Thrombolysis for acute ischaemic stroke: can brain imaging and consent processes before treatment be improved?

Dr Ingrid Kane BSc MBBS MRCP

Submitted to the University of Edinburgh
in candidature for the degree of Doctor of Medicine 2008

Dedicated to my Grandfather
Dr Gunvald Christian Gundersen
(1908 – 1982)
who inspired me to follow a career in medicine

Abstract

In the United States one person a second suffers a stroke. In England more than 110,000 will suffer a stroke each year and approximately one third of those will die within a year. This costs the NHS over £2.8 billion. With an ageing population in the UK stroke will be a major cause of death and disability for years to come. It is vital that stroke services are improved to try and improve patient care and reduce the burden on an over stretched NHS. Rapid access to brain imaging and expert stroke care in the acute stage is an important part of that process.

Over the last ten years the availability of, and access to, CT imaging in particular, has improved. The Royal College of Physicians now recommend that all stroke patients should be imaged within 24 hours of symptom onset and early access to CT has been shown to be cost effective. However, CT is not the only imaging modality available to acute stroke patients. Advanced scanning with magnetic resonance imaging looks a promising alternative to CT, particularly when selecting patients for thrombolysis, the only currently available acute stroke treatment which has been shown to benefit patients.

The general aim of my period of research was to work on streamlining and improving a few key areas in the care for patients with stroke, particularly those likely to be candidates for thrombolysis. I focussed on: optimising the imaging method for patient selection; assessing the availability of different imaging methods; and evaluating a range of options for obtaining consent for treatment or research in this setting.

In the imaging work of this thesis I discuss some aspects of the two major imaging modalities available to stroke patients – computerised tomography (CT) and magnetic resonance imaging (MRI) and the evidence available for the treatment of acute stroke with thrombolysis (Chapter 1). I then explore the evidence lying behind the use of some of the advanced MR imaging modalities and how they may assist in the selection of patients for thrombolysis. Using a systematic review, I pay particular attention to the

evidence behind the MR perfusion diffusion mismatch theory and the interaction with thrombolysis (Chapter 2). Having analysed the evidence available on 'mismatch' and thrombolysis I go on to compare the many techniques available for measuring the perfusion lesion and the problems that arise as a result of this in Chapter 3. In Chapter 4 I move from the more complex details of specific MR techniques to the practicalities of imaging acute stroke patients with MR, dealing with a UK survey on the actual availability of MR scanners. Finally, in Chapter 5, I deal with patients who meet clinical and imaging criteria for thrombolysis who require consent. This is an important part of the process that each patient must undergo prior to treatment. This is a stage in the pathway to treatment that can cause huge delays, particularly with an acutely ill patient. The process of consent needs to begin before imaging. It is a vital first step in thrombolysis because, without it, patients can not undergo the complex MR imaging techniques that are discussed in earlier chapters of the thesis.

Declaration

I hereby declare that:

- I composed this thesis.

- I made a substantial contribution to the work: I performed the systematic review that formed the basis of Chapter 2. For the perfusion MRI study (Chapter 3) I drew around the individual perfusion lesions for each patient in the study and collated the baseline details of the patients along with their clinical and imaging results. I entered the data into Excel and SPSS in order to analyse the data. Professor J Wardlaw supervised the scientists (Dr M Bastin, Dr T Carpenter and Dr C Rivers) who assisted with the analysis the diffusion and perfusion images. For the MRI pilot study (Chapter 4) I designed the information and consent forms for patients potentially eligible for the study. I also designed the data collection forms. I collated a comprehensive database of all acute hospitals In the UK in order to perform the MRI survey. I analysed the data for the work on consent (Chapter 5). I was involved in assessing and recruiting a number of patients with acute stroke during my time in Edinburgh to the studies mentioned and several others.

- All of the work contributing to this thesis was undertaken whilst I was in post at the Western General Hospital, Edinburgh.

- This thesis has not been submitted in candidature for any other degree, postgraduate diploma or professional qualification.

Signed: _

Summary

In the United States one person suffers a stroke every second. In England more than 110,000 will suffer a stroke each year[1] and approximately one third of those will die within a year.[2] This costs the National Health Service (NHS) over £2.8 billion per year.[1] With an ageing population in the UK, stroke will be a major cause of death and disability for years to come. It is vital that stroke services are improved to try and improve patient care and reduce the burden on an over stretched NHS. Rapid access to expert stroke care and brain imaging in the acute stage is an important part of streamlining that process.

Over the last ten years the availability of, and access to, computerised tomography (CT) imaging in particular, has improved. The Royal College of Physicians now recommend that all stroke patients should be imaged within 24 hours of symptom onset[3] and early access to CT has been shown to be cost effective.[4] However, CT is not the only imaging modality available to acute stroke patients. Advanced scanning with magnetic resonance imaging is suggested as a promising alternative to CT by some stroke experts, particularly when selecting patients for thrombolysis, the only currently available acute stroke treatment which has been shown to benefit patients.[5]

Much of the financial burden of stroke lies in providing care for those unfortunate patients left with a major disability following their stroke. Acute treatments, such as thrombolysis, decrease the number of patients dead and dependent as a result of their stroke.[5] It is therefore important that further studies are carried out into such treatments (e.g. the Third International Stroke Trial, IST-3[6]) to widen the number of people potentially eligible to treatment and hopefully reduce the burden of stroke in the future.

The general aim of my period of research was to work on streamlining and improving a few key areas in the care for patients with stroke, particularly those likely to be candidates for thrombolysis. I focussed on: optimising the imaging method for patient

selection; assessing the availability of different imaging methods; and evaluating a range of options for obtaining consent for treatment or research in this setting.

Brain imaging forms a vital part of the assessment and management of patients with acute stroke, but the choice of which of several brain imaging techniques requires clarification. In ischaemic stroke it is well recognised that early imaging (to exclude haemorrhage) and treatment with aspirin are beneficial. Over the last ten years or so access to CT has improved dramatically and this is reflected in the Royal College of Physicians guidelines which recommend a CT within 24 hours of stroke onset. My survey of imaging facilities in the UK certainly suggests that the majority of acute hospitals (97%) have on site CT. However, with acute treatments such as thrombolysis, the key to success is to select those patients who will benefit most from thrombolysis and avoid treating those in which it will cause harm. One of the ways to do this is to look at imaging features, hence the interest in advanced imaging techniques such as magnetic resonance imaging (MRI).

In the imaging work of this thesis I discuss some aspects of the two major imaging modalities available to stroke patients – computerised tomography (CT) and magnetic resonance imaging (MRI) and the evidence available for the treatment of acute stroke with thrombolysis (Chapter 1). I then explore the evidence lying behind the use of some of the advanced MR imaging modalities and how they may assist in the selection of patients for thrombolysis. Using a systematic review, I pay particular attention to the evidence behind the MR perfusion diffusion mismatch theory and the interaction with thrombolysis (Chapter 2). Having analysed the evidence available on 'mismatch' and thrombolysis I go on to compare the many techniques available for measuring the perfusion lesion and the problems that arise as a result of this in Chapter 3. In Chapter 4 I move from the more complex details of specific MR techniques to the practicalities of imaging acute stroke patients with MR, dealing with a UK survey on the actual availability of MR scanners. Finally, in Chapter 5, I deal with patients who meet clinical and imaging criteria for thrombolysis who require consent. This is an important part of

the process that each patient must undergo prior to treatment. This is a stage in the pathway to treatment that can cause huge delays, particularly with an acutely ill patient. The process of consent needs to begin before imaging. It is a vital first step in thrombolysis because, without it, patients can not undergo the complex MR imaging techniques that are discussed in earlier chapters of the thesis.

As I demonstrate in this thesis there has been a great deal of interest in the MR perfusion diffusion mismatch theory in acute stroke, but most of the studies are woefully small, retrospective and do not provide enough evidence on which to base treatment decisions. Perfusion imaging, if it is to be used requires clarification in larger studies to define which post processing method and perfusion lesion should be used for treatment decisions. In addition the substantial barriers to practical routine use of MR imaging in acute stroke need to be addressed before it is advocated by experts more widely. It simply creates false expectations and creates greater confusion when a clear message of '1st line CT unless a very good reason' might help remove one barrier, some of the time delay, to thrombolysis.

The broad aim of this thesis is expressed in the title. The answers to the question, arising from the work in this thesis are summarised below under implications for clinical practice and implications for research.

Implications of this thesis for clinical practice

1. CT is widely and rapidly available in the UK for patients with acute stroke, and should therefore remain the 'work horse' imaging modality for these patients.

2. Advanced imaging with MR may provide us with more information on which patients are likely to benefit from, and which are likely to be harmed by thrombolysis. Since the current evidence base on MR is lacking, no clear recommendations on the best approach is possible.

3. There are many different MR methods to assess cerebral perfusion and perfusion diffusion mismatch, and there is no consensus on which is best.

4. The perfusion measures which correlate best with baseline stroke severity are arterial input function (ATF), peak time fitted (PTF), time to peak (TTP), full width half maximum (FWHM) and first moment (rMTT); with clinical outcome, ATF and with radiological outcome ATF, PTF, TTP, rMTT, FWHM, relative cerebral blood flow (rCBF), quantitative cerebral blood flow (qCBF) and cerebral blood volume (CBV).

5. Simple techniques may be more practicable for use in routine clinical practice (i.e. relative measures of MTT) and more complex and time consuming ones will have greater application in research studies.

6. A feasibility study of MR in acute stroke at WGH demonstrated that – despite access to a research-dedicated MR scanner, with the resources available at the time – MR was not a practicable tool for pre thrombolysis. Better and more rapidly responsive clinical systems of care for patients with suspected acute stroke would be needed for optimal use of MR technology.

7. Although MR is more readily available than it used to be five years ago, rapid access for stroke patients is still poor in the UK. Combined with the MR availability survey data, this suggests MR will have very limited applicability in the UK NHS routine acute stroke care for the next few years.

8. Flexible consent procedures are important so that a wide variety of patients have access to trial treatments.

9. When considering the development of alternative forms of consent it is important to include the public in discussions and to incorporate their views wherever possible.

Implications of this thesis for research

1. There is an urgent need to standardise definitions of techniques used in advanced MRI research in stroke, in particular the term 'mismatch' and the use of perfusion imaging. If terms are standardised then different research groups can at least combine results and analyse the data in meta analyses. The time has not yet arrived for CT to be superseded and it should remain the 'work horse' for imaging patients with acute stroke.

2. Although MR techniques are exciting and may offer a greater insight into the pathophysiology of acute stroke, they are not ready to take over from CT yet. In fact, in the UK, access to MR is so poor that we should be concentrating on research studies involving more advanced CT methods in helping us to select patients for thrombolysis.

3. Further research on MR is needed to determine if it is useful in assisting in the selection of certain groups of patients with acute stroke, such as patients who present later i.e. extending the time window for thrombolysis to be given.

4. Currently in the UK CT is the most accessible imaging technique for stroke physicians. Therefore more work needs to be done on advanced CT techniques, such as CT perfusion to see if this helps improve the selection of patients for thrombolysis. However, CT perfusion techniques must also be standardised so that similar problems that have affected some of the advanced MR techniques are not repeated.

5. If advanced MR or CT perfusion techniques are to be useful, a large study of patients with and without mismatch randomised to thrombolysis or control needs to be undertaken.

6. A study examining correlations between acute MR changes and corresponding changes on CT may mean that early CT changes in stroke become more useful when making treatment decisions.

7. The issue of consent is very important to consider in trials of acute medicine, especially where there is little time available for people to consider treatment options.

8. Restrictive consent procedures are a major obstacle to evaluating interventions that could have substantial impact on mortality and disability. This must be remembered and flexible consent procedures considered and incorporated into new trials where at all possible.

Note: All identifiers have been removed from any images used in this thesis. The images are printed in standard radiological format i.e. the patient's left is on the right hand side of the page.

References

1. http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/Stroke/fs/en

2. http://www.stroke.org.uk/

3. Royal College of Physicians. National Clinical Guidelines for Stroke (second edition). Prepared by the Intercollegiate Stroke Working Party. June 2004.

4. Wardlaw JM, Seymour J, Cairns J, Keir S, Lewis S, Sandercock P. Immediate computed tomography scanning of acute stroke is cost effective and improves quality of life. *Stroke* 2004;35:2477-2483.

5. Wardlaw JM, del Zoppo G, Yamaguchi T. Thrombolysis for acute ischaemic stroke (Cochrane Review). Oxford: Update software, 2003.

6. http://www.ist3.com

1 Background

1.1 Introduction

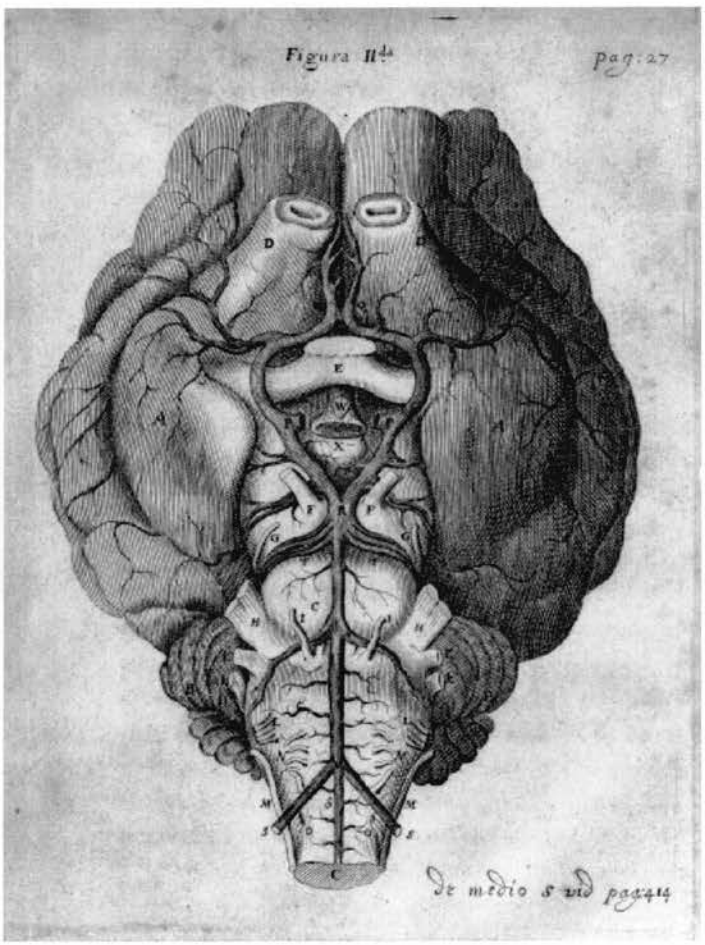
The first possible reports of stroke were recorded in ancient Egypt on the Edwin Smith Papyrus. This is a copy of an ancient manuscript which was thought to have been written between 3000 and 2500 BC. It contains the first accounts of brain injuries, which were noted to be associated with changes in the function of other parts of the body and, in one case, hemiplegic contractures.[1]

Hippocrates (460-370 BC) described stroke as the sudden onset of paralysis with the term 'apoplexy'. At that time apoplexy referred to anyone suddenly struck down with paralysis and referred to a general disorder of the brain, rather than the focal pathology which underlies the modern definition of stroke. Little was known about the complex anatomy of the cerebral circulation and stroke was thought to be due to an imbalance in the four humours: blood, phlegm, black bile and yellow bile.[2]

The Swiss physician, Johann Jacob Wepfer (1620-95), identified signs of bleeding in the brain at postmortem in patients who had died of apoplexy. He was also the first to suggest that apoplexy could not only be caused by bleeding into the brain, but also by blockage of an artery supplying the brain. Around the same time Thomas Willis (1641-75) described the vascular connections at the base of the brain – now known as the 'Circle of Willis' (Figure 1) – a key advance in the understanding of the cerebral circulation.

Leon Rostan (1790-1866), recognised that that lesions occurring in the brain were more often due to softening of the cerebral tissue rather than haemorrhage, although there was still no clear understanding of the causative lesion. It was not until Virchow (1821-

Figure 1: The Circle of Willis



Courtesy of the Welcome Library

1902) that there was a general understanding that vascular disease was usually due to atherosclerotic and not inflammatory disease of blood vessels.[3]

Since then our knowledge of the pathophysiology of stroke has increased further, aided by new imaging techniques to investigate the pathological state of the blood vessels in the brain, and the dynamics of the pathophysiology in the acute and recovery phase. X rays were discovered in 1896, and although intracranial angiography was introduced in the 1920's, it was really the advent of CT and then MR in the mid 1970's and 1980's respectively that has made major recent progress possible. There are two main types of stroke – infarct and haemorrhage – with ischaemic stroke being the main focus of this thesis.

In an ischaemic stroke the blocked blood vessel causes a reduction in blood flow to the area of brain it supplies. The extent of the reduction in flow is important since different rates of flow equate to different degrees of tissue damage as demonstrated in Figure 2. In normal conditions the cerebral blood flow is determined by the cerebral perfusion pressure and the cerebrovascular resistance. In practical terms the measurement of cerebral blood flow (CBF) provides a challenge. One way of ascertaining CBF is to follow the concentration of an intravascular contrast agent within a given volume of interest over time. However, this is by no means straightforward. As contrast passes through a region of interest a concentration time curve of contrast agent within the tissue can be produced, C(t). Then, using principles of indicator dilution theory, C(t) within a region of interest (ROI) can be expressed as a convolution:

$$C(t) = \rho/\kappa_H \, (CBF) \, . \, (C_a(t) \times R(t))$$

where $C_a(t)$ is the arterial input function (AIF) i.e. the concentration of the tracer entering the ROI, and R(t) is the residue function, which describes the fraction of contrast agent remaining in the ROI at time t, following the injection of an ideal bolus at $t = 0$. Cerebral blood flow is CBF, ρ is the density of brain tissue and κ_H accounts for the difference in the haematocrit between capillaries and large vessels.[4] There are essentially two groups of methods to solve the above equation. One is by measurement

Figure 2: Cerebral blood flow thresholds

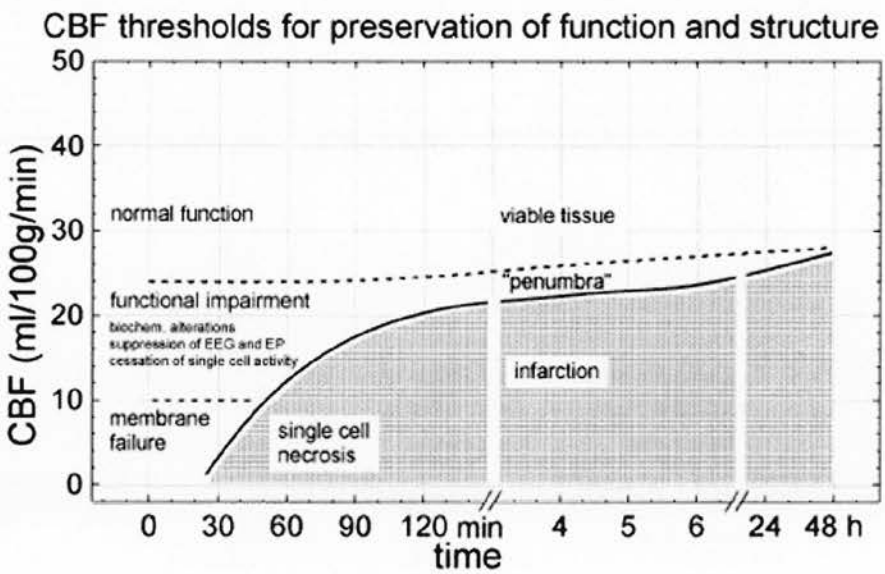


Diagram of CBF thresholds required for the preservation of function and morphology of brain tissue. The development of single cell necrosis and infarction is dependent on the duration of time for which CBF is impaired below a certain level. The solid line separates structurally damaged from functionally impaired but morphologically intact tissue (the 'penumbra'), and the dashed line distinguishes viable from functionally impaired tissue.[5]

of the AIF in order to perform the deconvolution of C(t), producing direct information about CBF, cerebral blood volume (CBV) and mean transit time (MTT), but this requires time consuming post processing of imaging data. The other group of methods use summary parameters calculated directly from the concentration time curve e.g. time to peak and full width half maximum (see Figure 2, Chapter 3, p.92 for more details). However these parameters only provide indirect measures of perfusion, taking no account of the variation in AIF and residue function (R(t) between individuals and different areas of the brain. To date a number of summary parameters have been calculated directly from the concentration time curve by various research groups and include:

- Arrival time fitted (ATF) – estimated delay of contrast in a voxel obtained from the curve fitting procedure
- Peak time fitted (PTF) – estimate of the time of maximum contrast concentration obtained from the fitted parameters
- Time to peak (TTP) – peak time fitted minus arrival time fitted
- Full width half maximum (FWHM) – width of the concentration/time curve at the point half way to the peak concentration
- First moment (rMTT) – first moment of the concentration time curve
- Peak concentration (Cmax) – maximum value of the fitted concentration/time curve
- Relative cerebral blood flow (rCBF) – rCBV/rMTT

The various perfusion parameters above will be discussed in more detail through the thesis, with further explanation as to how the parameters are calculated. The details above are simply an introduction to the concept. Using the central volume theorem MTT = CBV/CBF. This is an important concept which will be picked up and expanded on later in the thesis.

As introduced above, as imaging techniques have developed it is possible to image, not only the different pathological types of stroke, but also the stages of disease e.g. looking at flow rates and perfusion in areas of ischaemic stroke.

1.2 Why is imaging so important in stroke medicine?

1.2.1 The burden of disease and the lack of effective treatments

Stroke is a major cause of death and morbidity throughout the world. Currently it is the third most common cause of death. By 2020 it is estimated that stroke will not only account for 6.2% of the total burden of illness in the developed world[6] but will also be a significant problem in the developing world. The true global incidence of stroke is difficult to establish due to lack of data from the developing world. As incidence rises steeply with age, and as the number of people surviving in to old age increases, stroke will remain a major health problem for the foreseeable future.

Though knowledge of the cerebral circulation and the physiology of the brain has expanded enormously, it was only in 1997 that an effective treatment for acute stroke was found (aspirin); though its benefits were modest, the treatment could at least be used very widely.[7] Admission to hospital and care within a stroke unit that offers comprehensive care and multidisciplinary rehabilitation has more substantial benefits (and benefits all stroke types).[8,9] Thrombolytic therapy was first evaluated in stroke in the late 1950's.[10,11] However, since stroke was diagnosed clinically at that time, it was not possible to reliably exclude haemorrhage as the cause of the stroke, and so many patients with primary intracerebral haemorrhage died as a result of inappropriate treatment with thrombolysis, and the treatment was abandoned as too risky. Introduction of thrombolysis into acute stroke care had to await the development of CT scanning. Even then, a thrombolytic agent was not licensed for use until 1996 in the USA and in 2003 in Europe.

1.2.2 Different cerebral pathologies require different treatments

'Stroke' or 'non-stroke' pathologies

Imaging of the brain can determine both the pathological type of stroke and the territory of brain affected, but can also reveal non-stroke lesions which can present in a stroke-like fashion (Figure 3). It is important to identify focal areas due to venous infarction[12] and other stroke mimics such as primary brain tumours and cerebral abscesses so that appropriate treatment can be given as soon as possible.

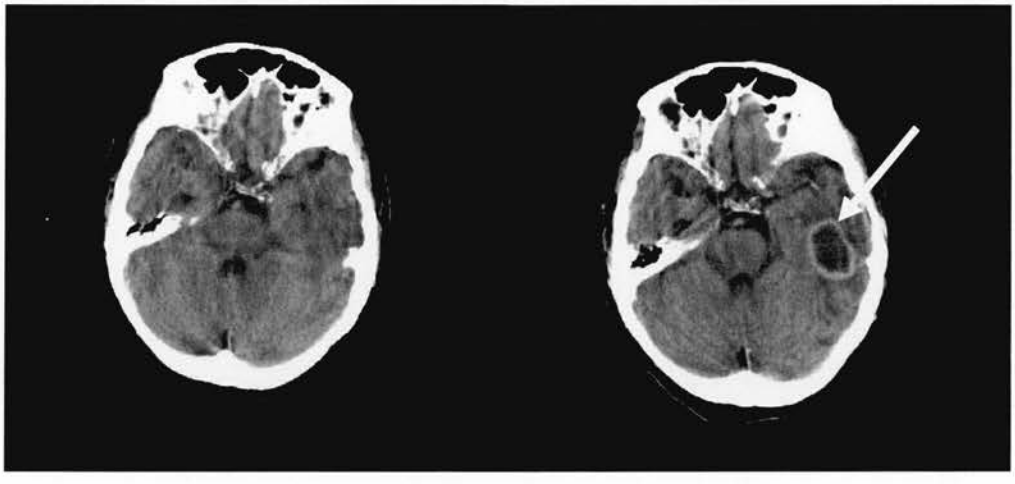
Infarction or haemorrhage?

Over four fifths of strokes are ischaemic and are due to the blockage of extra- or intracranial arteries by thrombus or embolic material. The remainder is caused by haemorrhage, either primary intracerebral (around 10%) or subarachnoid (approximately 5%). Brain imaging with CT or MR is therefore essential to distinguish between the main pathological causes of stroke, particularly when considering investigations and treatments that may affect the different pathological types of stroke in different ways (Table 1).

