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# Multiparametric magnetic resonance imaging of acute experimental brain ischaemia

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ABSTRACT

Ischaemia is a condition in which blood flow either drops to zero or proceeds at severely decreased levels that cannot supply sufficient oxidizable substrates to maintain energy metabolism *in vivo*. Brain, a highly oxidative organ, is particularly susceptible to ischaemia. Ischaemia leads to loss of consciousness in seconds and, if prolonged, permanent tissue damage is inevitable. Ischaemia primarily results in a collapse of cerebral energy state, followed by a series of subtle changes in anaerobic metabolism, ion and water homeostasis that eventually initiate destructive internal and external processes in brain tissue. $^{31}$P and $^{1}$H NMR spectroscopy were initially used to evaluate anaerobic metabolism in brain. However, since the early 1990s $^{1}$H Magnetic Resonance Imaging (MRI), exploiting the nuclear magnetism of tissue water, has become the key method for assessment of ischaemic brain tissue. This article summarises multi-parametric $^{1}$H MRI work that has exploited diffusion, relaxation and magnetisation transfer as 'contrasts' to image ischaemic brain in preclinical models for the first few hours, with a view to assessing evolution of ischaemia and tissue viability in a non-invasive manner.



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## 1. NMR spectroscopy of acute brain ischaemia

One of the very first biological applications for NMR was to observe breakdown of phosphate-containing metabolites in excised muscle effectively under ischaemic conditions [1]. The demonstration that metabolism could be non-invasively monitored in 'a living system' by $^{31}$P NMR led to a surge of interest among biochemists and physiologists in applying NMR for a variety of physiological and pathological conditions [2]. Among these was acute cerebral ischaemia [3–5], a disorder with immense clinical impact. Combining $^{1}$H with $^{31}$P NMR spectroscopy (MRS) achieved unprecedented access to cerebral metabolites that were intimately involved in metabolism in ischaemic brain *in vivo*. Concurrent use of invasive techniques to measure cerebral blood flow (CBF) combined with $^{1}$H and $^{31}$P MRS allowed determination of CBF thresholds for energy failure [decrease in phosphocreatine (PCr) and ATP and increase in inorganic phosphate ($P_i$)], tissue acidification (from the chemical shift of $P_i$) and non-oxidative glycolysis (from lactate accumulation) [4,6]. It turned out that the energy failure, drop in intracellular pH ($pH_i$), and initiation of lactate accumulation have common CBF thresholds in the range of 12–20 ml/100 g/min [6]. Using $^{1}$H/$^{31}$P MRS to examine brain metabolism post-ischaemia it was observed that recoveries of energy state and $pH_i$ have different time-courses than lactate wash-out [7], a finding that shed light on the plausible role of lactic-acidosis in development of ischaemic neuronal damage [8]. Studies of human stroke using $^{31}$P MRS showed, among other findings, an almost complete absence of $^{31}$P NMR-detectable metabolites in the infarct and alkaline $pH_i$ in infarct tissue [9,10]. Due to low inherent sensitivity, long acquisition time and need for specialised hardware, interest in $^{31}$P MRS in clinical stroke research has faded, however. $^{1}$H MRS, instead, is currently used by specialised stroke neurology centres owing to the value of metabolite profiles in informing about tissue viability and aiding prediction of tissue outcome in the acute phase of ischaemia [11–13]. The unprecedented value of the data on cerebral metabolism provided by $^{31}$P and $^{1}$H MRS paved the way for $^{1}$H MRI as an imaging modality for the assessment of brain tissue in acute ischaemia both preclinically and clinically.

