxy-Hb and deoxy-Hb respectively) were calculated from the RGBR signals according to [6]. FDG uptake kinetics were calculated with dynamic PET analysis [7]. rsMD data were analyzed with noise removal algorithm [8] and converted to dialysate concentrations.

Results and Discussion

MCAo group: Directly following MCAo, a wave of CBF, oxy- and deoxy-Hb changes spread concentrically from the MCA into the whole surrounding cortex. As a result a clear zonal gradation of perfusion and oxygenation developed: inner zones near the wave origin exhibited irreversible severe reductions of CBF and oxygenation (Figure 1A, top), and outer zones showed a milder perfusion and oxygenation deficit. In these regions, waves of CBF, oxy-Hb and deoxy-Hb continued to spontaneously spread, cycling around the inner ischemic zone. Three patterns of CBF, oxy-Hb and deoxy-Hb waves were observed:

- pattern A: monophasic hypoperfusion with monophasic decreased oxy-Hb and increased deoxy-Hb (Figure 1A, middle)
- pattern B: hypoperfusion followed by hyperperfusion along with a decrease followed by an increase in oxy-Hb and the inversed time course for deoxy-Hb
- pattern C: monophasic hyperperfusion with a monophasic increased oxy-Hb and decreased deoxy-Hb (Figure 1A, bottom)

We also observed zonal transitions from patterns C to B, and B to A with time. This could be the first real-time observation of the deterioration of OEF in the penumbral zone.

Simultaneously, kinetic modeling of the FDG-PET images could discriminate between infarct core and early viable tissue according to [9]. This purely metabolic tissue classification was in remarkable agreement with the dynamic perfusion and oxygenation measurements: no secondary circumferential waves propagated in the identified “core” region, A and B waves propagated in the regions classified as “penumbra” and pattern C in the “healthy” zone (Figure A). Previous similar studies reported the occurrence of such perfusion waves after MCAo [10] and here we show that these perfusion patterns can be predicted by the local metabolic conditions of the tissue.

Induced SD: SD waves were detected by LSF as propagating hyperemic waves. The response to one single SD wave was biphasic: 1) within 5 minutes, glucose dropped by 20%, lactate increased by 60%, oxygen consumption increased by 20% and FDG uptake rose above control, 2) during the next 65 minutes, glucose and oxygen consumption remained constant but lower than baseline, lactate had fully recovered and FDG uptake gradually declined to normal values (Figure 1B). After multiple SD waves, we observed a sustained increased energy demand, with an ever-decreasing extracellular glucose, a prolonged elevated lactate level, and an up to 40% increase in FDG uptake. All these data could be integrated into a kinetic model of brain metabolism. This model will be further discussed at the COSBID satellite meeting.
Figure 1. Metabolic response to SD waves. A. Three zones of tissue conditions were identified according to their FDG uptake (core, penumbra, healthy). In the corresponding zones, different patterns of SD wave associated perfusion (black) and oxygenation (oxy-Hb in red, deoxy-Hb in blue) were measured. B. Dynamic energy metabolism following single SD induced by needle prick (NP) or multiple SDs (KCl). After SD induction (t=0), FDG uptake increased departed from the contra-lateral side (top). Glucose and lactate concentration changes were also drastically disturbed compared to pre-SD values (bottom).

References