If stroke, brain scanning can determine the arterial territory

Location of arterial territory is important for a number of reasons. Knowledge of the likely location of the cerebral lesion (and its arterial territory) enables the clinician to assess the scan more critically to look for appropriate changes. If the clinical features do not match the scan appearances, the diagnosis may need to be reviewed. Secondly, brain imaging with CT or MR can help confirm the differentiation between carotid and vertebrobasilar circulation ischaemic events. It is known that carotid endarterectomy is beneficial for recently symptomatic severe carotid stenosis.[13,14] However, in asymptomatic patients up to 75 years of age, there is no net benefit of treating even a severe carotid stenosis of greater than 70% with carotid endarterectomy.[15] Follow up in the Asymptomatic Carotid Surgery Trial (ACST) is ongoing and will be necessary to establish whether the longer term benefits of treating asymptomatic patients are offset by

Figure 3: A stroke mimic



CT of a patient who presented with a history consistent with stroke. The image on the left is the unenhanced scan showing left temporal lobe hypoattenuation and sulcal effacemet. The image on the right, with contrast, revealed a ring enhancing lesion (arrow) consistent with an abscess.

the immediate surgical risk. Hence if a patient is found to have a severe right carotid stenosis, but the symptoms and brain imaging all point to an ischaemic event in the left cerebral hemisphere, or either side of the brainstem, or cerebellum, surgery on the asymptomatic right carotid is not needed. The third factor is that if the brain scan reveals that multiple arterial territories are affected, as opposed to a single territory, it may help reveal the cause of the stroke e.g. a cardio embolic source.

It is often possible to determine what arterial territory has been affected by the stroke from the symptoms described by the patient and the physical signs elicited by the clinician. Imaging can help confirm which territory of the brain is affected. Although clinical classifications, such as that derived by Bamford,[16] often correctly predict the arterial territory affected, they are by no means perfect. When the Oxford Community Stroke Project (OCSP) classification was first derived it was based on the clinical examination of patients at a mean of four days post stroke.[14] There are therefore questions as to whether it is suitable for use in the assessment of patients in the hyperacute stages of stroke. Several studies have shown that a patient's neurological deficit in the hyperacute stages of stroke may well change over the next few hours to days, suggesting that neurological deficit may not be fixed at the time of hypercute assessment.[17,18] However the OCSP is quick and simple to do and the combination of clinical assessment and simple structural CT imaging of the brain often allows a rapid and reasonably accurate localization of the arterial territory. The OCSP correlated well with CT findings in patients recruited and scanned within 48 hours of onset into IST-1[19] and among patients recruited and scanned under 6 hours in IST-3[20]. This is usually what is required when considering further investigations or treatment in the acute stages of stroke.

1.3 Methods of imaging acute stroke patents

1.3.1 Computerised Tomography (CT)

CT is the most commonly used technique to scan acute stroke patients and is currently the imaging method of choice recommended by the Royal College of Physicians.[21] It was developed by Godfrey Hounsfield in 1972,[22] and the first head CT scanners were installed for clinical use in 1975. It is based on a narrow beam of x-rays being passed through the area of interest from different angles around the circumference of an object. It soon became apparent that this technique was useful in the diagnosis of stroke[23] and Hounsfield shared the Nobel Prize for medicine with Allan Cormack in 1979 in recognition of this achievement and for such a step forward in medicine.

The single slice CT scanners, mostly operating in a slice by slice axial scanning mode, have largely been replaced by multislice CT. This technique utilises multidetector rows to allow fast helical scanning and rapid imaging of large volumes of the patient. The data obtained from each set of exposures are reconstructed into an image by computer manipulation.[24,25] Contrast can also be injected to highlight certain lesions. With this modern technology a standard head CT scan can be done rapidly, with image acquisition taking less than 2 minutes to perform.[26]

A major disadvantage of CT is the dose of radiation that the patient receives. The dose naturally depends on the inherent differences in CT equipment and variations in scanning protocols.[27] The mean radiation dose for an adult CT head is 1.5 millisieverts (mSv),[28] which is far smaller than for a CT of the abdomen. Therefore, the average CT head is comparable to about 8 months background radiation in the UK or 100 PA chest radiographs.[29]

Infarct versus haemorrhage

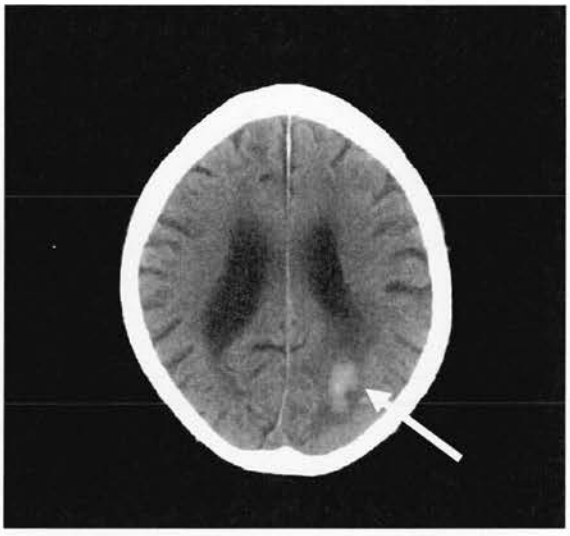
One of the most useful aspects of CT scanning is that, if it is done early on in the presentation of acute stroke, then it is possible to distinguish haemorrhage immediately – a tool that makes CT very useful in the selection of patients for thrombolysis. An acute intracerebral haemorrhage shows up distinctly as an area of higher density than normal brain tissue and looks 'whiter' on CT[30] (Figure 4). As the parenchymal haematoma is broken down over the days after the stroke, its CT attenuation (density) declines to a level similar to the surrounding brain. Thus, for many small intracerebral haemorrhages, after 7 to 10 days CT can no longer reliably differentiate haemorrhage from infarction. Small haemorrhages become isodense with brain faster than large haemorrhages. Eventually the haematoma site becomes hypodense and may be indistinguishable from the cerebromalacia that follows cerebral infarction. Therefore stroke patients should be scanned as soon as possible, and no more than seven days after stroke onset if using CT, to differentiate infarct from haemorrhage reliably.[31]

'Early infarct' changes

In the early stages of an acute ischaemic stroke, the CT scan may well be 'negative'.[32] Hence if a patient presents with stroke-like symptoms, and the CT is normal, the question arises "are the symptoms described by the patient due to a stroke?" This is not such a problem if the patient is to be given aspirin, but many physicians believe that positive evidence of an infarct would make it easier to justify the risks of thrombolysis.

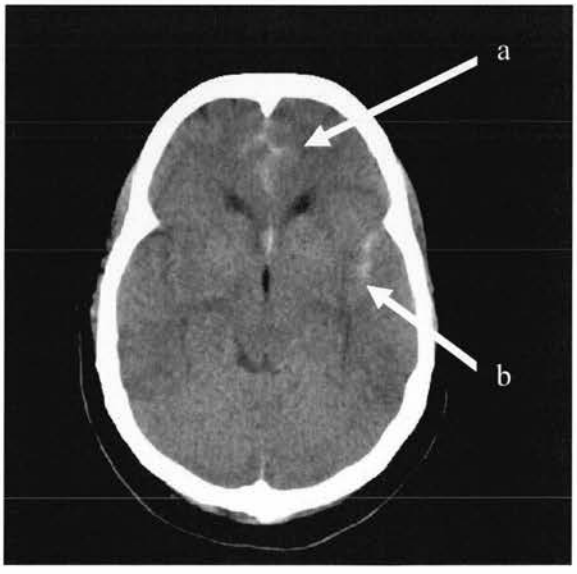
As technology has advanced, the diagnostic capabilities of CT images have improved, enabling the detection of early ischaemic changes consistent with acute stroke within just a few hours of onset in many patients with moderate to severe neurological deficits. The 'early ischaemic signs' that have been reported include loss of the insular ribbon, loss of grey-white matter differentiation (Figure 5) and the hyperattenuated artery sign (Figure 6).[30] However, small ischaemic lesions, such as might occur in patients with mild stroke, may never become visible on CT.

Figure 4a: Primary intracerebral haemorrhage on CT



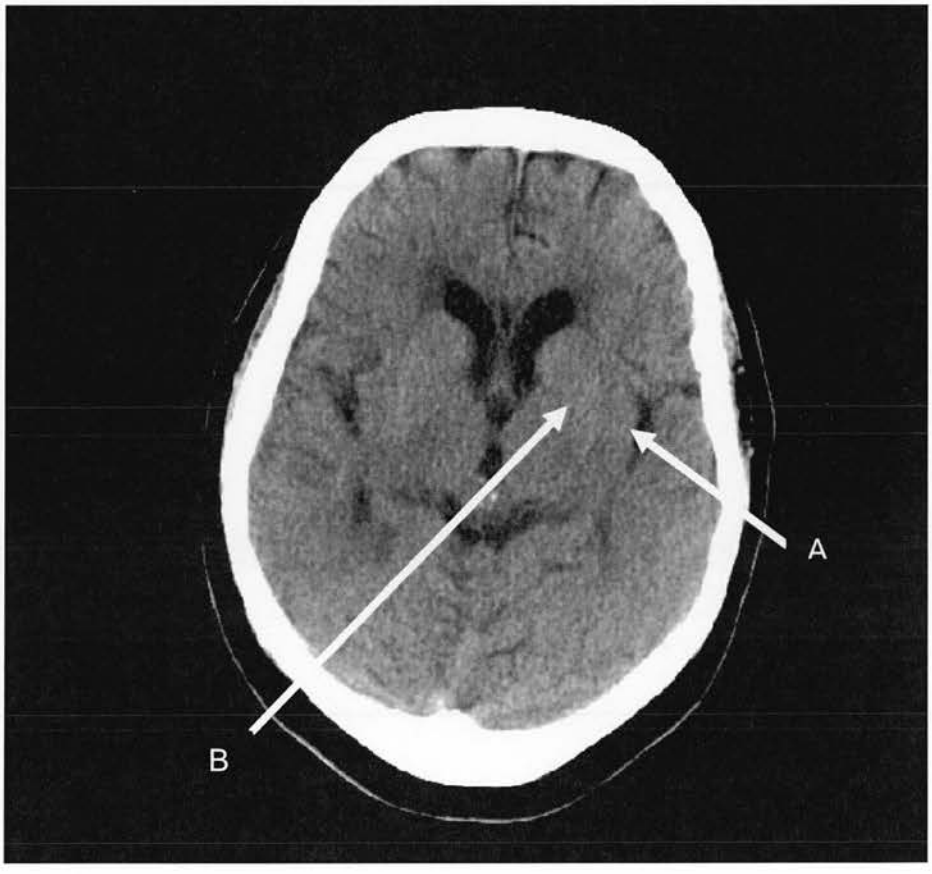
Left parietal hyperattenuation extending to the cortex, consistent with a primary intracranial haemorrhage due to amyloid angiopathy

Figure 4b: Subarachnoid haemorrhage



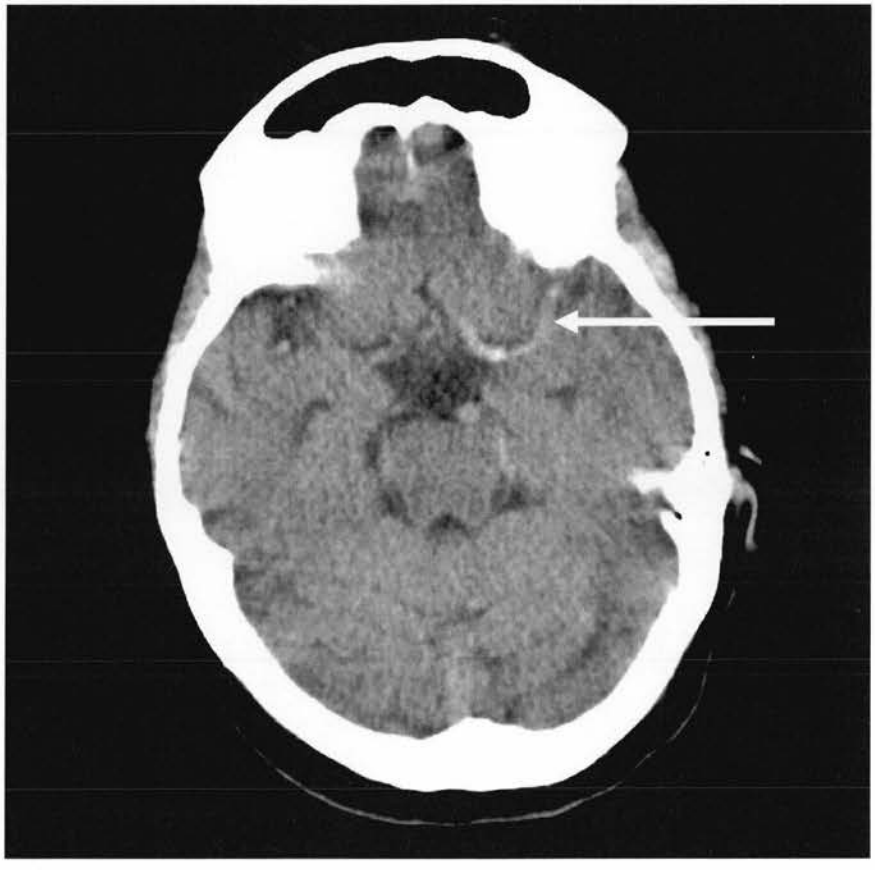
Subarachnoid haemorrhage showing blood in the anterior hemispheric fissure (a) and left sylvian fissure (b)

Figure 5: Early ischaemic change



Loss of the insular ribbon on the left (A) and loss of definition of the lentiform nucleus (B), early CT signs suggesting ischaemia in the territory of the left middle cerebral artery.

Figure 6: Hyperattenuated artery sign



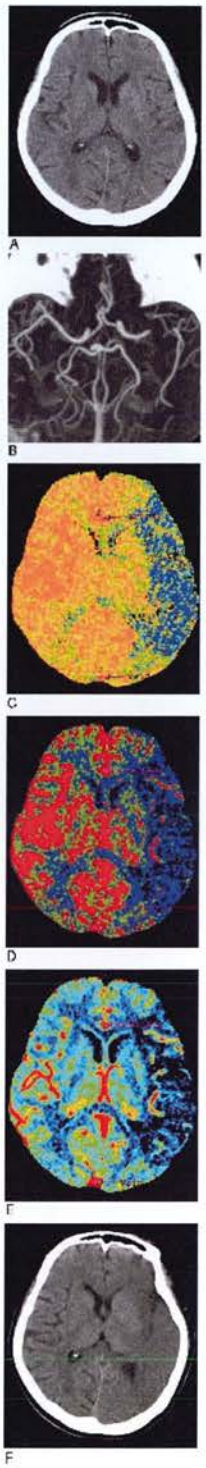
Left hyperattenuated middle cerabral artery sign, suggesting the presence of thrombus in the left middle cerebral artery.

The artery appears 'hyperattenuated' (white) because of the high attenuation due to the blood clot within it; the correlation of hyperdense artery with arterial occlusion has been confirmed since the hyperattenuated artery sign is associated with occlusion of the relevant artery on angiography[33] and disappearance of the sign with reperfusion.[34] However, calcified vessels or an increased haematocrit may also cause a similar appearance, though usually bilaterally and symmetrically.[35]

Imaging the vascular pathology

CT of the brain has continued to evolve. A variety of methods are now available to assess different aspects of vascular pathology: stable xenon-enhanced CT and dynamic CT perfusion. CT perfusion (CTP) holds promise for permitting a positive diagnosis of acute ischaemic stroke when the standard CT is normal by showing an area of reduced cerebral perfusion.[36] A plain CT is performed and shortly afterwards the patient's head is positioned according to a predetermined clinically suspicious slice, and fast repeated scans of the same slice are performed during the administration of a bolus of intravenous contrast. The resulting images require complex processing to produce colour maps representing parameters such as cerebral blood flow (see Figure 7).[37] Although several promising studies suggest that CTP may identify patients with perfusion deficits who might benefit from thrombolysis, there are uncertainties about how best to process the images to obtain this information, and more data are needed.

Figure 7: An example of CT perfusion



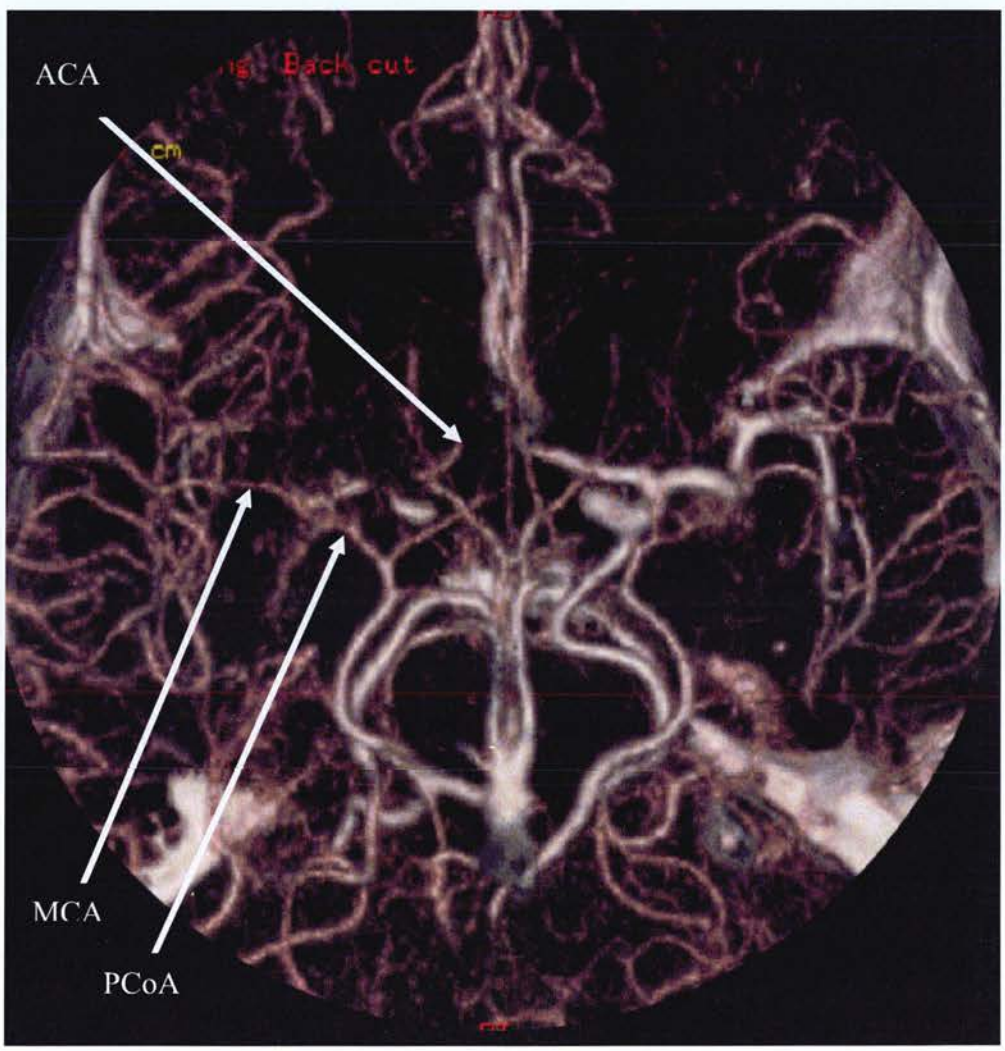
The initial CT (A), the CT angiogram (B) and the CT perfusion maps (C-E) were obtained approximately one hour after symptom onset in a 63 year old woman who presented with right sided weakness. A large perfusion deficit is visible in the left middle cerebral artery territory on the MTT (C), CBV (D) and CBF (E) maps. The area of infarction follow up CT at 24 hours is shown in F.[37]

Computed tomographic angiography (CTA) is another useful technique which can be used to study the cerebral arteries and veins. The arterial and venous system can be imaged by giving a rapid intravenous injection of contrast and timing the images to catch opacification in the vessels of interest. Although the base images are the most useful, these can be reconstructed (Figure 8) to produce 3 dimensional images which can be helpful in acute stroke by demonstrating the site of arterial occlusion.[38,39] When considering patients for thrombolytic therapy, time is critical and although CTA is a rapid procedure which may only require an extra five minutes scanning time and about five minutes reconstructing the images, if used inappropriately, it could introduce an unnecessary delay in treating the patient and exposes the patient to additional radiation. There are also concerns about the safety of contrast agents. X Ray contrast agents can cause allergic reactions and renal problems. More importantly, there is evidence that contrast agents may reduce the efficiency of thrombolytic drugs and increase time to clot lysis.[40] However if extra information is needed in an individual case, e.g. if the routine CT is normal and there is some doubt over the clinical history, then the time it takes to do CTA may be time well spent. As always a quick assessment of the risk/benefit ratio of the particular investigation must be made at the time. This will vary from patient to patient depending on their clinical condition, co morbidities and time since onset of stroke symptoms.

Cost effectiveness of CT

One of the most important issues regarding any form of imaging is cost. Funds within the UK National Health Service are limited and therefore an awareness of cost effectiveness is vital. A policy of 'CT all patients immediately' if they present with suspected acute stroke has been shown to be cost-effective using all data available at the time of the study.[41] These data come from a deterministic model based on data from the UK and therefore applicability to the rest of Europe may be questioned, but provide an excellent basis on which to look at this complex area. This policy was dominant under a variety of plausible scenarios examined in sensitivity analyses. The finding is robust.

Figure 8: CT angiography



This image demonstrates right internal carotid artery occlusion with poor filling of the first part of the anterior cerebral artery (ACA, A1) and middle cerebral artery (MCA, M1) from posterior cerebral artery collaterals through the posterior communicating artery (PCoA). The A1 segment of the ACA also appears acutely blocked.

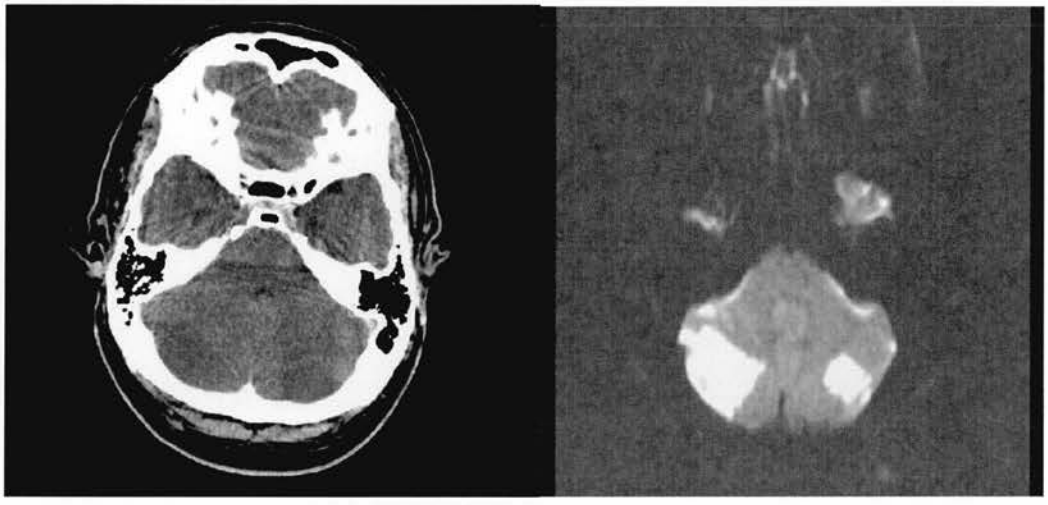
Although implementing this strategy might mean higher initial costs, depending on availability of staff and equipment at the point where the policy is implemented, these are offset by savings in length of inpatient hospital stay as well as lower costs of community care and better quality of life. As a result of these reliable results, this approach is being adopted by NHS, European (2007) and USA (2007) policy makers.

1.3.2 Magnetic Resonance Imaging (MRI) to image the ischaemic brain lesion

MR is more sensitive than CT for detecting the subtle early ischaemic changes in patients with mild to moderate neurological deficits; hence the use of MRI for the assessment of acute stroke patients has increased. A specific sequence, diffusion weighted imaging (DWI), has been developed to detect the tissue changes of cerebral ischaemia at a very early stage (Figure 9). Clinicians have encouraged the use of DWI because of its apparent greater sensitivity and greater interobserver agreement for detecting early ischaemic signs in some studies compared with CT.[42] However this is a simplistic view and fails to take into account the impracticalities of MR in acutely ill patients with hyperacute stroke. In these patients CT is much more practical and nearly as sensitive and specific as MR.