## 2. Early Magnetic Resonance Imaging (MRI) investigations of brain ischaemia

Since the inception of MRI as an imaging technique it has become apparent that 'biological water' is an excellent 'indirect reporter molecule' for a number of key features in tissues, including anatomy, function and metabolism. This is owing to several factors, including the ubiquitous presence of water *in vivo* at high [$^{1}$H], interaction of water hydrogen atoms with those of macromolecules through multiple physico-chemical pathways and variation of 'internal magnetic fields' in response to metabolic demand. Given that $^{1}$H MRI provides sub-millimeter spatial and sub-second temporal resolution, it is understandable that acute brain ischaemia has been a subject of active imaging research employing MRI. Studies using animal models of ischaemia in the 1980s revealed that both $T_1$ and $T_2$ relaxation times increase in gerbil brain 2 h after carotid ligations [14]. The changes in relaxation times and signal intensity in proton density images were shown to take place parallel to net water accumulation into the infarcting tissue [15]. It was deduced from these and subsequent studies that neither $T_1$- nor $T_2$-weighted images were able to highlight consequences of ischaemia for the first 2–3 h [16–19]. MRI was incorporated into clinical stroke imaging in the late 1980s, predominantly using $T_2$-weighted MRI [20] to delineate irreversibly damaged tissue, a concept that is still deeply imbedded in clinical radiology [21].

This picture was challenged as early as in 1983 by a case report from an acute haemorrhagic stroke patient scanned for $T_1$-weighted MRI at 0.17 T briefly after symptom onset [22]. The report indicated that $T_1$-weighted MRI signal is decreased in the acutely ischaemic parenchyma at the time when computed X-ray tomography is normal, and importantly, abnormal $T_1$-weighted signal in ischaemic brain was reversed by successful restoration of blood flow [22]. This study reporting the first demonstration of reversible ischaemia by MRI received little attention, however. Few papers have evoked as much attention within the stroke imaging community as the publication by Moseley and colleagues on acute stroke using middle cerebral artery occlusion (MCAo) in cats [23]. It was shown that hyperintensity in diffusion-weighted MR images appears within the first hour of ischaemia, whereas $T_2$-weighted images remained unchanged at that time, and that diffusion-weighted hyperintensity correlated with energy failure, as revealed by $^{31}$P MRS [23]. A quantitative diffusion MRI study [24] found that the apparent diffusion coefficient (ADC) of brain water decreases earlier that $T_2$-weighted signal increases, providing a physical explanation for the diffusion hyperintensity in acute ischaemia [23]. Extensive literature both from experimental [25,26] and clinical settings [20,27] accumulated so far allows us to conclude that diffusion MRI is a powerful and unambiguous technique for the diagnosis of acute ischaemia well before the shift to an irreversible tissue state.

This article deals mainly with preclinical work on acute brain ischaemia and stroke assessed by means of quantitative multiparametric MRI. Since the early 1990s a wealth of studies has demonstrated that not only diffusion but also NMR relaxation times of cerebral water dramatically change after few seconds of ischaemia, and thus multiparametric MRI opens avenues to observations of time-dependent tissue alterations with high anatomical precision in the brain [28–31]. Despite extensive preclinical MRI literature on acute stroke, translation of MRI into patient management has been slow largely because there are only limited licensed drugs for pharmaco-therapy of acute stroke which must be administered within the tight timeframe needed for improvement of patient outcome [32]. The current evidence overwhelmingly points to a conclusion that MRI not only provides unambiguous diagnosis of acute stroke, but also that it makes assessment of tissue viability and outcome feasible earlier than any other non-invasive imaging modalities.

## 3. Acute brain ischaemia

From a haemodynamic view point there are many forms of compromised haemodynamic conditions leading to ischaemia. These include (a) global complete and (b) global incomplete ischaemia resulting from systemic collapse of blood flow, (c) focal transient and (d) focal permanent ischaemia due to obstruction of blood flow often in a single artery or in one of its branches. In clinical settings there are three types of ischaemic brain events: (a) global ischaemia associated with haemodynamic catastrophe, for instance following severe cardiac insufficiency or arrest, (b) transient ischaemic attack due to a short-lasting focal reduction of blood flow and (c) focal ischaemia (the so-called stroke) caused by occlusion of an artery and/or a haemorrhage. These conditions differ widely in their clinical picture, outcome, anatomical distribution of damage and pathophysiology leading to tissue damage in ischaemia. For instance, certain brain regions, including the hippocampus and middle cell layers in neocortex, are vulnerable to global ischaemia (the so-called selective vulnerability [33]), whereas persistent focal ischaemia results in pan-necrosis in the