Improvements in MRI have made it potentially even more useful in the scanning of acute stroke patients and some advocate its use for all stroke patients.[43] The newer MRI techniques with ultrafast imaging methods e.g. echoplanar imaging (EPI) have reduced scanning times (useful for restless acute stroke patients). DWI using EPI sequences can image the whole brain (20-30 slices) in a few minutes. During these sequences, strong diffusion-sensitising gradients are used to make the MRI signal sensitive to the random movement of water protons. In protons that are stationary, the symmetrical diffusion-sensitising gradients will led to a dephasing and then exact rephasing of the water

Figure 9: Diffusion weighted imaging (DWI)



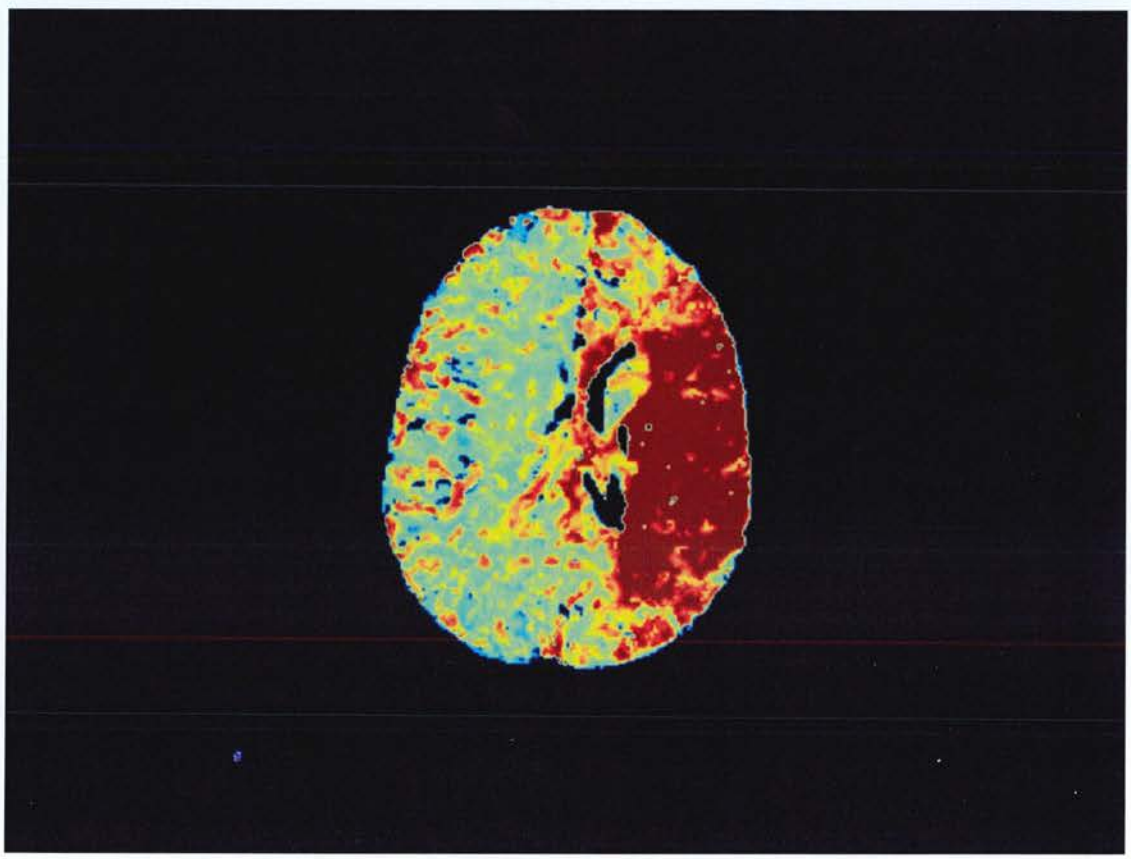
Bilateral cerebellar infarcts. On the CT image on the left the changes are less obvious, but are seen clearly on the DWI MR image on the right.

protons in each voxel. However, if water protons move due to diffusion, phase shifts occur and subsequently imperfect rephasing, which in turn leads to a smaller DWI signal. In an area of acute cerebral ischaemia, intracellular water content increases and cells swell (cytotoxic oedema), which reduces the extracellular space and hence restricts diffusion of extracellular water protons. The resulting area of reduced diffusion appears bright (white) on DWI images.[44] The hyperintensity on DWI can appear within minutes of an ischaemic event, as demonstrated in both experimental and human stroke.[45,46] However, such changes on DWI are not specific for ischaemic stroke. Stroke mimics such as encephalitis, hypoglycaemia, multiple sclerosos and brain abscesses can also show as bright lesions on DWI.[30] MR DWI may also fail to detect ischaemic lesions. In one series of patients with definite ischaemic stroke, 20% had a negative DWI within 24 hours of stroke onset.[47] When DWI was first introduced, it was thought increased signal invariably represented irreversibly damaged tissue, but more recent studies have shown that this is not always the case and that DWI abnormalities can resolve without subsequent infarction developing.[48,49]

MR to image the vascular pathology

Perfusion imaging (PWI) is a method of assessing blood flow in the brain, introduced in the late 1990s but still undergoing evolution. It is based on the same concept as the more recently introduced CTP and many earlier brain perfusion imaging techniques. There are two methods that can be used; contrast bolus tracking or arterial spin labelling. In acute stroke patients, the method that has been most commonly used is contrast bolus tracking, also known as dynamic susceptibility contrast imaging (DSC). A bolus of exogenous contrast agent (gadolinium) is injected intravenously and a series of brain scans then rapidly performed over the next couple of minutes as the contrast bolus passes through the brain. This produces a signal-time curve from which information about the amount of blood flowing through the brain per unit of tissue and time can be derived. The details will be described in later chapters. Processing of these images can

Figure 10: Mean transit time (MTT) perfusion map



Reduced blood flow in the left MCA territory

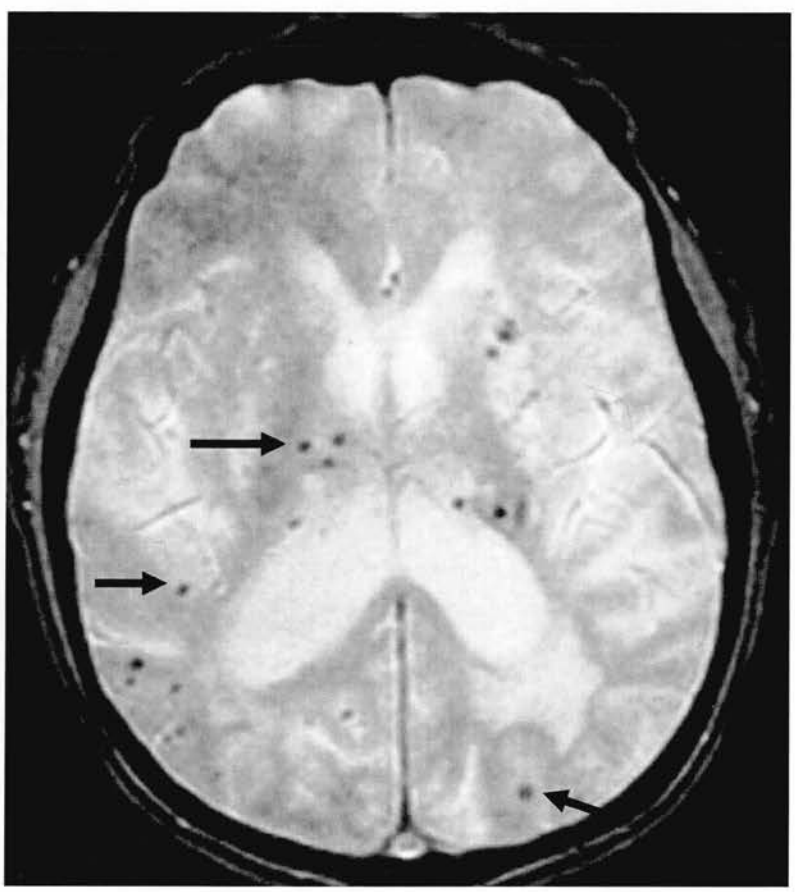
then reveal the areas with altered blood flow e.g. Figure 10. The chief problem with PWI is that post processing of the images is required and the extent of this processing and the time it takes depends on the perfusion method being used. Thus any gain in diagnostic information with PWI must be balanced against the extra time required, especially if thrombolysis is being considered. There are a number of perfusion parameters that have been measured (e.g. time to peak, mean transit time), but as yet there is no clear consensus on which method is best[50] and this will be discussed later.

MR to select patients likely to respond to thrombolysis

In acute ischaemic stroke, if the perfusion lesion is larger than the diffusion lesion, a PWI/DWI 'mismatch' is said to exist. This area of mismatch is thought to represent the ischaemic penumbra i.e. the area of tissue that is under perfused but has the potential to recover from the ischaemic insult if the affected area of brain is reperfused.[51] Hence, it has been suggested that patients with evidence of a significant degree of mismatch would be ideal candidates for thrombolytic treatment. However the destiny of the tissue in the area of PWI/DWI mismatch area has remained unpredictable and it is also apparent that the DWI lesion may expand or shrink without treatment. The topic of mismatch will be discussed in greater detail later in this thesis.

MR gradient echo imaging (GRE) is very sensitive at detecting the haemosiderin deposits in the brain which are the residue of intracerebral haemorrhage and appear as areas of signal loss (i.e. dark). These persist for months and years after a bleed. If the lesions are very small and punctuate, they are referred to as 'microbleeds' (Figure 11). There have been suggestions that microbleeds on MRI may be a marker of increased risk of intracranial bleeding in patients receiving thrombolytic therapy for acute ischaemic stroke.[52] However, among patients whose presenting problem is an acute ischaemic stroke, it is not yet clear whether the presence of microbleeds should be regarded as a contraindication to thrombolytic therapy or not.[53-56]

Figure 11: Microbleeds on GRE MR



Multiple areas of signal intensity loss i.e. microbleeds

1.3.3 MR to detect acute intracranial bleeding

MR imaging is not reliable in the detection of acute subarachnoid haemorrhage and hence CT is likely to remain the gold standard imaging tool for this condition for the foreseeable future. With regards to acute intracerebral haemorrhage, CT has been the investigation of choice, but with gradient echo MR sequences it has been suggested that MRI may be as accurate as CT for the detection of acute parenchymal haemorrhage in patients presenting with focal symptoms.[57] However there is less experience with acute cerebral haemorrhage than there is with acute ischaemic stroke, so the biggest problem with the more specialised MR sequences for detecting intracerebral haemorrhages is that the images may be difficult to interpret and require expert review.

1.3.4 Feasibility of CT versus MRI in the acute stroke patient?

The question of which scanning method should be used in acute stroke patients is contentious and a cause of much debate.[58] CT has the advantage that it is quick, accessible in most hospitals 24 hours a day and it reliably detects acute intracranial haemorrhage, which is of paramount importance in cases where thrombolysis is being considered. The main disadvantage of CT is that it uses ionising radiation, with one brain CT exposing the patient to the equivalent of one year of background radiation.[26] A further disadvantage is that it may not enable a positive diagnosis of ischaemic stroke to be made especially in patients with mild stroke.

Compared with CT, MRI has a large number of potential disadvantages. Firstly, because it involves placing the patient in a strong magnetic field, it can cause malfunction, movement and heating of any metal objects in the patient's body.[59,60] Hence patients with cardiac pacemakers, intracranial aneurysm clips, metallic foreign bodies in the eye or elsewhere should not be scanned. MRI scanners are also more claustrophobic[61] than CT scanners, although the modern designs have improved to some extent on this problem. Due to the length of time needed to acquire images, patients

have to lie supine for some time. This is not ideal in acutely ill stroke patients, many of whom have impaired swallowing ability and hence are at risk of aspiration if laid flat for too long.[62,63] In such unstable patients, there is the risk that they may not be able to protect their airway safely and aspirate and because of ventilation/perfusion changes in stroke may become hypoxic in the scanner.[64] Finally, MRI scans are noisy and despite providing patients with ear plugs they may not be able to tolerate the procedure, whilst others may simply be too ill to be submitted for such an investigation. In some series, between 20% and 40% of patients with acute stroke could not be scanned due to medical reasons.[62,63]

The availability of CT and MR scanners is also an issue. Four successive audits by the Royal College of Physicians Sentinel audit for stroke (last done in 2004) have shown that CT has become increasingly available to stroke patients in the UK and the majority of hospitals in the UK now have the facilities to CT scan a stroke patient acutely.[15] However the availability of MR scanners, although improving, appears relatively limited outside large teaching hospitals.

As mentioned earlier CT scanning is cost effective in acute stroke, but the relative cost effectiveness of CT and MR has not been determined. Hence, identifying effective and widely practicable imaging strategies for the management of stroke and the selection of patients for thrombolysis is a priority. In particular it is important to decide whether MR should replace CT scanning for some – or for all – categories of patient with acute stroke. This thesis will therefore examine several key aspects of imaging in acute stroke that should inform the development of policy in this area.

1.4 Thrombolysis

1.4.1 Background

Intravenous thrombolytic therapy with recombinant tissue plasminogen activator, rt-PA has been licensed for use in selected patients with acute ischaemic stroke. The idea behind thrombolytic therapy is that, by dissolving the clot occluding the cerebral artery, ischaemic brain tissue is reperfused quickly. Reperfusion should decrease the volume of brain tissue damaged by ischaemia, and hence lead to less neurological impairment and less disability. Thrombolysis for acute stroke is not new. The first trial of thrombolysis for acute stroke was published in 1958[10] and the first 'positive' trial was reported 10 years ago.[65] However, even in countries such as the USA, where it has been licensed since 1996, its use in routine clinical practice is limited and variable (an average of 4% of all strokes, with a range from 0% to 12%).[66,67] Since then rt-PA has been licensed for the treatment of acute ischaemic stroke in Europe and many other parts of the world. Thrombolysis has the potential to benefit many more patients, if the ongoing trials show which categories of patient outside the current licence benefit from treatment. One theoretical model suggests that, if it could be used in 30% of patients in Europe, up to 14000 ischaemic stroke patients could avoid death or disability each year.[68] A major problem with the current approval is that patients must be treated within 3 hours of symptom onset. At present this is a difficult target to achieve.[69] There may be delays at every stage: recognition of symptoms as stroke, calling emergency services, getting to hospital, clinical examination, bedside investigations and brain imaging (which is necessary to exclude intracranial haemorrhage and stroke mimics). Even in hospitals that have a large throughput of stroke patients and well organised acute stroke services this is a time consuming process. Some centres do not have acute stroke experts on site and here processes such as telemedicine[70] are being introduced to try and increase access to the treatment and hence improve equity of care across different regions. Before this drug can reach its full potential it is vital that hospitals have organised acute stroke care,

to include streamlined imaging and a well organised acute stroke unit. This requires not only reorganisation of existing services but also a large investment of time and money.

1.4.2 The evidence for thrombolysis in acute ischaemic stroke

Thrombolytic therapy has now been evaluated in several randomised trials in acute ischaemic stroke. The summary of the randomised trial evidence in the 2003 Cochrane systematic review[71] is being updated, but until the results of two large ongoing trials (ECASS III and IST-3) are known, the conclusions of the 2003 review are unchanged. By 2003 there had been 18 randomised trials including 5727 patients. The agents tested include urokinase, streptokinase and recombinant pro-urokinase. About half the data relates to recombinant tissue plasminogen activator (rt-PA, alteplase) and, as mentioned before this is the only thrombolytic drug currently licensed for acute stroke treatment. In an analysis of 'any thrombolytic agent versus control' given up to six hours after stroke there was a significant reduction in death or dependency with thrombolysis; 53.3% of those allocated to thrombolytic therapy compared to 58% of those allocated to control (OR 0.84, 95% CI 0.75 to 0.95, p=0.004). This is the equivalent to 43 fewer patients dead or dependent (Rankin 3-6) per 1000 patients treated.[71] The review permitted an indirect comparison of the effect of rt-PA with other thrombolytic agents. The authors stated that 'Trials testing intravenous recombinant tissue plasminogen activator suggested that it may be associated with slightly less hazard and more benefit than other drugs when given up to six hours after stroke but these are non-random comparisons - death within the first ten days OR 1.24, 95% CI 0.85 to 1.81, death at the end of follow-up OR 1.17, 95% CI 0.95 to 1.45, dead or dependent at the end of follow-up OR 0.80, 95% CI 0.69 to 0.93. However, no trial has directly compared rt-PA with any other thrombolytic agent.

In 2003 a cumulative meta-analysis of all the rt-PA trials was published.[72] Data on 2830 patients from 8 trials, since 1992, were included. The cumulative analysis confirmed there were net benefits in treating patients with alteplase, despite the hazards. For every

1000 patients treated with rt-PA up to 6 hours, approximately 55 more patients will be independent at the end of follow-up, including the 'cost' of about 20 extra deaths.[72]

Individual data on 2775 patients from six trials (NINDS part 1 and 2, ECASS-I, ECASS-II and ATLANTIS part A and B) were pooled by the rt-PA study group.[73] This analysis has the advantage of enabling the effect in some specific subgroups to be explored. Multivariate analysis showed that the main factor associated with a favourable outcome (based on Rankin, Barthel and National Institutes of Health Stroke Survey (NIHSS) stroke scores) was early onset of treatment. The analyses were consistent with the Cochrane review and also suggested that there may be worthwhile benefit from thrombolysis up to 6 hours from stroke onset for some patients. However, at all time points the confidence intervals were wide and, hence the estimates of effect were imprecise.

Overall there is good evidence to support the use of alteplase in highly selected patients with ischaemic stroke, aged under 80 years, treated in well-organised centres within 3 hours of symptom onset. However the trial data suggest a wider variety of patients might benefit from thrombolysis, though this hypothesis needs to be tested in further larger scale trials. The most notable group is the elderly. To date the elderly have been under represented in the trials of thrombolysis for stroke, despite the fact that stroke is a disease of the elderly. In the UK, for example, about 20 000 patients aged over 80 have an acute stroke each year. As a consequence of many of the trials setting an upper age limit (only three of the recent trials have not had an upper age limit), only 42 patients aged over 80 have been included in randomised controlled trials[61] and hence alteplase is only licensed - in Europe - for acute stroke in those patients under the age of 80.

More needs to be known about which factors really influence the benefit of treatment e.g. age, concomitant aspirin use, blood pressure, the presence on the pre-treatment CT scan of 'early infarct' signs, or the degree of diffusion/perfusion mismatch on MR

scanning to name but a few. Once more is known about these factors we will be better able to assess the balance of risk and benefit for each individual patient.

Another concern is the under-utilisation of rt-PA within the licence, and the wide variation between centres and countries. The SITS MOST registry reported in March 2005 a fifty-fold variation between European countries in the use of rt-PA for stroke between Finland (about 50 treatments per million population) and France and Portugal (about 1 per million).[74] This prospective observational study has now been published and suggests that rt-PA is safe and effective when given according to strict criteria.[75] However, data from those patients who did not fulfill all the prespecified eligibility criteria were not reported. Therefore, figures relating to symptomatic intracranial haemorrhage and outcome have to be interpreted with caution. At least part of the explanation for the variation in the use of rt-PA must be the lack of really large-scale randomised trial evidence. The example of the implementation of thrombolytic therapy for acute myocardial infarction is illuminating. Before the late 1980's there was similar under-utilisation of the treatment and enormous variation between centres. It was not until randomised trial data were available on over 60000 patients that cardiologists finally accepted the benefits of thrombolysis and then vigorously implemented it in routine clinical practice, which changed extremely rapidly after he publication of the large-scale trials (ISIS-2 and GISSI).[76,77] In stroke, the evidence base is much smaller (just 2800 patients), and I suggest this lack of large scale evidence must be contributing to the poor uptake in routine practice. The ongoing randomised trials of alteplase in acute stroke should help to improve the situation, though none are of 'cardiological' scale (IST-3, ECASS-III, EPITHET).[78]

An economic analysis (based on the UK NHS) of thrombolysis with alteplase for acute ischaemic stroke, found that the estimates of effectiveness and cost effectiveness were imprecise. Although the benefits of treatment up to 6 hours appeared promising, the data did not support the widespread use of thrombolytic therapy outside the terms of the current restricted licence in routine clinical practice in the NHS.[79]

1.4.3 Can imaging help select patients for thrombolysis?

Since treatment of acute ischaemic stroke with thrombolysis is associated with a 3% risk of fatal intracranial haemorrhage it would be of great benefit if there were imaging signs that could help us select those patients who would benefit most from thrombolysis and, just as importantly, help distinguish those who are most likely to be harmed by it.

Over the last decade various CT 'signs' have been proposed to identify the patients most likely to respond poorly to thrombolysis. The European Stroke Initiative recommendations for stroke management, updated in 2003[80] advise caution before giving rt-PA to a patient where the CT demonstrates extended early changes of a major infarction, such as sulcal effacement, mass effect and oedema. The American Stroke Association guidelines,[81] also published in 2003, recommend that patients who have a CT showing multilobular infarction (hypodensity greater than one third of the cerebral hemisphere) should not be treated with rt-PA. These recommendations are based on data from the ECASS trial.[82] In that study, patients with CT evidence of low attenuation involving more than one third of the territory of the middle cerebral artery (MCA) were less likely to have a good outcome after treatment with rt-PA than those who received placebo. However, the radiologists reading the scans were not blinded to follow up scans, so this analysis may have been biased by prior knowledge of subsequent events. Another study of thrombolysis with streptokinase for acute ischaemic stroke did not find any association between early ischaemic changes (categorized into no signs, $\leq 1/3^{rd}$ or $> 1/3^{rd}$ of the vascular territory) and major haemorrhage after thrombolytic therapy.[83] However even if this '$1/3^{rd}$ MCA rule' is to be advised (on the basis of little evidence) the question of how easy it is to estimate greater or less than $1/3^{rd}$ of the MCA territory remains. An objective CT grading scheme, such as the Alberta Stroke Programme Early CT Score (ASPECTS) may provide better inter rater agreement compared to the $1/3^{rd}$ MCA rule and at least ensures that inexperienced CT readers carefully examine all areas of the CT.[84] The Third International Stroke Trial (IST-3) will provide further

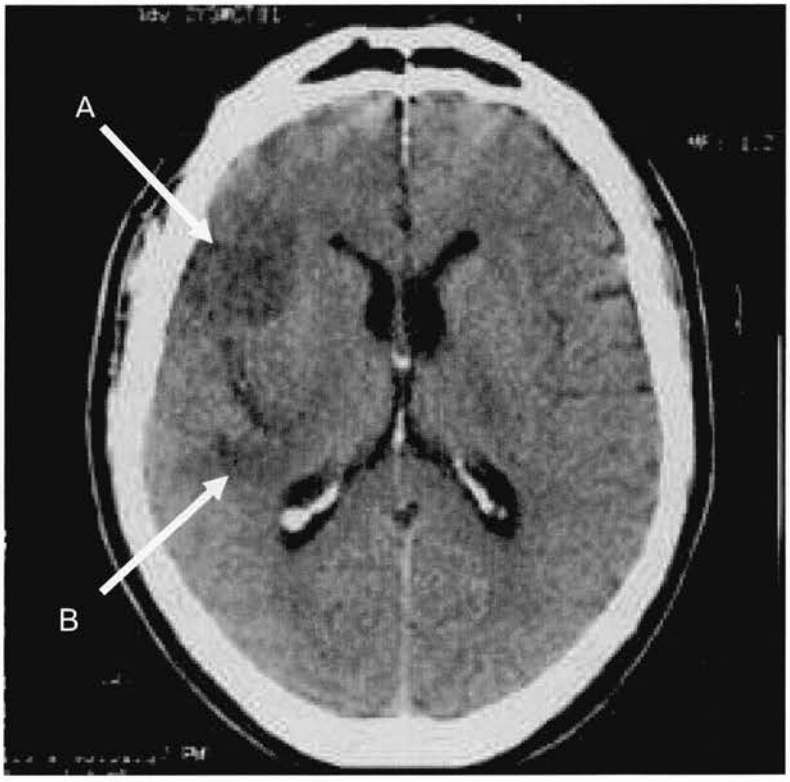
prospective data on whether CT features influence the response to rt-PA, and, if so, which are the most important. To date a systematic review of early infarct signs and interaction with thrombolysis did not find any association between early infarct signs and poor outcome.[85] When examining the CT, clinicians should look for CT signs that don't fit with the clinical history. For example, a patient with right hemisphere stroke may have anosognosia and hence not realise when their stroke symptoms started. In the example in Figure 12, the lesion on the CT scan looks more hypoattenuated than would be expected for a stroke onset of just 2.5 hours. In this case, it was later established that onset was probably 8 hours before the scan (hence indicating that the patient was ineligible for thrombolysis). In general, if the clinical history and CT do not match, then extreme caution should be advised in proceeding with thrombolytic therapy. It is often advisable to revisit the history again if there is a clinical-CT mismatch.

1.5 Consent

It is important to evaluate new interventions for the treatment of medical emergencies (such as acute stroke) by means of randomised controlled trials. Advanced MR imaging may assist in the selection of patients for thrombolysis, and although limited availability of MR in the UK may limit its use, it may be valuable in other countries. After imaging, the next step in the process of care is to streamline the process of consent.

The standard approach to recruitment in a randomised trial of a non-emergency treatment is to require fully informed written consent after giving the patient sufficient time to consider the matter. This is clearly not practicable in the emergency treatment of acute stroke, where patients may have a variety of neurological deficits which either impair effective spoken or written communication and/or writing (e.g. coma, confusion, paralysis, aphasia).[86,87] There is substantial variation between countries in the legal and regulatory requirements for consent procedures for trials being conducted in such patients. In Europe and the USA, such research can only be conducted if several

Figure 12: CT scan showing changes which suggest apparent time of stroke onset may be incorrect



This patient has a well defined, sharp edged, hypoattenuated wedge-shaped lesion in the right posterior frontal region (A) and a smaller similar low density area in the right posterior sylvian region (B). The patient's symptoms were initially said to have started 2.5 hours prior to the scan. However, this lesion is well and sharply demarcated and very hypoattenuated suggesting that the onset of the infarct was more than 2.5 hours previously. Further questioning revealed that the patient's stroke symptoms had probably started 8 hours earlier.

stringent conditions are met, which may render some types of research impractical. Further issues surrounding consent will be discussed later.

1.6 Conclusion

Advanced MRI techniques clearly have great potential for wider use in acute stroke. In the imaging part of this thesis I will concentrate on what one particular MRI technique, the 'perfusion diffusion mismatch concept', may add to CT in the diagnosis of acute ischaemic stroke, and in particular how it might influence the selection of patients for thrombolysis. MRI scan times have become shorter and the availability of multichannel phased array brain coils and the development of parallel imaging techniques such as sensitivity encoding (SENSE) allow comprehensive MR stroke imaging to be completed in under five minutes.[88] However, these advantages may – for many acutely ill patients – be offset by lack of access, contraindications to MR and the difficulty of ensuring patient safety in the scanner. This thesis therefore focuses on three questions relevant to selecting patients for thrombolysis: 1) Can MRI assist in the selection of patients with acute ischaemic stroke for thrombolysis?; 2) If it does, is MR available to patients with acute stroke in the UK? and 3) For patients who meet clinical and imaging criteria for thrombolysis, what methods to obtain consent are most relevant?

1.7 Summary

- Stroke is a disorder which places a huge burden on medical resources and on society and is likely to continue to do so for the foreseeable future.

- In combination with the history and clinical findings, imaging of acute stroke patients has made it possible to make rapid and accurate diagnoses in patients presenting early with stroke syndromes.

- CT scanning is the standard technique for brain imaging in patients with suspected acute stroke
  - It excludes major stroke mimics (e.g. tumour)
  - It identifies ICH and SAH rapidly and reliably (particularly important in patients being considered for thrombolysis).
  - If done within 7 days, is suitable for excluding haemorrhage among patients being considered for treatment with antiplatelet, anticoagulation, or carotid endarterectomy
  - However, it does expose the patient to a dose of radiation (1.5mSv)

- Expert clinical assessment and prompt CT scanning are often sufficient to select patients for treatments such as thrombolysis.

- If CT is normal in the context of a patient with a suspected acute ischaemic stroke, there is no positive evidence of ischaemia to support a decision to use thrombolysis (with its associated risks).

- When CT scans are assessed by clinicians with specific scoring systems or after training better detection of 'early ischaemic signs' is possible, which may often be helpful when selecting patients for thrombolysis.

- CT perfusion and CT angiography can demonstrate the underlying vascular pathology, but require extra time and carry the associated risks from the use of intravenous contrast.

- MR (DWI) may be more sensitive at detecting early ischaemia than CT.

- MR GRE is able to provide evidence of previous intracerebral bleeding which may represent a contraindication to thrombolysis.

- MR PWI/DWI 'mismatch' potentially identifies tissue at risk of infarction which may be 'rescued' by thrombolysis.

- MR and CT have advantages and disadvantages in terms of feasibility, safety, availability and cost effectiveness.

- The process of consent should begin immediately and continue in parallel with early clinical assessment and be completed after imaging.

- Many patients suitable for thrombolysis are not competent to give fully informed written consent; a range of methods are needed.

Table 1: Interventions (specific investigations, procedures and treatments) commonly used in patients with acute cerebrovascular disease, and the frequency with which they are used in routine practice

INTERVENTION	**STROKE TYPE**		
Treatments	**Infarct**	**ICH**	**SAH**
Aspirin	Yes	Avoid	Avoid
Anticoagulants	Sometimes	Avoid	Avoid
Thrombolysis	Sometimes	Avoid	Avoid
Carotid endarterectomy	Sometimes	Avoid	Avoid
Endovascular treatment	Very rare	Very rare	Often
Investigations			
Lumbar puncture	Rarely	Rarely	If CT negative
Angiogram	Rarely	Sometimes	Usually

ICH = intracerebral haemorrhage
SAH = subarachnoid haemorrhage

References

1. Wilkins RH. *J Neurosurg* 1964;240-244.

2. Clarke E. Apoplexy in the Hippocratic writings. *Bulletin of the History of Medicine* 1963;37:301-314.

3. Warlow C, Dennis MS, van Gijn J, Hankey GJ, Sandercock PAG, Bamford J et al. Development of knowledge concerning cerebrovascular disease. *Stroke. A practical guide to management*, 2 edn. Blackwell publishing, 2002:4-27.

4. Perthen J, Calamante F, Gadian D, Connelly A. Is quantification of bolus tracking MRI reliable without deconvolution? *Magn Reson Med* 2002;47:61-67.

5. Heiss W-D, Graf R. The ischaemic penumbra. *Curr Opin Neurol* 1994;7:11-19.

6. Menken M, Munsat TL, Toole JF. The Global Burden of Disease Study. Implications for neurology. *Arch Neurol* 2000;57:418-420.

7. Gubitz G, Sandercock P, Counsell C. Antiplatelet therapy for acute ischaemic stroke (Cochrane Review). In: The Cochrane Library. Issue 3. 2001. Oxford: Update Software; 2001.

8. Sinha S, Warburton EA. The evolution of stroke units - towards amore intensive approach? *Q J Med* 2000;93:633-638.

9. Department of Health (UK). *National service framework for older people modern standards and service models*. London Department of Health, 2001.

10. Sussman BJ. Thrombolysis with fibrinolysin in cerebral arterial occlusion. *JAMA* 1958;167:1705-1709.

11. Meyer JS, Gilroy J, Barhart MI, Johnson JF. Therapeutic thrombolysis in cerebral thromboembolism. *Neurol* 1963;13:927-937.

12. van den Bergh WM, van der Schaaf I, van Gijn J. The spectrum of presentations of venous infarction caused by cerebral vein thrombosis. *Neurol* 2005;65:192-196.

13. Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB et al. Benefits of carotid endarterectomy in patients with moderate or severe stenosis. *NEJM* 1998;339:1415-1425.

14. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998;351:1379-1387.

15. MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet* 2004;363:1491-1502.

16. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet* 1991;337:1521-1526.

17. Toni D, Fiorelli M, Gentile M, Bastanello S, Sacchetti ML, Argentio C et al. Progressing neurological deficit secondary to acute ischaemic stroke. A study on predictability, pathogenesis and prognosis. *Arch Neurol* 1995;52:670-675.

18. Heinsius T, Bogousslavsky J, van Melle G. Large infarcts in the middle cerebral artery territory: eitiology and outcome patterns. *Neurology* 1998;50:1940-1943.

19. Woldeck A, Sarzynska-Dlugosz, Sandercock P, Czlonkwska A. Agreement between the clinical Oxfordshire Community Stroke Project classification and CT findings in Poland. *Eur Radiol* 2004;11:91-96.

20. Kobayashi A, Bembeneck J, Sandercock P, Kane I, Skowronska M, Czlonkwska A et al. Correlation of stroke subtype in OCSP classification and early ischaemic changes on CT: an analysis based on the first 389 patients from the IST-3 trial. *Cerebrovas Dis* 2006;21(suppl 4);35.

21. www.rcplondon.ac.uk.

22. Hounsfield GN. Computerized transverse axial scanning (tomography) 1. Description of system. *Br J Radiol* 1973;46:1016-1022.

23. Hayward RD, O'Reilly GV. Intracerebral haemorrhage: accuracy of computerised transverse axial scanning in predicting the underlying aetiology. *Lancet* 1976;1:1-4.

24. Prokop M. General principles of MDCT. *Eur J Radiol* 2003;45:S4-10.

25. Kalender W. *Computed tomography*. New York: John Wiley and sons, 2000.

26. Hankey GJ, Wardlaw JM. Neurologic diagnosis. *Clinical Neurology*, 1 edn. Manson Publishing Ltd, 2002:11-43.

27. Smith A, Shah GA, Kron T. Variation of patient dose in CT head. *Br J Radiol* 1998;71:1296-1301.

28. Shrimpton PC, Hillier MC, Lewis MA, Dunn M. National survey of doses from CT in the UK: 2003. *Br J Radiol* 2006;79:968-980.

29. http://www.radiologyinfo.org.

30. Warlow CP, Dennis MS, van Gijn J, Hankey GJ, Sandercock PAG, Bamford JM et al. What pathological type of stroke is it? *Stroke. A practical guide to management*, 2 edn. Blackwell Science, 2001:151-222.

31. Dennis M, Bamford J, Molyneux A, Warlow C. Rapid resolution of signs of primary intracerebral haemorrhage in computed tomograms of the brain. *BMJ* 1987;279:379-381.

32. Campbell JK, Houser OW, Stevens JC, Wahner HL, Baker HL, Folger WN. Computed tomography and radionuclide imaging in the evaluation of ischaemic stroke. *Radiology* 1978;126:695-702.

33. Leary MC, Kidwell CS, Villablanca JP, Starkman S, Jahahn R, Duckweiler GR et al. Validation of computed tomographic middle cerebral artery "dot" sign: an angiographic correlation study. *Stroke* 2003;34(11):236-240.

34. Arnold M, Nedeltchev K, Schroth G, Baumgartner RW, Remonda L, Loher TJ et al. Clinical and radiological predictors of recanalisation and outcome of 40 patients with acute basilar artery occlusion treated with intra-arterial thrombolysis. *J Neurol Neurosurg Psych* 2004;75(6):657-662.

35. Rauch RA, Bazan C, Larsson EM, Jinkins JR. Hyperdense middle cerebral arteries identified on CT as a false sign of vascular occlusion. *Am J Neuroradiol* 1993;14:669-673.

36. Parsons M, Pepper E, Chan V, Siddique S, Rajaratnam S, Bateman G et al. Perfusion computed tomography: prediction of final infarct extent and stroke outcome. *Ann Neurol* 2005;58:672-679.

37. Lee DH, Kang D-W, Ahn JS, Choi CG, Kim SJ, Suh DC. Imaging of the ischaemic penumbra in stroke. *Korean J Radiol* 2005;6(2):64-74.

38. Knauth M, Kummer R, Jansen O, et al. Potential of CT angiography in acute ischaemic stroke. *Am J Neuroradiol* 1997;18:1001-1010.

39. Graf J, Skutta B, Kuhn FP, et al. Computed tomographic angiography findings in 103 patients following events in the posterior circulation: potential and clinical evidence. *J Neurol* 2000;247:760-766.

40. Morcos SK, Thomsen HS, Exley CM. Contrast media: interactions with other drugs and clinical tests. *Eur Radiol* 2005;15:1463-1468.

41. Wardlaw JM, Seymour J, Cairns J, Keir S, Lewis S, Sandercock P. Immediate computed tomography scanning of acute stroke is cost-effective and improves quality of life. *Stroke* 2004;35:2477-2483.

42. Saur D, Kucinski T, Gryzyska U, et al. Sensitivity and interrater agreement of CT and diffusion-weighted MR imaging in hyperacute stroke. *Am J Neuroradiol* 2003;24:878-885.

43. Chalela JA, Kidwell CS, Nentwich LM, Luby M, Butman JA, Demchuk AM et al. Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke:a prospective comparison. *Lancet* 2007;369:293-298.

44. Neumann-Haefelin T, Moseley ME. MRI in acute stroke. In: Hennerici MG, editor. *Imaging in stroke*, 1 edn. Remedica publishing Ltd, 2003:43-61.

45. Moseley ME, Cohen Y, Mintorovitch J, et al. Early detection of regional cerebral ischaemia in cats: comparison of diffusion and T2-weighted MRI and spectroscopy. *Magn Reson Med* 1990;14:330-346.

46. Warach S, Chien D, Li W, et al. Fast magnetic resonance diffusion-weighted imaging of acute human stroke. *Neurol* 1992;42:1717-1723.

47. Lovblad K-O, Laubach H-J, Baird AE, et al. Clinical experience with diffusion-weighted MR in patients with acute stroke. *Am J Neuroradiol* 1998;19:1061-1066.

48. Fiehler J, Foth M, Kucinski T, Knab R, von Bezold M, Weiller C et al. Severe ADC decreases do not predict irreversible tissue damage in humans. *Stroke* 2002;33(1):79-86.

49. Kidwell CS, Saver JL, Matiello J, Starkman S, Vincela F, Duckweiler G et al. Thrombolytic reversal of acute human cerebral ischaemic injury shown by diffusion/perfusion magnetic resonance imaging. *Ann Neurol* 2000; 47:462-469.

50. Butcher K, Parsons M, Baird T, Barber A, Donnan G, Desmond P et al. Perfusion thresholds in acute stroke thrombolysis. *Stroke* 2003;34:2159-2164.

51. Schlaug G, Benfield A, Baird AE, Siewert B, Lovblad K-O, Parker RA et al. The ischemic penumbra. Operationally defined by diffusion and perfusion MRI. *Neurol* 1999;53:1528-1537.

52. Kidwell CS, Saver JL, Villablanca JP, Duckwiler G, Fredieu A, Gough K et al. Magnetic resonance imaging detection of microbleeds before thrombolysis. An emerging application. *Stroke* 2002;33:95-98.

53. Cordonnier C, Al-Shahi R, Wardlaw J. Spontaneous brain microbleeds: systematic review, subgroup analyses and standards for study design and reporting. *Brain* 2007.

54. Kidwell CS, Saver JL, Villablanca JP, Duckwiler G, Fredieu A, Gough K et al. Magnetic resonance imaging detection of microbleeds before thrombolysis: an emerging application.[see comment]. *Stroke* 2002;33(1):95-98.

55. Kim HS, Lee DH, Ryu CW, Lee JH, Choi CG, Kim SJ et al. Multple cerebral microbleeds in hyperacute ischaemic stroke: impact on prevalence and severity of early haemorrhagic transformation after thrombolytic treatment. *Am J Roentgenol* 2006;186(5):1443-1449.

56. Derex L, Nighoghossain N, Hermier M, Adeleine P, Phillipeau F, Honnorat J et al. Thrombolysis for ischaemic stroke in patients with old microbleeds on pretreatment MRI. *Cerebrovas Dis* 2004;17:238-241.

57. Kidwell CS, Chalela JA, Saver JL, Starkman S, Hill MD, Demchuk AM et al. Comparison of MRI and CT for detection of acute intracerebral haemorrhage. *JAMA* 2004;292:1823-1830.

58. Lev MH. CT versus MR for acute stroke imaging: is the "obvious" choice necessarily the correct one? *Am J Neuroradiol* 2003;24:1930-1931.

59. Shinbane JS, Corretti PM, Shellock FG. MR in patients with pacemakers and ICDs: defining the issues. *J Cardiovasc Magn reson* 2007;1(9):5-13.

60. Boutin RD, Briggs JE, Williamson MR. Injuries associated with MR imaging: survey of safety records and methods used to screen patients for metallic foreign bodies before imaging. *Am J Roentgenol* 1994;11(162):189-194.

61. McIssac HK, Thordarson DS, Shafran R, Rachman S, Poole G. Claustrophobia and the magnetic resonance imaging procedure. *J Behav Med* 1998;3(21):225-268.

62. Hand PJ, Wardlaw JM, Rowat AM, Haisma JA, Lindley RI, Dennis MS. Magnetic resonance brain imaging in patients with acute stroke: feasibility and patient related difficulties. *J Neurol Neurosurg Psych* 2005;11(76):1525-1527.

63. Singer OC, Sitzer M, du Mesnil de Rochement R, Neumann-Haefelin T. Practical limitations of acute stroke MRI due to patient related problems. *Neurol* 2004;10(62):1848-1849.

64. Rowat AM, Dennis MS, Wardlaw JM. Hypoxaemia in acute stroke is frequent and worsens outcome. *Cerebrovas Dis* 2006;21:166-172.

65. National Institute of Neurological Disorders and stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischaemic stroke. *NEJM*1995;333:1581-1587.

66. Johnston S, Fung L, Gillum L, Smith W, Brass L, Lichtman J et al. Utilization of intravenous tissue-type plasminogen activator for ischaemic stroke at academic medical centres: the influence of ethnicity. *Stroke* 2001;32:1061-1068.

67. Reed SD, Cramer SC, Blough DK, Meyer K, Jarvik JJ. Treatment with tissue plasminogen activator and inpatients mortality rates for patients with ischemic stroke treated in community hospitals. *Stroke* 2001;32:1832-1840.

68. Kwan J, Leigh Brown A, Hand P, Sandercock P. In Europe, how many stroke patients can be treated with and benefit from intravenous rt-PA within 6 hours? *Stroke* 200;31:2837.

69. Kwan J, Hand P, Sandercock P. A systematic review of barriers to delivery of thrombolysis for acute stroke. *Age and Ageing* 2004;33:116-121.

70. Levine S, Gorman M. "Telestroke" the application of telemedicine for stroke. *Stroke* 1999;30:464-469.

71. Wardlaw JM, del Zoppo G, Yamaguchi T. *Thrombolysis for acute ischaemic stroke (Cochrane Review)*. Oxford: Update software, 2003.

72. Wardlaw JM, Sandercock P, Berge E. Thrombolytic therapy with recombinant tissue plasminogen activator for acute ischaemic stroke. Where do we go from here? A cumulative meta-analysis. *Stroke* 2003;34:1437-1442.

73. The ATLANTIS EaNN-PSGI. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS and NINDS rt-PA stroke trials. *Lancet* 2005;363:768-774.

74. http://www.acutestroke.org

75. Wahlgren N, Ahmed N, Davalos A, Ford GA, Grond M, Hacke W et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST): an observational study. *Lancet* 2007;369:275-282.

76. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994;343:311-322.

77. Peto R, Collins R, Gray R. Large-scale randomized evidence: large, simple trials and overviews of trials. *J Clin Epidemiol* 1995;48(1):23-40.

78. http://strokecenter.org/trials/

79. Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J et al. A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS. *NHS HTA Programme Monograph* 2002;6(26).

80. The European Stroke Initiative executive committee and the EUSI writing committee. European Stroke Initiative recommendations for stroke management-update 2003. *Cerebrovasc Dis* 2003;16:311-337.

81. Adams HP, Adams RJ, Brott T, del Zoppo G, Furlan A, Goldstein LB et al. Guidelines for the early management of patients with ischemic stroke. A scientific statement from the stroke council of the American Stroke Association. *Stroke* 2003;34:1056-1083.

82. Davalos A, Toni D, Iweins F, Lesaffre E, Bastanello S, Castillo J. Neurological deteriorationin acute ischaemic stroke: potential predictors and associated factors in the European Cooperative acute Stroke Study (ECASS) I. *Stroke* 1999;30(12):2631-2636.

83. Gilligan AK, Markus R, Read S, Srikanth V, Hirano T, Fitt G et al. Baseline blood pressure but not early computed tomography changes predicts major haemorrhage after streptokinase in acute ischaemic stroke. *Stroke* 2002;33:2236-2242.

84. Pexman JH, Barber PA, Hill MD, Sevick RJ, Demchuk AM, Hudon ME et al. Use of the Alberta Stroke Programme Early CT Score (ASPECTS) forr assessing CT scans in patients with acute stroke. *Am J Neuroradiol* 2001;22:1534-1542.

85. Wardlaw J, Mielke O. Early signs of brain infarction on CT:observer reliability and outcome after thrombolytic treatment - systematic review. *Radiol* 2005;235:444-453.

86. Bateman BT, Meyers PM, Schumacher HC, Mangla S, Pile-Spellman J. Conducting stroke research with an exception from the requirement for informed consent. *Stroke* 2003;34:1317-1323.

87. Demarquay G, Derex L, Nighoghossain N, Adeleine P, Phillipeau F, Honnorat J et al. Ethical issues of informed consent in acute stroke. *Cerebrovas Dis* 2005;19:65-68.

88. U-King-Im JM, Trivedi RA, Graves MJ, Harkness K, Eales H, Joubert I et al. Utility of an ultrafast magnetic resonance imaging protocol in recent and semi-recent strokes. *J Neurol Neurosurg Psych* 2005;76:1002-1005.

2 MR Perfusion Diffusion Mismatch

2.1 Introduction

In the UK the most commonly used imaging modality in the assessment of acute stroke patients is CT. The main reason being, as mentioned in chapter 1, that it is an excellent technique to detect early haemorrhage and stroke mimics such as tumours. However, MR imaging is constantly being refined and one form of MR imaging concept that has been enthusiastically promoted is that of the 'perfusion-diffusion (PWI/DWI) mismatch'.

The theory behind 'mismatch' came from studies of experimental large artery occlusion stroke models in the 1970s. Following middle cerebral artery occlusion, microelectrode studies in the baboon cortex demonstrated that some reduction in cerebral blood flow (CBF) abolished evoked potentials, and further reduction abolished spontaneous activity of cortical neurons.

The term 'ischaemic penumbra' was defined by Astrup and colleagues in 1981[1] and referred to brain tissue which is perfused between the thresholds of functional impairment (reduced or absent electrical activity) and loss of morphologic integrity (cell disruption and death). This is illustrated in the image in the introduction (p15). Cells whose perfusion has been reduced to this level of functional impairment have the capacity to recover if perfusion is improved.[2] However the penumbra is not a static entity, but a dynamic process, dependent on residual flow and the duration of flow disturbance.[3] In order to transfer this concept from animal experiments to man the definition of three critical values are required (all of which are difficult to calculate in the acute stages of an ischaemic stroke):

- The flow threshold for functional impairment – to identify functionally impaired tissue
- The flow threshold for morphologic damage – to identify irreversibly damaged tissue
- The time period that a tissue tolerates decreased flow before it becomes irreversible damaged – to predict recovery of function with reperfusion.[2]

In the 1980s and 1990s other experiments were performed in different animal models, from gerbils and rats to cats and monkeys, which further explored the penumbra and factors influencing it, including duration of ischaemia, cerebral blood flow levels and metabolic changes.[4-9] Similar critical blood flow levels were found in all species, bearing out the penumbra concept, although the precise levels varied to some extent between species and experiments.

Attempts to study the critical flow levels and penumbra in man started with a radionuclide imaging technique called positron emission tomography (PET). PET has been used to determine pathophysiological changes occurring shortly after ischaemic stroke in man and animals. It permits major aspects of brain physiology to be investigated, depending on the properties of the radiotracer used and biomathematical models selected.[10] PET provides a method for assessing physiological variables without the need for invasive procedures that were used in the early animal experiments to explore the penumbra. Although multitracer PET cannot accurately measure the penumbra by its original definition, the use of this technique was an important step in moving from investigating the penumbra in experimental animal models to evaluating patients with acute stroke.

PET allows several variables to be mapped. These include regional cerebral blood flow (rCBF), regional cerebral blood volume (rCBV), regional cerebral metabolic rate for oxygen ($rCMRO_2$) and regional cerebral metabolic rate for glucose ($rCMR_{glc}$). $CMRO_2$ and CMR_{glc} are both useful values when looking at cell viability, since they indicate

oxygen consumption and glucose consumption, respectively of the cells. Whilst cells are still using oxygen and glucose they must still be viable.

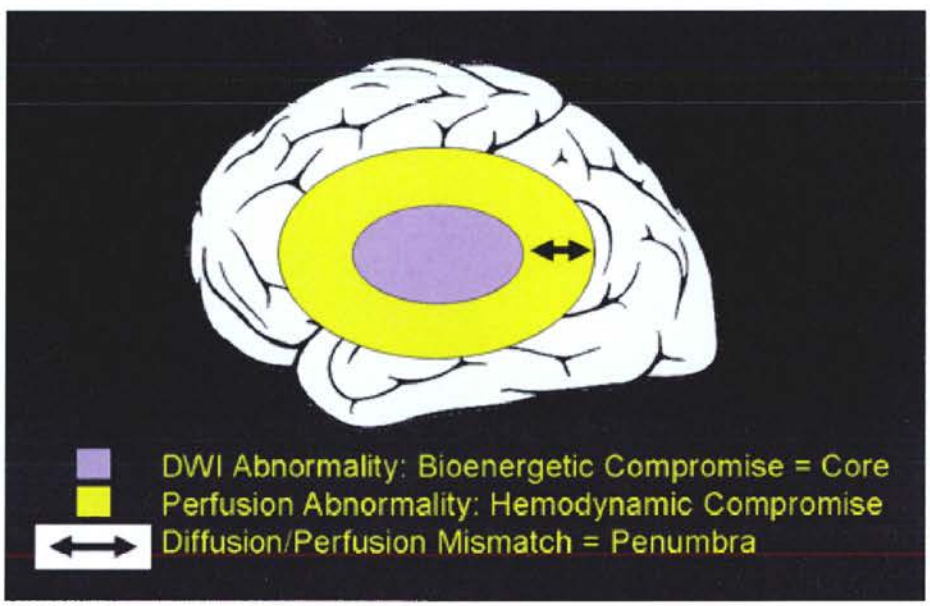
Using advanced PET techniques, both baboon and cat models of stroke after middle cerebral artery occlusion have been studied.[11-13] In cats CBF decreases in the whole vascular territory, possibly reflecting a model more akin to humans. One study of middle cerebral artery occlusion in cats sequentially studied CBF, $CMRO_2$ and CMR_{glc} before, during, and up to 24 hours after vascular occlusion.[14] This found that CBF decreased to less than 30% compared to control in the middle cerebral artery territory on arterial occlusion. $CMRO_2$ was less diminished and was preserved at an intermediate level. Consequently, oxygen extraction fraction (OEF) was increased indicating 'misery perfusion'. The ischaemic penumbra spread from the core to the borders of the MCA territory over time and was generally followed by a marked decrease in OEF, reflecting impairment of metabolism and transition to necrotic tissue. The infarcts were generally complete after 18-24 hours, although occasionally spontaneous collateral reperfusion resolved the penumbra condition. However most animal experiments are small, PET is expensive, labour intensive and technically quite difficult. Therefore the data are helpful, but limited, in their generalisability to what might be happening in a broader range of stroke patients.

Moving a step closer to the clinical situation, PET studies were carried out in humans with the aim of identifying irreversibly damaged tissue and compromised, but viable tissue. PET with ^{15}oxygen tracers became regarded as the gold standard for the pathophysiological changes in early stroke.[15] The quantitative measurement of variables such as CBF, OEF and $CMRO_2$ allowed the independent assessment of perfusion and energy metabolism. However, using such techniques is complicated and requires multitracer application, limiting its use in the clinical setting. Numerous studies have been performed in an attempt to identify values for the penumbra threshold and the infarction threshold. In the late 1990s detailed PET studies in patients studied 5-18 hours after symptom onset reported a CBF penumbra threshold of around 17-22

ml/100g/min, and an infarction threshold of about 7-10/ml/100g/min (although the values quoted vary between studies) and 0.87mls/100g/min for CBF and oxygen consumption, respectively.[16-18] These analyses indicated that increased OEF is a poor predictor of tissue viability, and that isolated flow measurements at a single time point might be confusing if the pattern over time is unknown. Other markers of neuronal integrity have been explored including flumazenil (a neuronal benzodiazepine/$GABA_A$ receptor ligand). Flumazenil only binds to active GABA receptors and therefore areas of cerebral tissue with reduced flumazenil binding may indicate areas of reduced cell viability. In one study it was proposed that the penumbra threshold was best defined by CBF, and the infarction threshold by flumazenil uptake.[19]

PET is never going to be a widely available technique suitable for stroke. Since multitracer PET is not practical in the acutely ill and very rarely available in the clinical setting, researchers moved on to test a potentially more widely available imaging method of investigating the penumbra, with MRI. Initially, experimental models of stroke using MRI suggested that DWI would be a useful marker of probably infarcted tissue and perfusion imaging would show areas of reduced perfusion at critical levels which would be at risk of infarction. This led to the concept, in the mid 1990s, that the mismatch between the larger perfusion lesion and the smaller diffusion lesion would indicate 'penumbra' tissue at risk. Diffusion weighted imaging was thought to provide a measure of tissue bioenergetic compromise and perfusion weighted imaging a measure of haemodynamic compromise.[20] From early reports of DWI and PWI, the theory developed that the difference between the two acute lesions (i.e. the mismatch – see Figure 1) represented the ischaemic penumbra (i.e. hypoperfused tissue that has the potential to be salvaged).[21]

Figure 1: The initial diffusion perfusion model

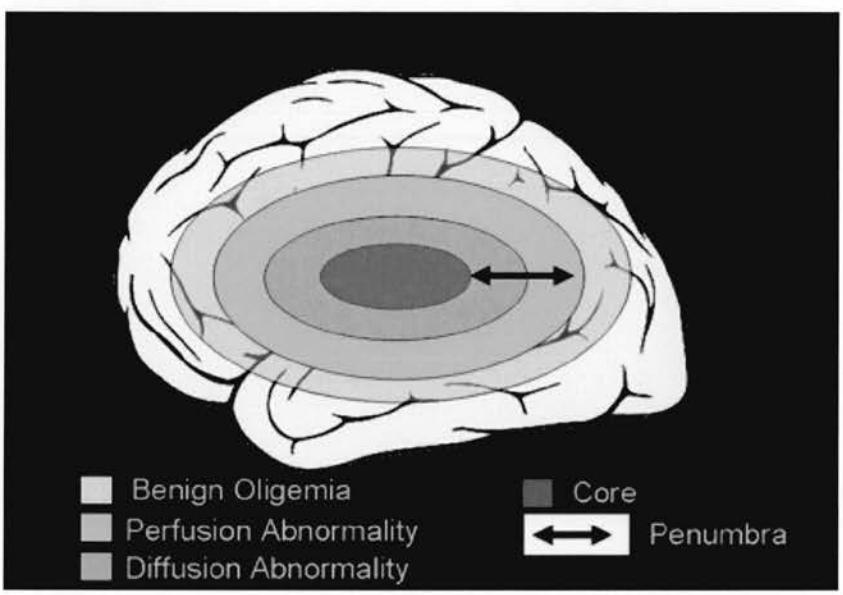


Schematic of the mismatch model for defining the ischaemic penumbra.[20]

This model has evolved further (Figure 2) and it is now thought that some of the DWI lesion is not necessarily irreversibly damaged and so can be salvaged.[22] Furthermore the PWI abnormality includes tissue which is destined to have a relatively benign outcome. The evolution of this theory is important, since it suggests that some patients who do not have mismatch at baseline may still benefit from interventions such as thrombolysis. The presence of 'mismatch' is increasingly being used as one of the selection criteria for inclusion in clinical trials of reperfusion therapies[23,24] and also in routine clinical practice (where the equipment is available).

However, there are a number of inherent problems with what seems, at first glance, a very attractive theory. There are no clear definitions of what constitutes mismatch and no substantial randomised trial evidence to justify its use. As mentioned before, it is now known that the DWI lesion is not irreversible (initial DWI lesions may disappear spontaneously or following thrombolysis).[25] Alternatively patients may have a scan with no visible DWI lesion in the acute setting despite the clinical findings suggestive of stroke. In around fifty percent of such patients ischaemic tissue will be found at follow up.[26] In such DWI negative cases the perfusion image is an important part of the acute MR imaging sequence, since many patients will have a PWI deficit. Such a situation i.e. PWI lesion with no DWI lesion may indicate ischaemic tissue which has not yet reached the point of cell membrane compromise and so is still potentially viable at the time of the scan. There have also been reported cases of DWI and PWI negative acute scans which may go on to show evidence of ischaemic disease e.g. lacunes in the brain stem.[27] In other cases a DWI negative scan may suggest that there is an alternative underlying clinical diagnosis such as migraine or epilepsy. For the PWI lesion, it is increasingly apparent that its appearance depends on which of the many methods available to calculate it was used. Different perfusion parameters (e.g. mean transit time (MTT), regional CBF),[28] and arterial input function (AIF)[29] have been used in different studies but give different perfusion lesion volumes in the same patient, and it is unclear which represents the 'at risk' tissue. For example, perfusion lesions calculated using MTT were larger than CBF or CBV lesions.[28]

Figure 2: The modified diffusion perfusion model



Modified view of MRI-defined ischaemic penumbra in which the penumbra equals not only regions of diffusion-perfusion mismatch, but also a portion of the diffusion abnormality itself.[20]

In addition it appeared that different methods of measuring the same type of perfusion lesion, and underlying vasculopathy have a direct impact on the size of the calculated PWI.[30] Thus it is unclear whether the presence (vs. absence) of mismatch affects prognosis and how mismatch should be calculated. If mismatch is to be used to select patients for acute stroke treatments such as thrombolysis, then the key point is to determine whether thrombolysis has a greater prognostic effect in the presence, rather than in the absence, of mismatch. This requires a randomised controlled trial in which patients with and without mismatch are randomised to receive thrombolysis or control, an expensive and difficult undertaking given that a large sample size would be needed to account for any difference.[31]

As there was already considerable literature on the MR mismatch concept, I undertook a systematic review to assess the evidence on the effect of MR PWI/DWI mismatch in acute ischaemic stroke on outcome (clinical and radiological) and whether this was modified by thrombolysis. I set rigorous pre-specified inclusion and exclusion criteria based on scientific principles for observational studies and randomised trials to minimize bias.

2.2 Magnetic resonance perfusion diffusion mismatch and thrombolysis in acute ischaemic stroke: a systematic review of the evidence to date

2.2.1 Methods

Design

A systematic review of publications describing PWI/DWI mismatch in patients with acute stroke and the relationship to outcome in the presence or absence of thrombolytic treatment. A pre-specified aim of the review was to examine the technical detail of the methods used, and to extract details of the results from the reports. Previous work on systematic reviews of diagnostic tests by members of the Department has shown that, by contrast with reports of randomised trials, abstracts reporting imaging studies do not contain sufficient detail to permit meta analysis (Wardlaw, Sandercock, personal communication). I therefore only included papers published in full in order to obtain detailed methodological data and results.

Search strategy

I developed a search strategy with advice from the Cochrane Stroke Group to identify potentially relevant articles published between January 1996 and May 2005. The search started in 1996 as MR DWI was not available prior to that time. I searched Medline and EMBASE (based on the terms 'diffusion weighted', 'perfusion weighted', 'thrombolysis', 'magnetic resonance imaging', exploded to maximise findings). I then searched the reference lists in the identified articles for further relevant papers. Abstracts from the major stroke meetings (European Stroke conference, World Stroke Congress and American Heart Association stroke meeting) were also searched for relevant studies (that might subsequently have been published in full) and to estimate whether there were likely to be a large number of unpublished studies. Full details of the strategy are given in Appendix 1.

Inclusion criteria

I included prospective studies of human acute stroke, which had included at least twenty patients, imaged at presentation with acute stroke with MR DWI and PWI, with clinical assessment at baseline and follow up at least one month after stroke using a recognised assessment scale, and - where possible - radiological follow up. I planned to include studies irrespective of whether patients received thrombolysis, as long as it was possible to tell which patients had received thrombolysis.

Exclusion criteria

I excluded articles published before 1996 (prior to that neither MR PWI/DWI or thrombolysis were widely used in acute stroke), retrospective studies (because of the potential for bias), studies with less than 20 patients (very small sample sizes are prone to bias, are difficult to blind and provide little robust data to inform clinical practice), and with functional and/or radiological outcome assessed at less than a month after stroke (prior one month would be too early to assess functional outcome; radiologically, ischaemic lesions may still be evolving,[32] fogging may cause underestimation,[33] and oedema may cause overestimation of the final lesion volume[34]).

Data extraction

I extracted data on to a standardised assessment form (Appendix 2). Queries were checked by another reviewer (Professor J Wardlaw) independently. I collected the sample size, patient clinical characteristics, clinical scores (e.g. National Institutes of Health Score, NIHSS), time from symptom onset to imaging, details of the MR sequences performed and perfusion post processing techniques, definition of PWI/DWI mismatch, evidence of infarct expansion (increase in the lesion volume from the acute baseline DWI to final T_2), whether interpretation of the MR images was blinded to clinical details or imaging, details of patients excluded from analysis, whether administration of thrombolysis was randomised or not and any information on functional or radiological outcome (whether or not patients received thrombolysis or had PWI/DWI mismatch). I compared imaging at presentation with final follow up performed at one

month or more. I did not examine scan data from intermediary time points (if available) because they are unreliable for estimation of final infarct extent (see above). I was careful to avoid including duplicate publications derived from the same patients. I defined poor functional outcome as modified Rankin score (mRS) > 1 or Barthel (BI) <90. Details of all the clinical scores cited in the studies are listed in Appendices 3-6 (p178-181).

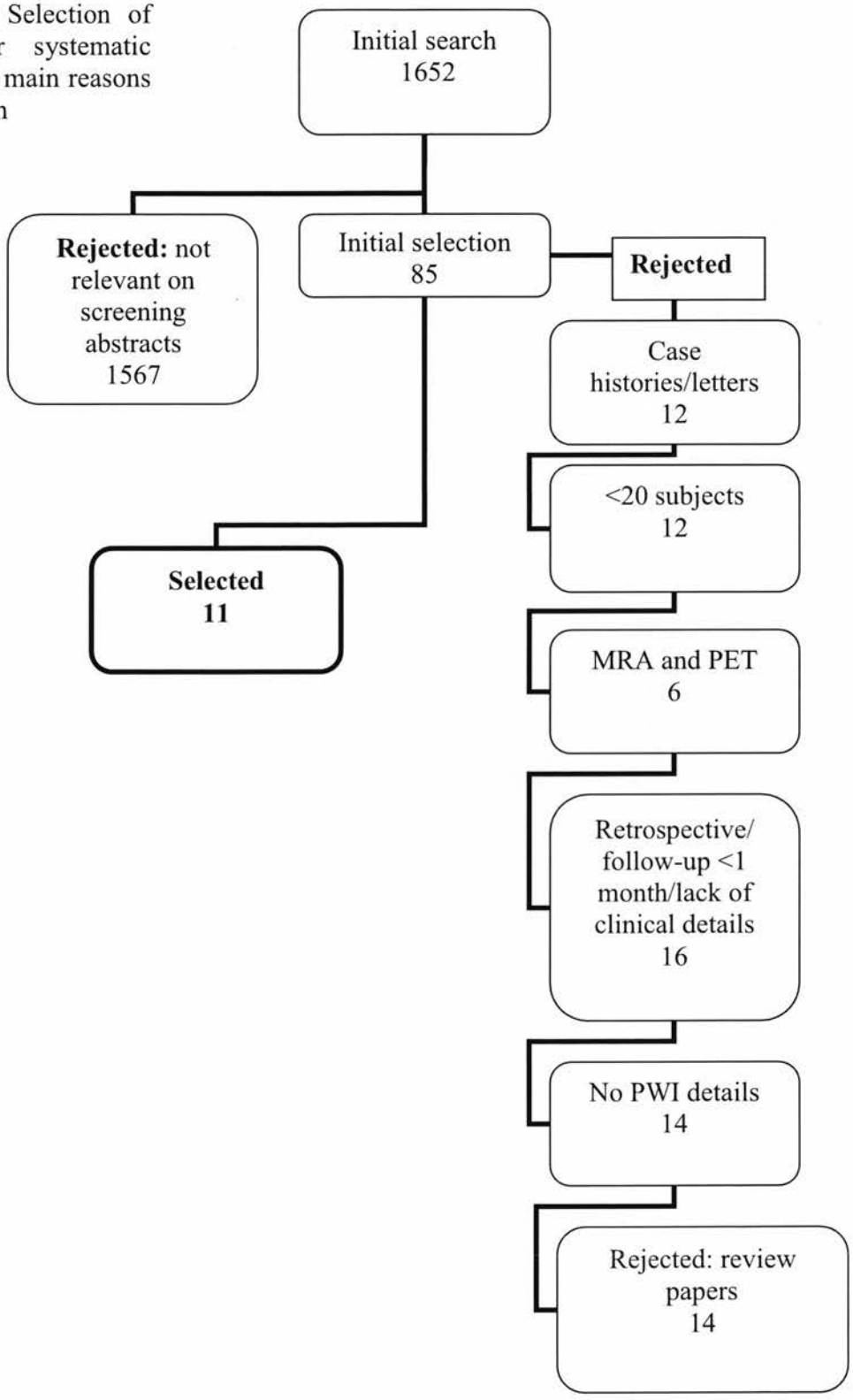
Analysis

I summarised study population demographics, proportions with or without mismatch, number treated with thrombolysis, with poor functional outcome or infarct expansion. I used odds ratios (OR) and 95% confidence intervals (CI) to determine associations between mismatch, infarct expansion, functional outcome and any influence of thrombolysis. I aimed to compare functional and radiological outcomes in patients with mismatch to those without mismatch, and to determine whether thrombolysis changed the relationship between mismatch and functional or radiological outcome.

2.2.2 Results

The search identified 1652 papers on any aspect of DWI and PWI, of which 85 were potentially relevant to DWI/PWI mismatch and outcome +/- thrombolysis. Eleven papers (641 patients) fulfilled all pre-specified inclusion criteria (reasons for rejection, often multiple, grouped by the primary reason are shown in Figure 1).

Figure 1: Selection of papers for systematic review and main reasons for rejection



Methodological details of included studies (Table 1)

Ten included reports[34-43] were prospective observational studies and one[23] was a placebo controlled, double blind, randomised, dose finding phase II trial of desmoteplase. These papers derived from six research groups. Median time to baseline MR imaging ranged from 1.5 to 6 hours after stroke. Six papers had obtained radiological follow up at one month or more[34-39] in most patients.

The most common baseline clinical score was the NIHSS, used in all but two papers,[42,43] by an individual explicitly stated to be trained in its use. In all but one paper,[34] other scores (e.g. BI and mRS) were recorded at follow-up. Eight papers gave incomplete details of blinding of clinical and radiological assessors. Three papers (27%)[40,41,43] did not mention blinding at all.

Measurement of perfusion lesion (Table 2)

All groups used gadolinium-based dynamic susceptibility contrast imaging to assess perfusion, the dose varying from 0.1-0.2mmol/kg. The method for perfusion lesion assessment varied: four papers calculated time to peak (TTP);[34,39,41,43] the others used some form of mean transit time (MTT) measurement, quantitative in 3 cases.[35,37,38]

Assessment of perfusion/diffusion mismatch (Table 2)

There was no consistent definition of mismatch. Amongst the eleven papers from six research groups, there were five different definitions of mismatch. Mismatch was determined by 'visual inspection' in two studies,[23,43] and by tracing the lesion volumes on a workstation in the rest, using various lesion boundary definitions (e.g. visual lesion edge estimation or specific perfusion thresholds e.g. MTT > 4s compared with the contralateral side).

Overall assessment of PWI/DWI mismatch on outcome and effect of thrombolysis

Amongst the 11 studies initially included in the review, I was only able to extract data regarding mismatch and outcome (without or with thrombolysis) from three.[34,37,38] Although all of these studies recruited at least 20 patients, not all of the original sample contributed to the data, mainly due to incomplete imaging (see Table 1). In the rest, it was not possible to separate the results for 'thrombolysis' from 'no thrombolysis' patients and for patients 'with' from 'without mismatch',[35,39,41] even though some did have outcome data. Some papers just reported recanalisation and outcome, not mismatch.[36,40]

All three papers with usable data included patients with and without mismatch and two[34,38] examined the effects of thrombolysis. In total there were 61 patients with, and 18 without, mismatch. Final follow up scans were not available (patient died or scan not done) for 7/61 patients, some with mismatch at baseline and some without. Only two papers reported functional outcomes.[37,38]

PWI/DWI mismatch and outcome: no thrombolysis (Table 3 and Figure 2)

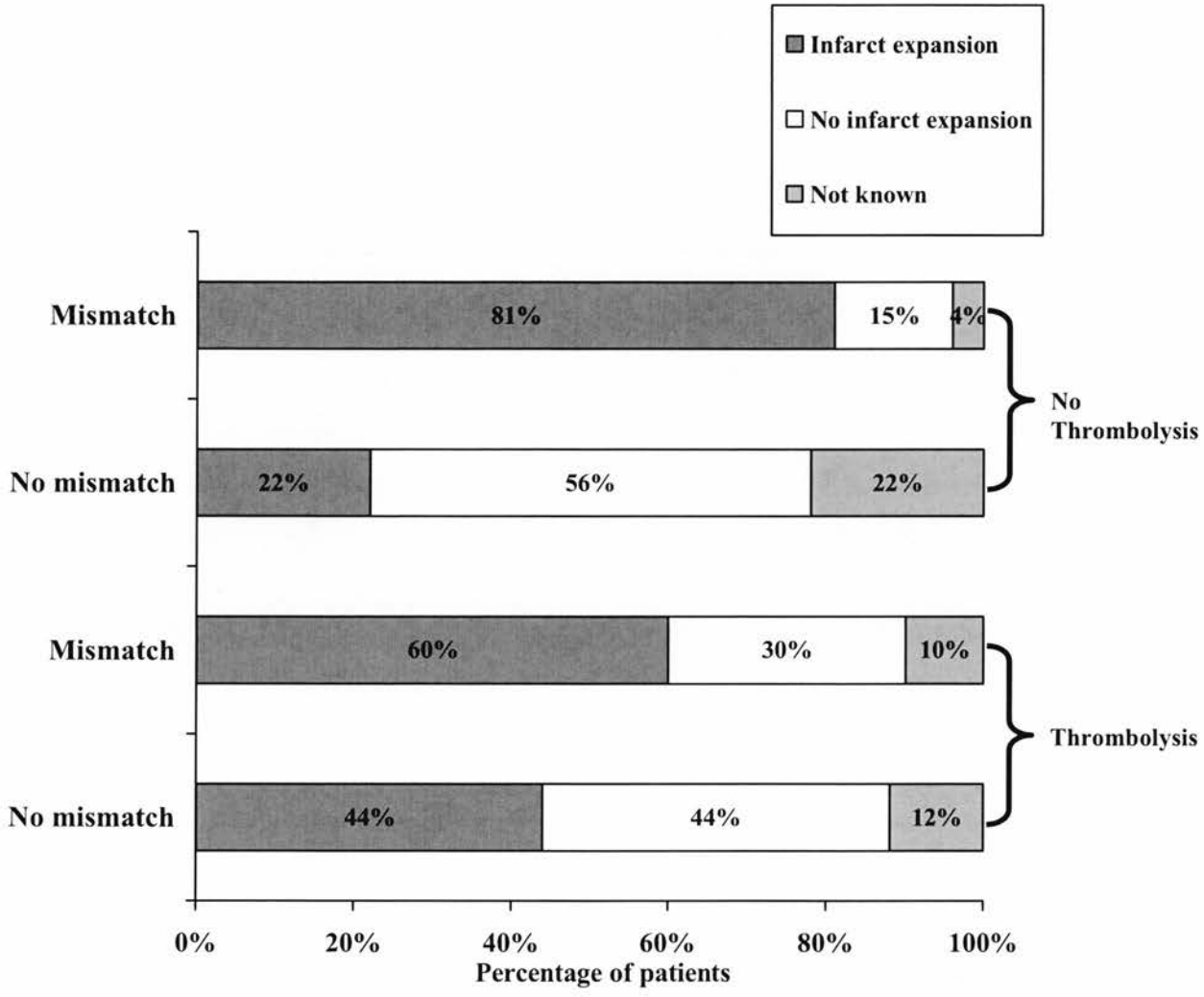
Two papers[37,38] provided data on mismatch and functional outcome and three[34,37,38] on infarct expansion at 1 month or more (total n=50 patients) in patients who did not receive thrombolysis: 41/50 patients had mismatch (by any definition), of whom 33/41 (80%) had any infarct expansion and 6/41(20%) did not (two patients were missing follow-up scans); 9/50 patients had no mismatch of whom 5/9(56%) developed infarct expansion. Therefore mismatch was associated with a non-significant two-fold increase in the odds of infarct expansion (OR 2.2, 95% CI 0.34-14.1). Note the wide confidence intervals include the possibility of both a reduction and an increase in the odds. Data on functional outcome were not presented in a way that allowed calculation of odds ratios. However, the mean BI or mRS at final follow up was non-significantly worse in those with mismatch at baseline than in those without mismatch.

PWI/DWI mismatch and outcome: with thrombolysis (Table 4 and Figure 2)

Two studies provided data on mismatch, radiological outcome (but only one on functional outcome[38]), and thrombolysis (total n=29).[34,38] Note that in one[34] thrombolysis was actually given immediately before the first MRI meaning that the baseline scans may have already been affected by thrombolysis, thus making interpretations about the effects of rt-PA in these patients difficult. However, we included these data on the basis that the effects of rt-PA are not instantaneous. With this in mind, 12/20(60%) with mismatch had infarct growth (data missing for 2 patients) following thrombolysis, 8/20 did not: 4/9(44%) without mismatch had infarct expansion (data missing for 1 patient) with thrombolysis, 5/9 did not. Thus there was a similar odds ratio for infarct expansion in the presence of mismatch with thrombolysis (OR 2.0, 95% CI 0.37-10.9) as without thrombolysis. The wide confidence intervals include the possibility of either reduction or increase in the risk of infarct expansion. The one paper with clinical outcome data[17] compared mismatch patients who received thrombolysis with 16 historical controls with mismatch who did not receive thrombolysis (Table 3), but such historical comparisons are prone to bias and unreliable. There are therefore no meaningful data on clinical outcomes in patients with or without mismatch in the presence of thrombolysis.

To account for missing follow-up scans, I calculated 'best' (assuming all the patients with missing data did not have infarct expansion) and 'worse' (assuming all the patients with missing data did have infarct expansion) case scenarios (Tables 3&4). In the best case scenario, mismatch without thrombolysis was associated with a 14-fold increase in the odds of infarct expansion (OR 14.4, 95% CI 2.5-83.2), and with thrombolysis was associated with a two-fold increase in the odds of infarct expansion (OR 2.5, 95% CI 0.48-12.9). In the worst case scenario, mismatch without thrombolysis was associated with a seven-fold increase in the risk of infarct expansion (OR 7.3, 95% CI 1.5-35.2) and with thrombolysis was associated with a two-fold increase in the odds of infarct expansion (OR 1.86, 95% CI 0.37-9.49). However, note that the marked change in odds

Figure 2: Fate of the acute MR DWI lesion in patients with or without mismatch with or without thrombolysis



ratio when outcome changed for only a few patients, combined with the wide CI's, indicates that these data, though promising, are unreliable and highly unstable and require confirmation in large, methodologically sound studies.

2.2.3 Discussion

This review highlights the need for more data to confirm (and refine) or refute the mismatch concept, and for standardisation of methods to assess mismatch and PWI lesions. Despite more than 1500 papers (primary studies and review papers) reporting some aspect of PWI/DWI mismatch, many advocating its use to identify 'tissue at risk', at the end of it all, there is very limited evidence even to say whether patients with mismatch have a different outcome from those without mismatch, or crucially whether the presence of mismatch modified the effect of rt-PA. These data were very fragmented and difficult to summarise. Indeed some might argue that I should have excluded even more data, such as the study which performed MR DWI/PWI just after rt-PA. However, I reasoned that others may have adopted the same approach without explicitly mentioning it (based on personal communications from various stroke research groups), and that this was a relatively minor flaw amongst many more fundamental ones. I searched conference abstracts for usable data (or at least to identify studies that might later appear in full publications). However, I found, as others in the Department who work on systematic reviews of diagnostic tests, that conference abstracts did not provide any usable data, either because numbers included were small or the abstract contained insufficient methodological details to decide if they were eligible. I did not seek additional unpublished information from authors because I anticipated very little useful additional information would be gained, and information in personal communications is not peer-reviewed. Experience of gathering such extra data for systematic reviews of trials show that it is a time-consuming and costly way to obtain data, which is often of poor quality. Furthermore, it would not have helped to overcome such basic flaws in study design as lack of blinding, small sample size and differences in outcome time and

measures. The published literature is the accessible knowledge base; current opinion should not be based on information which is absent from the published literature, because unpublished information is not accessible to all in order to evaluate and form their own opinion. The fact that I decided not to seek unpublished data is a limitation of the study which I acknowledge. On the other hand this is the first attempt that has been made to summarise these important but difficult data. This systematic review, despite its limitations, is an important step forward in studying this area of mismatch and defining how the methodology of such studies should be improved. Groups are currently using mismatch as a criteria for entry into some clinical trials with no good evidence on which to base this practice: this study at least starts to explore the problems associated with that practice.

The inclusion criteria for the review included studies with > 20 patients because of the well known problem of bias in smaller studies. Other criteria such as type and site of arterial occlusion were outside the scope of this systematic review and therefore not included. It was not possible to extract reliably any information on these points, and the small samples precluded any meaningful subgroup analyses.

There was no consistency in the DWI and PWI imaging methods. Perfusion imaging used different doses of contrast, different processing techniques, and measured different parameters in different ways. It is unclear whether one should use complex and time-consuming methods of analysis of PWI data incorporating the AIF (and if so which[29]) or, as suggested recently, simpler semi-quantitative methods like T_{max}.[44]

There was no consistency in the definition or measurement of mismatch. The five definitions from the six research groups ranged from a PWI lesion>acute DWI lesion[35,36,42] to a PWI lesion 50% > acute DWI lesion.[43] Two papers specified visual inspection but the others measured lesion volume on a workstation. Few studies[35,36,39] commented on the observer reliability of any of these PWI/DWI assessments. The reliability of assessing the percentage of diffusion perfusion mismatch has to be

addressed. One study has suggested that quantifying mismatch by the human eye is reproducible but not reliable amongst observers.[45] This does raise serious doubts over whether mismatch should be used for clinical decision making in the acute setting where rapid assessments need to be made.

Nonetheless, the pattern suggested by Figure 2 does indeed, rather tantalisingly, suggest that mismatch patients are more likely than non mismatch patients to have infarct growth, and that the proportion of patients with mismatch and subsequent infarct growth may be reduced by thrombolysis. However, there are no data on functional outcome (more relevant than radiological outcomes), and these data are not from randomised comparisons, but from rather small observational studies of different patients with widely differing definitions, sometimes with historical controls. What is clear is that some patients without mismatch definitely get infarct growth, so the absence of mismatch does not mean that there is no 'tissue at risk' of infarct growth. This suggests little justification for excluding patients without mismatch either from routine acute stroke treatments or possibly from trials. If the mismatch theory is correct, then there is a need to gather more robust evidence to support its application to patient selection. Alternatively, if the mismatch theory is not correct, i.e. that it does not identify a subgroup of patients at high risk of infarct growth and poor outcome, this might explain the failure of the recent DIAS 2[46] trial to show any benefit with desmoteplase.

In order to move forward, common standards and definitions for mismatch are needed. One of the biggest problems was the failure to include patients without mismatch in previous studies. Therefore a large randomised trial of thrombolysis against control in patients with and without mismatch is needed to reliably determine if the degree of mismatch really does influence response to thrombolytic treatment. The Echoplanar Imaging Thrombolysis Evaluation (EPITHET)[24] study has this design, although patients are recruited on the basis of their CT appearance and not on the presence or absence of MR mismatch, which may lead to an imbalance of patients with and without mismatch in the treatment and control groups. EPITHET recruitment is now complete and the

results are due to be presented in 2008 (S Davis, personal communication). The fact that it has taken the EPITHET group around six years to randomise 120 patients indicates that MR DWI/PWI may not be easy to apply in practice. Certainly, until there is better evidence, patients without mismatch should probably not be denied any routine acute treatments, because on current evidence about 50% will get infarct expansion which might be prevented by acute treatments like thrombolysis. The lack of data underpinning the mismatch theory should also be acknowledged in the design of any future trials of novel therapeutic agents (e.g. new thrombolytic or neuroprotective agents). In other words, it would be more informative to design trials which included patients with and without mismatch, rather than simply restrict trial entry to those with mismatch. The former design then enables the interaction between mismatch and response to treatment to be assessed.

2.3 Summary

- Diffusion perfusion MRI might help identify patients with cerebral tissue at risk of infarction, (even beyond the current three hour time window), thereby avoiding thrombolysis in those with little chance of benefit.

- However, the literature concerning perfusion diffusion mismatch and thrombolysis is limited and numbers very small, as demonstrated in the systematic review performed.

- There is no consistent definition of mismatch in the current literature. In the systematic review I performed there were five different definitions in six research groups. There is clearly a need to standardise the definition.

- The systematic review highlighted the lack of consistency with perfusion measurements. At least seven different measurements were used in the papers meeting the criteria for the review. There is clearly a need for a standard measure to be defined and accepted.

- Almost none of the studies provided information on inter- and intraobserver reliability of the measurement of mismatch.

- The data from the review suggested that mismatch (versus no mismatch) without thrombolysis was associated with a non-significant two-fold increase in the odds of infarct expansion (OR 2.2, 95% CI 0.34-14.1), which did not change with thrombolysis (OR 2.0, 95% CI 0.37-10.9).

- Half the patients without mismatch also had infarct growth.

- There were no extractable data on functional outcome in the patients. This is of utmost importance when assessing the benefit of any treatment.

- Although perfusion diffusion imaging remains a promising technique in selecting patients for thrombolysis, it needs to be studied further in randomised controlled trials to ascertain if the degree of mismatch really does identify a group of patients who will respond differently to thrombolytic treatment.

Table 1: Features of studies meeting methodological inclusion criteria

Author	Publication date	Sample size	Incomplete imaging*/died	Clinical score	Other outcome scores at≥ 1 month	Time to acute MRI	Time to final MRI (days)
Beaulieu C[34]	1999	21	6	NIHSS	None	Mean 5.2±1.2hrs	Mean 42±22
Barber P[35]	2004	49	4	NIHSS	BI&mRS	Median 4hrs (IQR 3.3-5)	Median 84 (IQR 70-89)
Rohl L[37]	2001	22	1	SSS	BI	Mean 5.0hrs	Range 22-42 (1@102)
Parsons M[38]	2002	40	4	NIHSS	mRS	Treatment group mean 3.8±1.2hrs Controls 3.7±1.2	Treatment group mean 77.9±17.1 Controls 81.4±12
Barber P[36]	1999	26	5	CNS	BI&mRS	Mean 12.1±7.6hrs	Mean 90.1±30.3
Hacke W[23**]	2005	104	18	NIHSS	BI&mRS	Median 325mins	Due at 30
Derex L[39]	2004	49	5	NIHSS	mRS	Mean 3hrs37±52mins	Due at 60
Schellinger P[40]	2001	51	1	NIHSS&SSS	BI&mRS	Mean 3.33±1.29hrs	Due at 5
Chalela J[42]	2004	42	5	NIHSS	mRS	Median to: DWI 84mins, PWI 92mins	Median to: DWI 253mins, PWI 269mins
Rother J[41]	2002	139	10	NIHSS	mRS	Median 180mins (75-360)	Due at 7
Ribo M[43]	2005	122	Not specified	NIHSS	mRS	Median group A: 136mins (60-180); Group B: 223mins (185-360)	**CT** 24-48hrs

SSS: Scandinavian Stroke Scale
CNS: Canadian Stroke Scale

*Imaging sequences incomplete/not performed
**Placebo controlled, double-blind, randomised dose-finding phase 2 trial

Table 2: Definition and frequency of PWI/DWI mismatch in studies meeting methodological inclusion criteria

Author	Definition of PWI/DWI mismatch	Workstation/ 'visual' measurement	Number with mismatch	Dose of gadolinium (mmol/kg)	Perfusion measure	Number treated with thrombolysis
Beaulieu C[34]	Differences of at least±10%	Workstation	11(52%) PWI>DWI 7(33%) PWI≤DWI	0.2	TTP*	11(52%)
Barber P[35]	PWI>acute DWI	"	77%	0.1	MTT**	12(24%)
Rohl L[37]	>10% difference between acute DWI lesion and MTT map lesion	"	18(82%)	0.1	MTT**	None
Parsons M[38]	Acute MTT (delay>4s) lesion volume 20%>DWI lesion	"	16(84%) treatment group 16(76%) control group	0.2	MTT**	19(48%)
Barber P[36]	PWI>acute DWI	"	14(56%)	0.1	rMTT*	None
Hacke W[23]	≥20% PWI/DWI mismatch	Visual initially then workstation	104(100%)	0.1	MTT*	75(72%)
Derex L[39]	PWI/DWI volume ratio≥1.2	Workstation	42(85%)	0.1	TTP*	All(100%)
Schellinger P[40]	PWI/DWI volume ratio of>1.2	"	40/51(78%)	25mls	MTT*	24(47%)
Chalela J[42]	MTT lesion minus DWI lesion at each time point.	"	Not specified	0.1	MTT*	All(100%)
Rother J[41]	PWI/DWI volume ratio>1.2	"	120/139(86.3%)	25mls	TTP*	76(55%)
Ribo M[43]	Group B: DWI/PWI mismatch>50%	Visual	Group B:43/122(35%)	Bolus	TTP*	All(100%)

*Semi-quantitative measure
**Quantitative measure

Table 3: Details of patients with and without mismatch **not treated** with thrombolysis

Author	Number with mismatch	Number without mismatch	Baseline NIHSS: mismatch Mean (range)	Baseline NIHSS: no mismatch Mean (range)	Outcome score: mismatch Mean (range)	Outcome score: no mismatch Mean (range)	Mismatch and no infarct expansion	Mismatch and infarct expansion	No mismatch and no infarct expansion	No mismatch and infarct expansion	No final follow up scan
Beaulieu C[34]	7	1	14(6-24)	7	No data	No data	2	3	1	0	2 (both mismatch)
Rohl L[37]	18	3	**SSS** 38(11-56)	**SSS** 41(31-56)	BI 86(25-100)	BI 98(94-100)	3	15	1	2	0
Parsons M[38]	16	5	15(7-20)	16(10-20)	mRS 3(0-6)	mRS 2(1-4)	1	15	3	0	2 (both no mismatch)
TOTAL	**41**	**9**					**6(15%)**	**33(81%)**	**5(56%)**	**2(22%)**	**4**
Best case* scenario							**8(20%)**	**33(81%)**	**7(78%)**	**2(22%)**	**0**
Worst case scenario**							**6(15%)**	**35(85%)**	**5(56%)**	**4(44%)**	**0**

* assumes no infarct growth occurred in patients with missing scans
** assumes infarct growth occurred in patients with missing scans

Table 4: Details of patients with and without mismatch **treated** with thrombolysis

Author	Number with mismatch	Number without mismatch	Baseline NIHSS: mismatch Mean (range)	Baseline NIHSS: no mismatch Mean (range)	Outcome score: mismatch	Outcome score: no mismatch	Mismatch and no infarct expansion	Mismatch and infarct expansion	No mismatch and no infarct expansion	No mismatch and infarct expansion	No final follow up scan
Beaulieu C[34]	4	6	14(8-24)	7(2-14)	No data	No data	0	3	3	3	1(mismatch patient)
Parsons M[38]	16	3	15(9-220	15(12-19)	mRS 2(1-6)	mRS 4(2-6)	6	9	1	1	2(1 mismatch, 1 without)
TOTAL	**20**	**9**					**6(30%)**	**12(60%)**	**4(44%)**	**4(44%)**	**3**
Best case scenario*							**8(40%)**	**12(60%)**	**5(56%)**	**4(44%)**	**0**
Worst case scenario**							**6(30%)**	**14(70%)**	**4(44%)**	**5(56%)**	**0**

* assumes no infarct growth occurred in patients with missing scans
** assumes infarct growth occurred in patients with missing scans

References

1. Astrup J, Siesjo BK, Symon L. Thresholds in cerebral ischaemia – the ischaemic penumbra. *Stroke* 1981;12:723-725.

2. Heiss W-D. Ischaemic penumbra: evidence from functional imaging in man. *J Cereb Blood Flow Metab* 2000;20:1276-1293.

3. Heiss W-D, Rosner G. Functional recovery of cortical neurons as related to degree and duration of ischaemia. *Ann Neurol* 1983;14:294-301.

4. Jones TH, Morawetz RB, Crowell RM, Marcoux FW, Fitzgibbon SJ, DeGirolami U, Ojemann RG. Thresholds of focal cerebral ischaemia in awake monkeys. *J Neurosurg* 1981;54:773-782.

5. Marcoux FW, Morawetz RB, Crowell RM, DeGirolami U, Halsey JH. Differential regional variability in transient focal ischaemia. *Stroke* 1982;13:339-346.

6. Pulsinelli WA, Brierley JB, Plum F. Temporal profile of neuronal damage in a model of forebrain ischaemia. *Ann Neurol* 1982;11:491-498.

7. Mies G, Iijima T, Hossman K-A. Correlation between peri-infarct DC shifts and ischaemic neuronal damage in rat. *NeuroReport* 1993;4:709-711.

8. Takano K, Latour LL, Formato JE, Carano RA, Helmer KG, Hasegawa Y, Sotak CH, Fisher M. The role of spreading ischaemia evaluated by diffusion mapping. *Ann Neurol* 1996;39:308-318.

9. Busch E, Gyngell ML, Eis M, Hoehn-Berlage M, Hossmann K-A. Potassium induced cortical spreading depressions during focal cerebral ischaemia in rats: contribution to lesion growth assessed by diffusion weighted NMR and biochemical imaging. *J Cereb Blood Flow Metab* 1996;16:1099-1099.

10. Hennerici MG. *Imaging in stroke*, 1st edn. Remedica Publishing, 2003.

11. Tenjin H, Ueda S, Mizukawa N, Imahori Y, Hino A Ohmori Y Yasukochi K. Positron emission tomographic measurement of acute haemodynamic changes in primate middle cerebral artery occlusion. *Neurol Med Chir* (Tokyo) 1992;32:805-810.

12. Pappata S, Fiorelli M, Rommel T et al. PET study of changes in local brain dynamics and oxygen metabolism after unilateral middle cerebral artery occlusion in baboons. *J Cereb Blood Flow Metab* 1993;13:416-424.

13. Heiss W-D, Graf R, Weinhard K, Löttgen J, Saito R, Fujitao T, Rosner G, Wagner R. Dynamic penumbra demonstrated by sequential multitracer PET after middle cerebral artery occlusion in cats. *J Cereb Blood Flow Metab* 1994;14:892-902.

14. Heiss W-D, Graf R, Löttgen J et al. Repeat positron emission tomographic studies in transient middle cerebral artery occlusion in cats: residual perfusion and efficacy of postischaemic reperfusion. *J Cereb Blood Flow Metab* 1997;17:388-400.

15. Baron JC, Frackowiak RSJ, Herholz K, Jones T, Lammertsma AA, Mazoyer B, Weinhard K. Use of PET methods for measurement of cerebral energy metabolism and haemodynamics in cerbrovascular disease. *J Cereb Blood Flow Metab* 1989;9:723-742.

16. Furlan M, Marchal G, Viader F, Derlon JM, Baron JC. Spontaneous neurological recovery after stroke and the fate of the ischaemic penumbra. Ann of Neurol 1996;40:216-226.
17. Marchal G, Beaudouin V, Rioux P, de la Sayette V, Le Doze F, Viader F et al. Prolonged persistence of substantial volumes of potentially viable brain tissue after stroke. A correlative PET-CT study with voxel based data analysis. *Stroke* 1996;27:599-606.
18. Marchal G, Benali K, Iglesias S, Viader F, Derlon JM, Baron JC. Voxel-based mapping of irreversible ischaemic damage with PET in acute stroke. *Brain* 1999;122:2387-2400.
19. Heiss W-D, Kracht LW, Thiel A, Grond M, Pawlik G. Penumbral probability thresholds of cortical flumazenil binding and blood flow predicting tissue outcome in patients with cerebral ischaemia. *Brain* 2001;124:20-29.
20. Kidwell CS, Alger JR, Saver JL. Evolving paradigms in neuroimaging of the ischaemic penumbra. *Stroke* 2004;35[suppl I]:2662-2665.
21. Baird AE, Benfield A, Schlaug G, Siewart B, Lovblad KO, Edelmann RR, Warach S. Enlargement of human cerebral ischaemic lesion volumes measured by diffusion-weighted magnetic resonance imaging [see comments]. *Ann Neurol* 1997;41:581-589.
22. Kidwell CS, Saver JL, Mattiello J, Starkman S, Vinuela F, Gobin YP, Jahan R, Vespa P, Kalafut M, Alger JR. Thrombolytic reversal of acute human cerebral ischaemic injury shown by diffusion/perfusion magnetic resonance imaging. *Ann Neurol* 2000;47:462-469.

23. Hacke W, Albers G, Al Rawi Y, Bogousslavsky J, Davlos A, Eliasziw M, Fisher M, Furlan A, Kaste M, Lees KR, Soehngen M, Warach S. The desmoteplase in acute ischaemic stroke trial (DIAS): A phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. *Stroke* 2005;36(1):66-73.

24. http://www.strokecenter.org/trials.

25. Fiehler J, Foth M, Kucinski T, Knab R, von Bezold M, Weiller C, Zeumer H, Rother J. Severe ADC decreases do not predict irreversible tissue damage in humans. *Stroke* 2002;33(1):79-86.

26. Ay H, Buonanno FS, Rordorf G et al. Normal diffusion-weighted MRI during stroke-like deficits. *Neurology* 1999;52:1784-1792.

27. Oppenheim C, Stanescu R, Dormont D et al. False-negative diffusion-weighted MR findings in acute ischaemic stroke. *Am J Neuroradiol* 2000;21:1434-1440.

28. Butcher K, Parsons M, Baird T, Barber A, Donnan G, Desmond P, Tress B, Davis S. Perfusion thresholds in acute stroke thrombolysis. *Stroke* 2003;34(9):2159-2164.

29. Thijs VN, Somford DM, Bammer R, Robberecht W, Moseley ME, Albers GW. Influence of arterial input function on hypoperfusion volumes measured with perfusion-weighted imaging. *Stroke* 2004;35:94-98.

30. Yamada K, Wu O, Gonzalez RG, Bakker D, Ostergaard L, Copen WA, Weisskoff RM, Rosen BR, Yagi K, Nishimura T, Sorensen AG. Magnetic resonance perfusion-weighted imaging of acute cerebral infarction. Effect of the calculation methods and underlying vasculopathy. *Stroke* 2002;33:87-94).

31. Schulz K, Grimes DA. Multiplicity in randomised trials II: subgroup and interim analysis. *Lancet* 2005;365:1657-1661.

32. Warach S, Gaa J, Siewert B, Wielopolski P, Edelman RR. Acute human stroke studied by whole brain echo planar diffusion-weighted magnetic resonance imaging. *Ann Neurol* 1995;37:231-241.

33. O'Brien P, Sellar RJ, Wardlaw JM. Fogging on T2-weighted MR after acute ischaemic stroke: how might this occur and what are the implications? *Neuroradiology* 2004:46:635-641.

34. Beaulieu C, de Crespigny A, Tong DC, Moseley ME, Albers GW, Marks MP. Longitudinal magnetic resonance imaging study of perfusion and diffusion in stroke: evolution of lesion volume and correlation with clinical outcome. *Ann Neurol* 1999;46:568-578.

35. Barber PA, Parsons MW, Desmond PM, Bennett DA, Donnan GA, Tress BM, Davis S. The use of PWI and DWI measures in "proof-of-concept" stroke trials. *J Neuroimaging* 2004;14:123-132.

36. Barber PA, Davis SM, Darby DG, Desmond PM, Gerraty RP, Yang Q, Jolley D, Donnan GA, Tress BM. Absent middle cerebral artery flow predicts the presence and evolution of the ischaemic penumbra. *Neurol* 1999;52(6):1125-1132.

37. Rohl L, Geday J, Ostergaard L, Simonsen CZ, Vestergaard-Poulsen P, Andersen G, Le Bihan D, Gyldensted C. Correlation between diffusion- and perfusion-weighted MRI and neurological deficit measured by the Scandinavian Stroke Scale and Barthel Index in hyperacute subcortical stroke (< or = 6 hours). *Cerebrovasc Dis* 2001;12(3):203-213.

38. Parsons MW, Barber PA, Chalk J, Darby DG, Rose S, Desmond PM, Gerraty RP, Tress BM, Wright PM, Donnan GA, Davis SM. Diffusion- and perfusion-weighted MRI response to thrombolysis in stroke. *Ann Neurol* 2002;51(1):28-37.

39. Derex L, Nighoghossian N, Hermier M, Adeleine P, Berthezene Y, Philippeau F, Honnorat J, Froment JC, Trouillas P. Influence of pretreatment MRI parameters on clinical outcome, recanalization and infarct size in 49 stroke patients treated by intravenous tissue plasminogen activator. *Journal of the Neurological Sciences* 2004;225(1-2):3-9.

40. Schellinger PD, Fiebach JB, Jansen O, Ringleb PA, Mohr A, Steiner T, Heiland S, Schwab S, Pohlers O, Ryssel H, Orakcioglu B, Sartor K, Hacke W. Stroke magnetic resonance imaging within 6 hours after onset of hyperacute cerebral ischemia. *Ann Neurol* 2001;49(4):468-469.

41. Rother J, Schellinger PD, Gass A, Siebler M, Villringer A, Fiebach JB, Fiehler J, Jansen O, Kucinski T, Schoder V, Szabo K, Junge-Hulsing GJ, Hennerici M, Zeumer H, Sartor K, Weiller C, Hacke W, Kompetenznetzwerk Schlaganfall Study Group. Effect of intravenous thrombolysis on MRI parameters and functional outcome in acute stroke <6 hours. *Stroke* 2002; 33(10):2438-2445.

42. Chalela JA, Kang DW, Luby M, Ezzeddine M, Latour LL, Todd JW, Dunn B, Warach S. Early magnetic resonance imaging findings in patients receiving tissue plasminogen activator predict outcome: Insights into the pathophysiology of acute stroke in the thrombolysis era. *Ann Neurol* 2004;55(1):105-112.

43. Ribo M, Molina CA, Rovira A, Quintana M, Delgado P, Montaner J, Grive E, Arenillas JF, Alvarez-Sabin J. Safety and efficacy of intravenous tissue plasminogen activator stroke treatment in the 3- to 6-hour window using multimodal transcranial Doppler/MRI selection protocol. *Stroke* 2005;36(3):602-606.

44. Butcher K, Parsons M, MacGregor L, Barber PA, Chalk J, Bladin C, Levi C, Kimber T, Schultz D, Fink J, Tress B, Donnan G, Davis S, for the EPITHET Investigators. Refining the perfusion-diffusion mismatch hypothesis. *Stroke* 2005;36:1153-1159.

45. Coutts SB, Simon JE, Tomanek AI, Barber PA, Chan J, Hudon ME, Mitchell JR, Frayne R, Eliasziw M, Buchan AM, Demchuk AM. Reliability of assessing the diffusion-perfusion mismatch. *Stroke* 2003;34:1681-1683.

46. Eng P. Desmoteplase in acute ischaemic stroke – 2. Presented at the European Stroke Conference 2007.

3 The MR perfusion lesion – a comparison of different processing methods and parameters

3.1 Introduction

As highlighted in chapter 2, some of the advanced MR imaging techniques are promising, but need more data to support their use in routine clinical practice. Methods of calculating MR parameters need to be standardised across the research community in order that concepts, such as mismatch, can be considered as useful clinical tools in the treatment of patients with acute stroke.

As the previous systematic review suggested, there are several different methods for measuring the perfusion lesion. Different studies used different parameters, but no study to date has compared all of the most commonly used methods in the same group of patients. A recent systematic review looking specifically at different methods of imaging cerebral blood flow (CBF), did not identify any reliable threshold for infarcted and salvageable brain tissue.[1] I therefore investigated the different methods of calculating the perfusion lesion in each one to see how this influenced the degree of mismatch present and whether one method of calculation correlated best with the patient's clinical and radiological outcome.

3.2 Measuring the MR perfusion lesion

3.2.1 Background

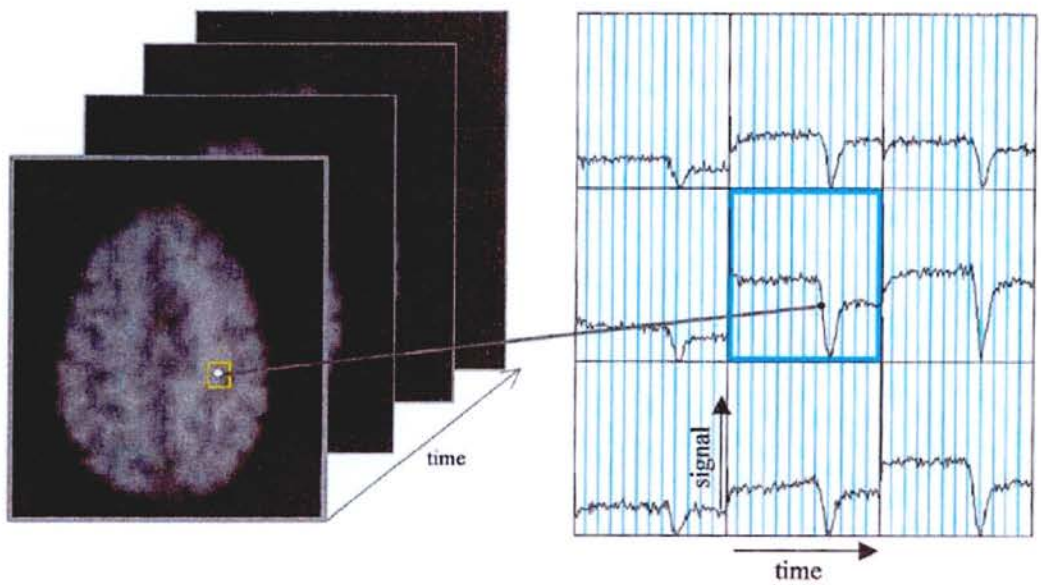
The term 'perfusion' normally refers to the delivery of blood at the level of the capillaries, where exchange of oxygen and nutrients between blood and tissue takes

place.[2] As indicated earlier neurological dysfunction occurs when the cerebral blood flow falls below about 18 – 20 ml/100g of cerebral tissue per minute.[3] At levels of cerebral blood flow less than 10 ml/100g of tissue per minute rapid cell death occurs, but between cerebral blood flows of 10 and 20mL/100g of tissue per minute there is the potential for this tissue to be salvaged.[4] However, as mentioned in Chapter 2, there is some imprecision around the levels. This has led to research in stroke patients to try and investigate areas of potentially viable tissue within an area of acute ischaemia, so these can be targeted with agents (e.g. thrombolytics) that may reverse ischaemia and so have the potential to improve patient outcome.

3.2.2 Perfusion measurements researched to date

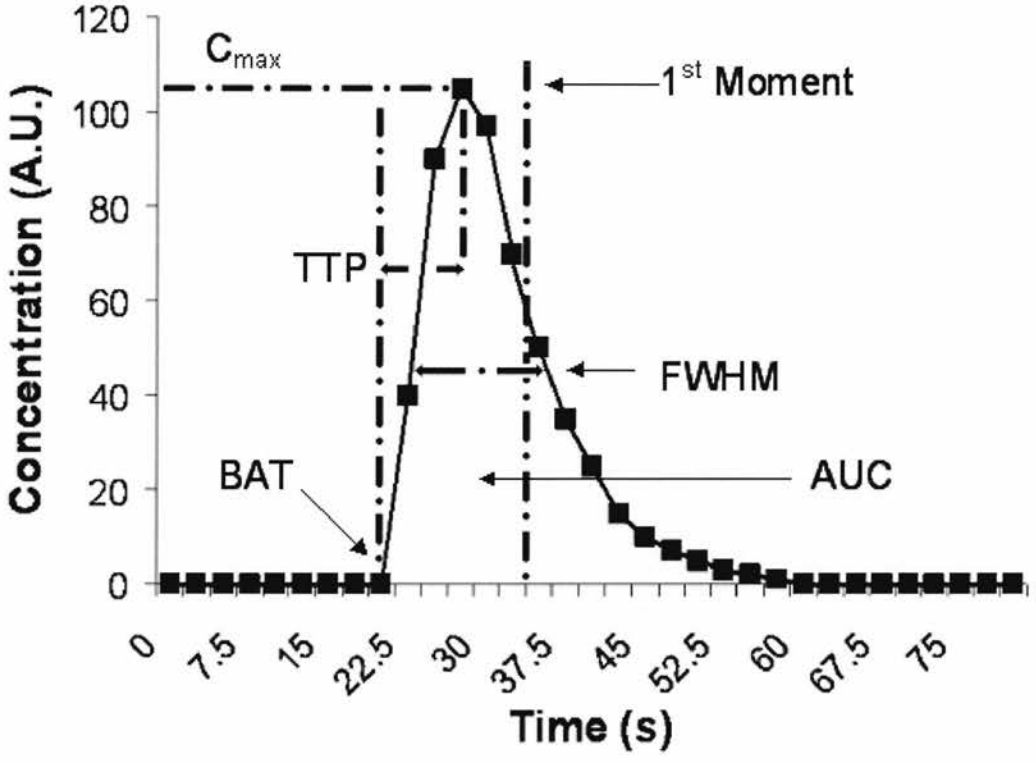
There are two types of perfusion MR: a) the first pass bolus tracking technique dynamic susceptibility contrast (DSC) imaging and b) the arterial spin labelling technique (ASL).[5] The DSC method is generally used in acute stroke patients because imaging time is shorter than with arterial spin labelling and ASL requires considerable patient cooperation. To obtain the images a bolus of contrast (usually gadolinium based) is injected by a power injector into the vein in the antecubital fossa. Once the contrast reaches the brain the MRI signal drops, and then returns to normal as the contrast is washed out. The raw signal-time curve[6] (Figure 1) of perfusion data obtained from all MRI machines is essentially the same but once these data have been obtained they may then be analysed in several different ways to yield relative or quantitative values[2,7] (Figure 2, Table 1). These post processed values vary markedly between imaging centres because of the use of different processing methods. Relative values require less complex data processing and are often immediately accessible from the scanner console (e.g. time to peak, TTP, full width half maximum, FWHM). However, relative measurements do not usually take account of the arterial input function (AIF), which may introduce large errors.[8-10] Quantitative perfusion parameters, which overcome some but not all[3,11] of the limitations of relative parameters, can be calculated (e.g. quantitative cerebral blood flow, qCBF, or cerebral blood volume CBV)[12] but this

Figure 1: The raw signal time curve



An example of the raw signal-time curve perfusion data obtained when performing PWI using the bolus tracking technique (DSC). A contrast is injected intravenously during the acquisition of series of images, with the MRI signal dropping as the contrast reaches the brain. Once obtained, this data can be processed in a number of ways.[6]

Figure 2: Contrast time curve



The raw signal-time curve data (Figure1) are converted to a contrast-time curve (Figure 2), with concentration in arbitrary units (AU). Different parameters are used to estimate perfusion. Full width half maximum (FWHM); 1st Moment='Balancing point' of curve along the time axis; Cmax=Maximum concentration value (also known as Peak Height); Time to peak (TTP)=Time from arrival of contrast to Cmax (also known as Tmax after deconvolution); BAT = bolus arrival time; AUC=Area under curve. (Figure prepared by Dr T Carpenter, University of Edinburgh).

requires off line processing including deconvolution, and the perfusion image takes longer to produce.[3] In the case of quantitative perfusion measurements a measure of the arterial input function (AIF) is necessary in order to perform the deconvolution of the concentration time curve of contrast agent within the tissue, C(t) using the equation first mentioned in the introduction i.e.

$$C(t) = \rho/\kappa_H \, (CBF) \, . \, (C_a(t) \times R(t))$$

From a mathematical point of view deconvolution is an algorithm based process used to reverse the effects of convolution on the recorded data. This is a concept widely used in image processing. One approach uses the singular value decomposition method (SVD) to perform the deconvolution but this does not account for the time delay between the AIF and tissue concentration time curves. One way to overcome this is to fit gamma variate functions which allows the arrival time of the bolus of contrast to be identified and so the delay is removed prior to SVD deconvolution, giving more accurate perfusion parameters.

A recent summary of the literature and survey of centres with an interest in stroke imaging indicated that different PWI parameters were used in different centres, underlying the problem of lack of standardisation identified in Chapter 2.[13] PWI lesions which reflect CBF are generally smaller than those which reflect mean transit time (MTT),[14-18] and even different ways of estimating a single PWI parameter like MTT may yield different-sized PWI lesions.[19] Some authors have compared the ability of various different relative and/or quantitative PWI lesions to predict infarct growth but with differing results,[19-21] possibly due to differences in patient case mix, or timing of scanning as well as to variations in the combinations of PWI processing methods used. No studies have compared all the potential quantitative and relative PWI parameters. Thus there is no clear consensus on which PWI parameter should be used; different PWI lesions yield different estimates of the extent of DWI/PWI mismatch; and so variation in estimates of potentially salvageable tissue. I therefore undertook this comparison.

3.3 Comparison of ten different MR perfusion imaging processing methods in acute ischaemic stroke: effect on lesion size and the proportion of patients with diffusion perfusion mismatch

3.3.1 Methods

Patients

We recruited patients presenting with their first ever acute ischaemic stroke. Patients were imaged as soon after stroke onset as possible, and within an absolute maximum of twenty four hours. A trained stroke physician assessed all patients as soon as possible and assigned a stroke subtype according to the Oxfordshire Community Stroke Project (OCSP) classification.[22] We included all ischaemic stroke subtypes.

Image acquisition

We performed all imaging on a GE Signa LX 1.5 T (General Electric, Milwaukee) magnetic resonance imaging (MRI) scanner with a birdcage quadrature coil with a standardised protocol for acute stroke previously described.[16] The spin-echo echo-planar imaging (EPI) diffusion-tensor axial sequences with six gradient directions and dynamic susceptibility contrast EPI perfusion-weighted imaging both had 15 axial slices each of 5mm thickness with an interslice gap of 1mm, the imaging matrix was 128 x 128 encompassing a 240 x 240 mm field of view. Additionally for PWI, a gadolinium-based contrast agent (Gadovist 1M solution 10 ml or Omniscan 0.5 M solution 20 ml) was injected with imaging starting 10 seconds after the start of contrast injection, continuing over a period of 85 seconds, collecting thirty four volumes of 15 axial slices with TE of 30 ms and TR of 2.5 s.

Image processing

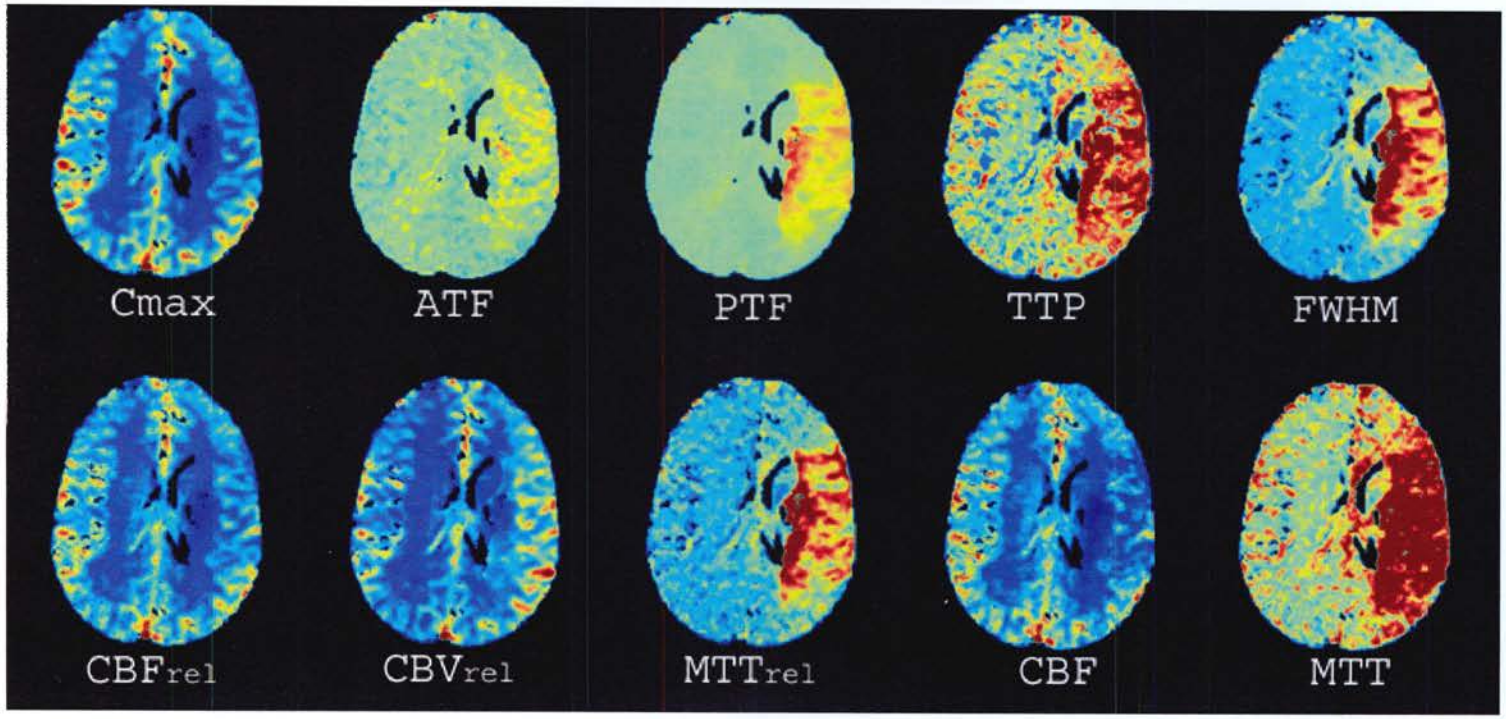
We performed all image processing blind to the clinical and any other imaging data. We co-registered the individual DWI and PWI data using open access software FLIRT (www.fmrib.ox.ac.uk/fsl). We obtained the volumes of the DWI lesions by manual tracing round the edge of the hyperintense lesion on a workstation as described previously.[16] Note, as with PWI, the raw data obtained across different MRI machines are similar assuming the same number of gradient directions (e.g. 6 in this case) are kept the same. There is interest in testing different diffusion sensitisation values (B_0, B_{100}) but most centres use parameters as supplied by the manufacturer for clinical imaging. The gradient directions would be the minimum. There is likely to be more variation in the measurement of the DWI lesion itself depending on how this is performed in a particular centre and whether the 'apparent diffusion coefficient' (ADC) map, and if so what threshold, is used or the DWI lesion. We chose to use the DWI lesion as there is no consensus on which ADC threshold should be used. All thresholds miss ischaemic tissue and erroneously include normal brain in the lesion and it is hard to appreciate a dark lesion on a dark background. In addition it is the DWI lesion that is routinely looked at clinically.[23]

We produced the perfusion-weighted images as follows. The first acquisition volume was discarded (as is standard), and the remaining signal time course in each voxel (Figure 1) was converted to a concentration time curve (Figure 2). We fitted a gamma variate function to the concentration data in every voxel which showed enhancement greater than 3x above the standard deviation (SD) of the pre-contrast points. Voxels not meeting the >3x SD criterion were given a negative value in the perfusion maps, representing either CSF or other tissue not accessible to contrast (e.g. centre of infarct) and were excluded unless a lesion volume completely encircled negative voxels, in which case these voxels were included in the calculation of the lesion volume. The anatomical distribution of negative voxels was visible to the observer so as to be able to include/exclude those within the infarct and those in the CSF (e.g. ventricles) respectively.

We defined the arterial input function (AIF) from the fitted data by averaging the concentration time data from voxels corresponding to the lumena of both internal carotid arteries (ICA) on the first volume of the registered data (to limit effects of any carotid stenosis). We chose this approach for several reasons: to be more relevant to an acute situation where the only knowledge of infarct location (prior to DWI/PWI data processing) may come from symptoms; to characterise brain blood supply as a global 'normalising' factor (the ICAs being prior to the Circle of Willis represent the available blood supply less the contribution from the basilar artery); and lastly because the ICAs are aligned perpendicular to the plane of imaging and hence avoid problems associated with partial volume. Care was taken to ensure the regions drawn within the ICA corresponded to the lumen (2 or 3 voxels per vessel).

We calculated maps of relative cerebral blood volume (rCBV), relative mean transit time (rMTT), relative cerebral blood flow (rCBF), the arrival time fitted (ATF), peak time fitted (PTF), and the time to peak (TTP), the full width half maximum (FWHM) of the concentration time curve and the maximum value of the fitted concentration time curve (Cmax). We normalized the parameter value in each voxel by the sample mean of the parameter value in the voxels used to define the AIF. Normalising the rCBV value by the rCBV sample mean of the voxels used to define the AIF results in the quantitative CBV (qCBV) hence this parameter is not mentioned below. We produced maps of quantitative cerebral blood flow and mean transit time (qCBF and qMTT respectively) by deconvolving the peak voxel concentration time curves with the concentration time curve of the AIF to obtain a scaled estimate of the voxel residue response.[12,24] The deconvolution was performed by singular value decomposition (SVD),[11,23] with the addition of a block-circulant discretion scheme to remove the dependency upon arrival time in the calculated qMTT maps. We did not cross-calibrate the PWI data with an assumed value for CBF for normal white matter, or use the patient's white matter to provide an assumed normal value, as in this older patient population, the white matter is unlikely to be standard. Note the routine use of an assumed normal CBF value for white matter derived from young normal people is likely to be another source of variation and

Figure 3



The ten different perfusion maps generated by the ten different perfusion processing methods for the same brain slice from one patient. See Table 1 for abbreviations and definitions.

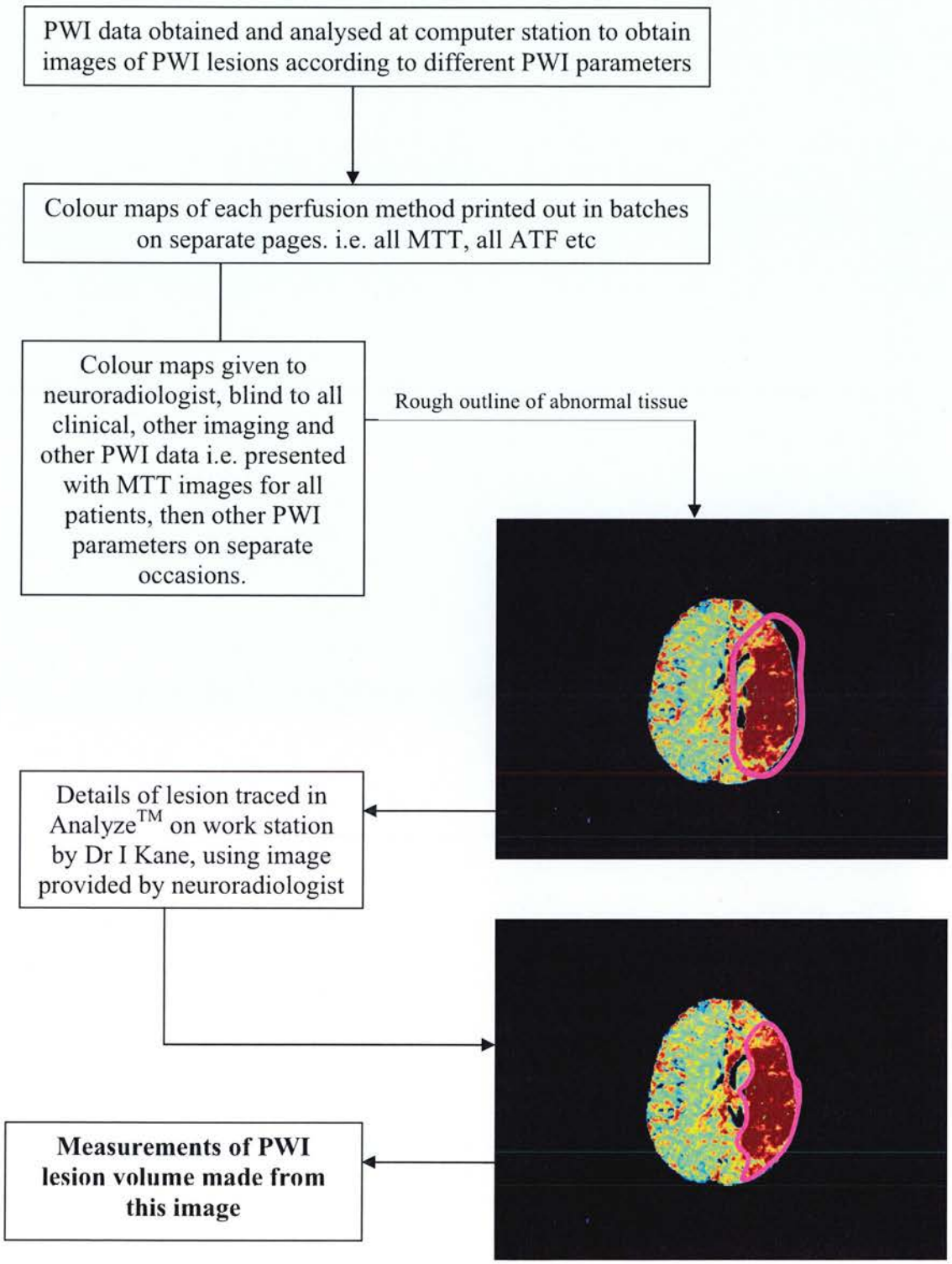
bias in previous studies. We then scaled the individual perfusion maps at a constant level chosen to encompass the range of parameter values across all the subjects, to give a consistent image presentation across all subjects. The thresholded maps (Figure 3) were then converted to Analyze™ format for measurement of perfusion lesion volumes.

The flow diagram (Figure 4) shows the process by which the PWI images were processed and analysed. We printed in colour each PWI parameter map (all 15 slices) on a separate page. These images were presented to the neuroradiologist in batches i.e. all MTT, followed by all ATF so that each PWI parameter for each patient was interpreted blind to the appearance of the other PWI parameters for that patient. The neuroradiologist, blind to all clinical, other imaging and other PWI data, provided an initial rough outline of the lesion by identifying areas of altered signal from the perfusion distribution, taking account particularly of any differences between the two hemispheres. This was to guide the researcher (Dr I Kane, not a neuroradiologist) when doing detailed tracing of the images in the Analyze™ software. The indication of the lesion by the neuroradiologist was also included to mimic the process of identifying a perfusion deficit in the acute situation where there would be little time for image analysis. I then outlined the lesion outline on the electronic Analyze™ format images using Analyze™ version 7.8 to derive PWI lesion volumes by counting the number of voxels within the defined region on each slice on which the lesion was visible. The DWI lesion volumes were traced separately using a similar approach whereby the neuroradiologist outlined the lesion roughly on a printed image and an observer then did detailed tracing of the image in Analyze™ on a workstation. We defined the DWI/PWI mismatch as the acute PWI lesion volume minus the acute DWI lesion volume, calculated from the DWI and PWI electronic values.

Statistical analysis

The data were not normally distributed (Kolmogorov-Smirnov test). I compared the median PWI lesion volumes and the PWI/DWI mismatch volumes produced by the ten different PWI processing methods using the Friedman test for multiple non-parametric

Figure 4


PWI data obtained and analysed at computer station to obtain images of PWI lesions according to different PWI parameters
Colour maps of each perfusion method printed out in batches on separate pages. i.e. all MTT, all ATF etc
Colour maps given to neuroradiologist, blind to all clinical, other imaging and other PWI data i.e. presented with MTT images for all patients, then other PWI parameters on separate occasions.
Rough outline of abnormal tissue
Details of lesion traced in Analyze™ on work station by Dr I Kane, using image provided by neuroradiologist
Measurements of PWI lesion volume made from this image

related measurements. I compared the proportion of patients with or without DWI/PWI mismatch by each PWI processing method using the Chi-Square test. All analyses were performed in SPSS version 13 for Windows.

3.3.2 Results

A total of 32 patients were recruited into the study (Table 2). Of those, 13 were female and 19 male, with a mean age of 70 years (range 36-93). The median time to MR was 7.27 hours. The time to imaging was less than six hours from symptom onset in 12/32 (38%), 6-12 hours in 8 (25%) and between 12 and 24 hours in 12 (37%).

The PWI lesion size varied markedly with the method of calculating the PWI lesion (Table 3, Figure 2). The median PWI lesion volume varied significantly from 0 voxels (Cmax, rCBF, CBV) to 14,882 voxels (TTP) (Friedman test 121.5, $p<0.0001$). In general, the measurements reflecting MTT (e.g. TTP and PTF) produced larger PWI lesions whilst the measures of CBF gave smaller lesion volumes, with CBV giving the smallest PWI lesions (Table 3). The number of patients with no PWI lesion by at least one method (Table 3) varied from 7/32 (22%, rMTT, FWHM, PTF) to 19/32 (59%, CBV) (Chi-Square $p<0.001$). As a consequence of the variation in PWI lesion size, the median volume of mismatch tissue varied from zero (actually minus 1849 voxels, CBV) to the smallest positive value of 715 voxels (ATF) to the largest of 9684 voxels (rMTT) (Friedman test 123.8, $p<0.0001$). Four of the perfusion parameters (CBV, rCBF, qCBF and Cmax) had negative median mismatch values because the median DWI lesion was larger than the PWI lesion. The proportion of patients with mismatch varied considerably (Table 3) from 3/32 (9%, CBV) to 23/32 (72%, rMTT, FWHM) (Chi-Square 48, $p<0.0001$).

3.3.3 Discussion

Different PWI parameters produce very different estimates of the extent of abnormal perfusion, and hence very different estimates of the volume of "tissue at risk". For example, if only patients with DWI/PWI mismatch were to receive thrombolysis, then selection based on time to peak (TTP) would result in 20/32 (63%) patients receiving treatment, whereas selection on Cmax would result in only 7/32 (22%) patients being treated. Such a variation is not acceptable if PWI is to be used to guide treatment in routine clinical practice. However, despite this major limitation, both of these parameters are commonly quoted in the literature, and separate experts have recommended their use.

Non-quantitative PWI parameters have the advantage that they are quick to measure on the scanner console, but may introduce unacceptable variability between patients. Quantitative PWI parameters reduce the difference in lesion volume between the PWI parameters, but would still result in discrepancies in the number of patients treated: 18/32 (56%) with qMTT, 13/32 (41%) with qCBF, and 3/32 (9%) with qCBV. Furthermore, complex and time-consuming off-line processing is needed to produce perfusion parameter maps. There were even differences between calculated parameters which purport to reflect only MTT function or only CBF function. For example, with relative CBF, 5/32 (16%) of patients had mismatch and with qCBF 13/32 (41%) patients had mismatch; with any of the relative MTT measures, 18/32 to 23/32 (56-72%) had mismatch and with qMTT 18/32 (56%) had mismatch.

These results are in agreement with other studies which compared fewer PWI lesions derived by processing the raw data in different ways. We compared a wider range of relative and quantitative parameters, and also determined the effect on PWI lesion volume and mismatch. The maximum PWI parameters compared in previous studies were nine,[20] six,[14] four[19,21] and three,[15,18] but these studies did not quantify the difference in visible lesion volume or the impact of that difference on DWI/PWI mismatch. Instead,

previous studies focussed predominantly on determining perfusion values in different parts of the ischaemic lesion (e.g. in mismatch, DWI-abnormal, or final infarct tissue) in an attempt to define thresholds for tissue recovery.

In this study we used visual assessment of the PWI lesions, where a focal abnormality was carefully sought by the observer by comparing mirror image regions of the cerebral hemispheres, because visual assessment is the fastest method for detecting the acute lesion in the clinical setting. Cross calibration (scaling to a fixed value of presumed normal white matter) was not used in this study so as to preserve information in the perfusion maps about the underlying perfusion status of all tissues. While scaling to white matter may allow the different PWI parameter images to be scaled directly into the same windowing, in the population that is typically affected by stroke, the white matter is often not normal, so applying an arbitrary scaling factor might not improve image accuracy or interpretability. In addition, this may skew the scaling of some parameters so as to actually reduce the visibility of some lesions. Instead, we normalised the individual perfusion parameter maps to the average value of that parameter in the region used to define the arterial input function (AIF). This approach was taken because the underlying model commonly applied to perfusion (convolution of an AIF with a kernel, the basis of the quantitative processing methodology) indicates that properties of the AIF (e.g. maximum contrast value, area under curve) are linearly associated with the corresponding quantities in the tissue, Cmax, rCBV, etc. Hence, normalisation by the average parameter value within the AIF region of interest reduces variation in the calculated relative perfusion parameters (resulting from the differing arrival rate of contrast in the brain between patients), and hence is preferable to scaling to presumed normal white matter.

I have not attempted to identify perfusion thresholds in the present work. The more important first step was to define the visual differences resulting from applying different PWI processing methods. I used manual tracing of the PWI lesion volume not thresholding or automated lesion edge detection, because it is unclear what, if any,

threshold should be used. None of the previous studies identified a consistent or reliable threshold, nor was any consistent threshold identified in a recent systematic review of all human perfusion imaging modalities.[25] The failure thus far to identify a consistent human threshold for salvageable/unsalvageable tissue may simply reflect, amongst other factors, the wide variation in apparent perfusion abnormality produced simply by processing the enhancement/time curve in different ways, as shown here. Individual differences between patients e.g. due to age, time from stroke to imaging, may also be major factors, though have yet to be fully explored. As large differences in perfusion lesion volume can be produced when the same middle cerebral artery occlusion model is applied under identical experimental conditions in two different genetic strains of laboratory rat (Sprague-Dawley and Wistar-Kyoto),[26] there is clearly a need for more research into reasons or differences between individuals in their response to apparently similar arterial occlusions.

Which perfusion data processing method is best? Some PWI lesions overestimate tissue at risk and others probably underestimate it. The ideal test for detecting abnormal perfusion should be: quick to acquire and process (necessary in an acute setting); produce a reliable image of abnormal perfusion (i.e. the same image even when processed by different operators); and show a clinically-relevant relationship with a clinical outcome (and not merely some radiological surrogate). We have not evaluated the effect of having different operators process the PWI data (all data were processed by one observer to produce the PWI images); neither has anyone else. Nor have we, or others, determined the inter- or intra-observer variability of measuring PWI lesion volume (all PWI lesions were measured once by the same person). These would be other factors that would need to be assessed if PWI were to become an essential tool on which to base treatment decisions. In the next section I will discuss further aspects of the above work, paying particular attention to the relationship between the perfusion lesion and clinical scores and radiological outcome.

3.4 Comparison of ten different MR perfusion imaging processing methods in acute ischaemic stroke: relationship between clinical scores and radiological outcome

3.4.1 Background

The size of the PWI lesion depends on the method used for calculation. It therefore seems likely that the method used will also affect the relationship between the PWI (or DWI/PWI mismatch) lesion presence or size and the neurological severity of the stroke at baseline. The penumbral tissue will contribute to the patient's neurological deficit (by definition), so knowing which PWI baseline lesion is most closely associated with the neurological score would be useful to identify which PWI lesion most closely identifies the 'shut down' but potentially still viable tissue. Several studies have reported correlations between perfusion parameters and stroke severity at presentation; two[27,28] reported that time to peak (TTP, a relative measure of MTT), correlated with baseline NIHSS; two[17,29] suggested a correlation between qMTT (quantitative) and baseline NIHSS; and one[30] suggested a correlation between qMTT and the Scandinavian Stroke Scale (SSS). No study examined the full range of PWI lesions and stroke severity.

If baseline imaging features are to guide the use of thrombolysis in practice or as a research tool, then it is important to know which baseline PWI lesion(s) best relates to final infarct extent and clinical functional outcome. The measures which predict these two outcomes may be different and may be different to the PWI lesions that correlate with the baseline neurological deficit. Although several studies have examined relationships between PWI lesions in the acute phase and later radiological outcomes, most have used very early timepoints (between 24hrs and about 1 week after stroke) to determine the 'final' infarct extent, which is too early to be 'final'.[20,31] Three studies that examined later timepoints only compared perfusion values, not lesion extent, but found associations between measures of MTT and 60 or 90 day infarct size measured

with T2 MR.[27,28,32] A correlation between the acute PWI lesion and functional clinical outcome was found between TTP and mRS,[28] rMTT and mRS,[33] and qMTT and Barthel Index (BI).[30] No studies examined a full range of PWI lesions.

I therefore explored the association between ten different MR PWI parameters and the National Institutes of Neurological Disorders and Stroke (NIHSS) score on admission, the Rankin score (mRS) at three months after stroke, the final infarct size on T2-weighted imaging obtained at least one month after stroke, and infarct growth between baseline and final T2-weighted imaging.

3.4.2 Methods

Patients

We recruited patients presenting with their first ever acute ischaemic stroke as detailed in section 3.3 of this chapter. A trained stroke physician assessed all patients and assigned a stroke subtype according to the Oxfordshire Community Stroke Project (OCSP) classification,[22] and determined the stroke severity using the NIHSS. We measured functional outcome at three months using the mRS, assessed blind to baseline features and imaging.

Image acquisition and processing

We performed diffusion and perfusion weighted imaging as soon as possible after admission within a maximum of 24 hours of stroke onset (as detailed in section 3.3.1 p97), and final follow up T2-weighted imaging at ≥ 1 month. The final T2-weighted lesion volume was measured by the neuroradiologist on a workstation in Analyze™ blind to other imaging and clinical data. For the purpose of this study, we defined infarct expansion as any increase in size from the acute DWI lesion to the final T2 lesion and the degree of mismatch (DWI/PWI) as the baseline PWI lesion volume minus the baseline DWI lesion volume.

Statistical analysis

The data were not normally distributed (Kolmogorov-Smirnov test). Therefore to look for any relationship between the various PWI methods, clinical scores and radiological outcome, we compared the different PWI volumes with the DWI lesion volume, the NIHSS at baseline, T2-weighted imaging final infarct volume and functional outcome (mRS) at three months with linear regression. We took each PWI parameter in turn as the dependent variable and the DWI lesion volume, NIHSS, T2-weighted final infarct volume and mRS as the independent variables. We transformed the PWI lesion volume data by taking the cube root to minimize the effect of outliers. We used Fisher's exact test to investigate any correlation between the presence or absence of mismatch at baseline and the presence or absence of infarct expansion on the final T2 image. All analyses were performed in SPSS version 13 for Windows.

3.4.3 Results

There were 32 patients into the study as detailed in section 3.3.2 (p 100). Only one PWI measure (Table 4) was associated with both baseline clinical severity (NIHSS) and clinical outcome (mRS at 3 months); ATF regression slope 0.209 (p=0.006) and 0.049 (p=0.035) respectively. No other PWI measures were associated with clinical outcome although p values for PTF, TTP and rMTT nearly reached significance.

Four other PWI measures (Table 4) were associated with baseline NIHSS (numbers indicate slope of regression line): PTF 0.210 (p=0.005), TTP 0.193 (p=0.006), FWHM 0.180 (p=0.006), and rMTT 0.206 (p=0.005). All were relative measures of MTT.

Eight PWI measures (Table 5) were associated with radiological outcome (final T2 infarct size), of which the four reflecting MTT reached greater significance (regression slopes were: ATF 0.330 p=0.002, PTF 0.292 p=0.007, TTP 0.286 p=0.004, and rMTT 0.303 p=0.004). Four others, one which reflected MTT (FWHM 0.214 p=0.025), two

reflecting CBF (rCBF 0.324 p=0.036, qCBF 0.236 p=0.025) and one which reflected cerebral blood volume (CBV 0.392 p=0.032) achieved lesser significance.

Figure 3 shows the variation in the median PWI volumes and the median acute DWI and final T2 lesion volumes.

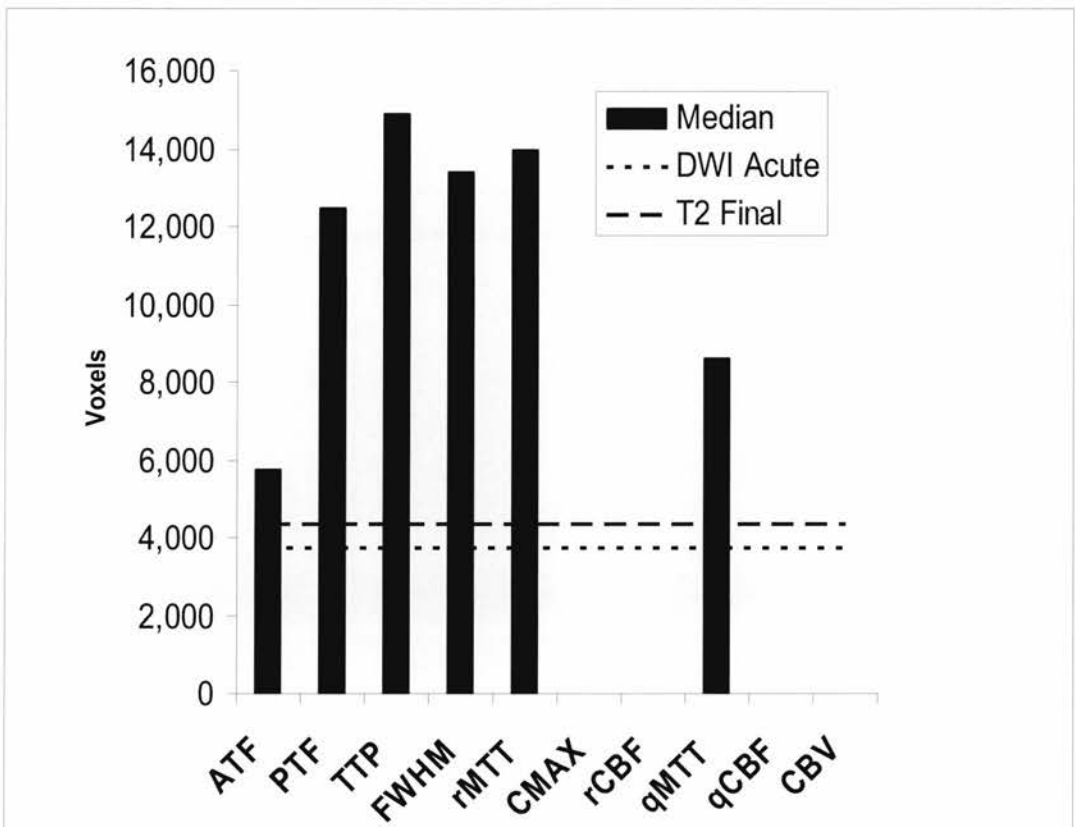
There was no significant relationship between the presence or absence of mismatch at baseline and infarct expansion at ≥1 month for any of the ten PWI parameters using Fisher's exact test (all p values were greater than 0.183).

3.4.4 Discussion

Five MR perfusion parameters reflecting MTT were associated with clinical scores of acute stroke severity and one, also reflecting MTT, with functional outcome. These overlapped with perfusion parameters that were associated with final T2 lesion volume, although the PWI lesions that reflected MTT in general produced stronger associations than did those reflecting CBF or CBV. Our results are in agreement with previous work that found both TTP and qMTT correlated with baseline NIHSS.[15,25-27] However, we also demonstrated that in this series ATF, PTF, FWHM, rMTT and rCBF were associated with baseline stroke severity measured with NIHSS.

One of the perfusion parameters (ATF) was also associated with functional neurological outcome at three months, although three other perfusion parameters achieved very weak associations with p values bordering on significant (PTF, TTP, and rMTT). All four are relative measures of MTT. These results differed from those of some[28] and supported others.[33] In summary, the results suggest that, in general, relative measures of MTT correlate with both baseline stroke severity and clinical functional outcome. These are relatively quick to perform and easy to obtain (no deconvolution required) and therefore are more practical in the acute setting.

Figure 3



The variation in the median size (voxels) for all 32 patients of the perfusion lesion measured by 10 different PWI processing methods. The median baseline DWI (DWI acute) and final infarct extent (T2- final) lesion volumes are also indicated. Note the median lesion volumes for Cmax, rCBF, qCBF and CBV were zero due to the large proportion of patients with no visible PWI lesion.

A wider range of acute PWI parameters were associated with the final T2 infarct extent in this patient group, with ATF, PTF, TTP and rMTT being most closely associated and FWHM, rCBF, qCBF and CBV achieving less strong significance. Note that these latter (apart from FWHM) tend to produce smaller PWI lesions. However, how useful are the acute PWI parameters that reflect final T2 lesion extent in clinical practice? The most important outcomes are those that define the patient's functional status. Recent data suggest that the final T2 lesion extent does not reflect the total damage within the brain from the stroke. There may be histological evidence of damage outside the T2-visible lesion, including tissue inflammation and selective neuronal damage.[34,35] It may be that the total area of damage is greater than just that in the T2-visible lesion and includes tissue which fell within the acute MTT lesion. This might explain why, in this study, the correlations between baseline PWI lesion and functional outcome were strongest for relative MTT measures (i.e. large PWI lesions).

The present analysis included all patients, whether or not there was a detectable PWI lesion present, so as to be able to determine the relative predictive values of the different PWI processing methods, including those which less frequently produce a PWI lesion. I did not use an explicit correction for multiple comparisons, but the effect of doing so can be seen by ignoring any p values in Tables 3 and 4 which are larger than 0.01. It was not clear in other publications whether or not all patients, or just those with visible PWI lesions, had been included, which may explain some discrepancies between studies. The considerable variation in the presence of a PWI lesion would cause substantial variation in the recruitment to clinical trials if DWI/PWI mismatch were used as an entry criterion. Excluding patients without PWI lesions would result in a very skewed comparison – for example in our series, some PWI parameters (e.g. TTP) might contribute 23/32 patients whereas others like rCBF or CBV might only contribute 15/32 or even 13/32 and this again might explain differences between studies. Excluding patients without PWI lesions would provide no information on the clinical relevance of an examination that did not show a PWI lesion. In the acute situation, with limited time for multiple post processing attempts, one needs to use the PWI parameter which is most

likely to inform decision-making – choosing a PWI parameter that has a high probability of NOT producing a visible lesion combined with not knowing what the absence of a lesion means, is unlikely to be a helpful test.

Note: At the time of writing, an attempt to establish a consortium to agree the minimum standards for MR image acquisition and processing is being established – the group first met in September 2007 and are due to meet again in February 2008. A paper describing this process has been submitted to Stroke.

3.5 Summary

- There are a number of different ways of measuring the MR perfusion lesion; all of which require varying degrees of post processing.

- To date there is no consensus in the literature regarding the 'best' method for measuring the perfusion lesion in the clinical setting.

- The data from our study confirm that the size of the perfusion lesion varies markedly depending on the method used to measure it. This in turn impacts on the size of the so called perfusion diffusion mismatch, resulting in between 9% and 72% of patients having mismatch in our study.

- If treatment decisions for thrombolysis are based on a particular degree of mismatch, the number of patients treated would vary by an unacceptable level depending on the perfusion measurement.

- If trials recruited patients on the basis of mismatch then it could result in substantial variation in treatment rates.

- Relative perfusion methods, although quick, may produce unacceptable variability amongst patients.

- Quantitative PWI measures require more time consuming post processing, but reduce the difference in lesion volume between the PWI parameters.

- In this study five measures of rMTT were associated with the baseline NIHSS, one of which was also associated with clinical outcome.

- Final infarct size was most strongly associated with measures of rMTT and less strongly with CBF or CBV.

- No relationship was demonstrated between the presence/absence of mismatch at baseline and infarct expansion at $\geq$ 1 month, in broad agreement with data from the systematic review (Chapter 2).

- In summary, relative measures of MTT, which are quick to perform and are associated with stroke severity and functional outcome, may be more useful than PWI parameters that relate closely to radiological surrogates.

- There is an urgent need for standardisation of methods for processing perfusion data across the research community and amongst any clinical users of these techniques.

- Inter- and intra-observer reliability needs to be investigated further if PWI were to become an essential tool on which to base treatment decisions.

Table 1: Ten different PWI parameters, relative and quantitative estimates of CBF, MTT or CBV, and their definitions.

Perfusion method	**Parameter represented**	**Definition**
Arrival time fitted (ATF)	MTT : relative	Estimated delay in arrival of contrast in a voxel obtained from the curve fitting procedure
Peak time fitted (PTF)	MTT : relative	Estimate of the time of maximum contrast concentration obtained from the fitted parameters
Time to peak (TTP)	MTT : relative	Peak time fitted minus arrival time fitted
Full width half maximum (FWHM)	MTT : relative	Width of the concentration/time curve at the point half way to the peak concentration
First moment (rMTT)	MTT : relative	First moment of the concentration time curve
Peak concentration (Cmax)	CBF and MTT : relative	Maximum value of the fitted concentration/time curve
Relative cerebral blood flow (rCBF)	CBF : relative	rCBV/rMTT
Quantitative mean transit time (qMTT)	MTT : quantitative	qCBF/qCBV
Quantitative cerebral blood flow (qCBF)	CBF : quantitative	Maximum value of the scaled estimate of the voxel residue response
Cerebral blood volume (CBV)	CBV : relative or quantitative	Area under the concentration-time curve

Table 2: Summary of characteristics of patients recruited

Men	19
Women	13
Mean age	70.4 years (range 36-93)
Mean time to MR	7.27 hours (range 1.36-23.34)
Mean baseline NIHSS	9 (range 0-25)
Mean outcome mRS	2 (range 0-6)
Stroke subtype – TACS – PACS – LACS	 10 19 3

Table 3: Volumes of PWI lesions and mismatch tissue, number of patients with a PWI lesion and PWI/DWI mismatch by PWI processing method used. Mean and median PWI volumes are shown to overcome the "zero" medians.

Perfusion method	Mean volume of PWI lesion (voxels)	Median volume of PWI lesion (voxels)	Number with no PWI lesion at all	Number with mismatch (%)	Number without mismatch	Median volume of mismatch (voxels)
Arrival time fitted (ATF)	15106	5747	11	18 (56)	14	715
Peak time fitted (PTF)	21185	12478	7	21 (66)	11	7690
Time to peak (TTP)	22802	14882	9	20 (63)	12	8213
Full width half maximum (FWHM)	32260	13405	7	23 (72)	9	8748
First moment (rMTT)	23177	13996	7	23 (72)	9	9684
Peak concentration (Cmax)	5993	0	17	7 (22)	25	- 1224*
Relative cerebral blood flow (rCBF)	4162	0	17	5 (16)	27	- 1278*
Quantitative mean transit time (qMTT)	22167	8620	13	18 (56)	14	3853
Quantitative cerebral blood flow (qCBF)	12783	0	17	13 (41)	19	-492*
Cerebral blood volume (CBV)	2446	0	19	3 (9)	29	- 1849*

* Negative values indicate that the median DWI lesion is larger than the median acute PWI lesion

Table 4: Association between perfusion method, baseline clinical score (NIHSS) and functional outcome at 3 months (mRS). Significant associations highlighted in bold.

Perfusion method	**Slope of linear regression line with baseline NIHSS (p value)**	**Slope of linear regression line with 3 month mRS (p value)**
Arrival time fitted (ATF)	**0.209 (0.006)**	**0.049 (0.035)**
Peak time fitted (PTF)	**0.210 (0.005)**	0.042 (0.068)
Time to peak (TTP)	**0.193 (0.006)**	0.040 (0.066)
Full width half maximum (FWHM)	**0.180 (0.006)**	0.021 (0.313)
First moment (rMTT)	**0.206 (0.005)**	0.042 (0.067)
Peak concentration (Cmax)	0.147 (0.133)	0.018 (0.549)
Relative cerebral blood flow (rCBF)	0.206 (0.057)	0.035 (0.285)
Quantitative mean transit time (qMTT)	0.050 (0.456)	0.017 (0.407)
Quantitative cerebral blood flow (qCBF)	0.098 (0.195)	0.029 (0.202)
Cerebral blood volume (CBV)	0.236 (0.066)	0.042 (0.278)

Table 5: Association between perfusion method and final infarct extent on T2-weighted MR imaging (≥ 1 month after symptom onset). Significant associations highlighted in bold.

Perfusion method	Slope of linear regression line with final infarct size ≥ 1 month (p value)
Arrival time fitted (ATF)	**0.330 (0.002)**
Peak time fitted (PTF)	**0.292 (0.007)**
Time to peak (TTP)	**0.286 (0.004)**
Full width half maximum (FWHM)	**0.214 (0.025)**
First moment (rMTT)	**0.303 (0.004)**
Peak concentration (CMAX)	0.263 (0.059)
Relative cerebral blood flow (rCBF)	**0.324 (0.036)**
Quantitative mean transit time (qMTT)	0.162 (0.089)
Quantitative cerebral blood flow (qCBF)	**0.236 (0.025)**
Cerebral blood volume (CBV)	**0.392 (0.032)**

References

1. Bandera E, Botteri M, Minelli C, Sutton A, Abrams KR, Latronico N. Cerebral blood flow threshold of ischaemic penumbra and infarct core in acute ischaemic stroke: a systematic review. *Stroke* 2006;37:1334-1339.

2. Calamante F, Gadian DG, Connelly A. Quantification of perfusion using bolus tracking magnetic resonance imaging in stroke: assumptions, limitations, and potential implications for clinical use. *Stroke* 2002;33:1146-1151.

3. Latchaw RE, Yonas H, Hunter GJ, Yuh WT, Ueda T, Sorensen AG, Sunshine JL, Biller J, Wechsler L, Higashida R, Hademenos G. Guidelines and recommendations for perfusion imaging in cerebral ischemia: a scientific statement for healthcare professionals by the writing group on perfusion imaging, from the Council on Cardiovascular Radiology of the American Heart Association. *Stroke* 2003;34:1084-1104.

4. Hossman KA. Viability thresholds and the penumbra of focal ischaemia. *Ann Neurol* 1994;36:465-557.

5. Calamante F, Thomas DL, Pell GS, Wiersma J, Turner R. Measuring cerebral blood flow using magnetic resonance imaging techniques. *J Cereb Blood Flow* 1999;19:701-735.

6. Abu Hajir M, Rand SD, Krouwer HG, Schmainda KM. Noninvasive assessment of neoplastic angiogenesis. The role of MRI. *Semin Thromb Hemost* 2003;29:306-316.

7. Wintermark M, Sesay M, Barbier E, Borbely K, Dillon WP, Eastwood JD, Glenn TC, Grandin CB, Pedraza S, Soustiel JF, Nariai T, Zaharchuk G, Caille JM, Dousset V, Yonas H. Comparative overview of brain perfusion imaging techniques. *Stroke* 2005;36:e83-e99.

8. Perthen JE, Calamante F, Gadian DG, Connelly A. Is quantification of bolus tracking MRI reliable without deconvolution? *Magn Reson Med* 2002;47:61-67.

9. Thijs VN, Somford DM, Bammer R, Robberecht W, Moseley ME, Alberts GW. Influence of arterial input function on hypoperfusion volumes measured with perfusion-weighted imaging. *Stroke* 2004;35:94-98.

10. Rose SE, Janke AL, Griffin M, Finnigan S, Chalk JB. Improved prediction of final infarct volume using bolus delay-corrected perfusion-weighted MRI: implications for the ischemic penumbra. *Stroke* 2004;35:2466-2471.

11. Carpenter T, Armitage PA, Bastin ME, Wardlaw JM. DSC Perfusion MRI – quantification and reduction of systematic errors arising in areas of reduced cerebral blood flow. *Magn Reson Med* 2006;55:1342-1349.

12. Ostergaard L, Weisskoff RM, Chesler D, Gyldensted C, Rosen BR. High resolution measurement of cerebral blood flow using intravascular tracer bolus passages. Part I: mathematical approach and statistical analysis. *Magn Reson Med* 1996;36:715-725.

13. Hjort N, Butcher K, Davis SM, Kidwell CS, Koroshetz WJ, Rother J, Schellinger PD, Warach S, Ostergaard L. Magnetic resonance imaging criteria for thrombolysis in acute cerebral infarct. *Stroke* 2005;36:388-397.

14. Yamada K, Wu O, Gonzalez RG, Bakker D, Ostergaard L, Copen WA, Weisskoff RM, Rosen BR, Yagi K, Nishimura T, Sorensen AG. Magnetic resonance perfusion-weighted imaging of acute cerebral infarction: effect of the calculation methods and underlying vasculopathy. *Stroke* 2002;33:87-94.

15. Rose SE, Chalk JB, Griffin MP, Janke AL, Chen F, McLachan GJ, Peel D, Zelaya FO, Markus HS, Jones DK, Simmons A, O'Sullivan M, Jarosz JM, Strugnell W, Doddrell DM, Semple J. MRI based diffusion and perfusion predictive model to estimate stroke evolution. *Magn Reson Imaging* 2001;19:1043-1053.

16. Rivers CS, Wardlaw JM, Armitage P, Bastin ME, Carpenter TK, Cvoro V, Hand PJ, Dennis MS. Do acute diffusion- and perfusion-weighted MRI lesions identify final infarct volume in ischemic stroke? *Stroke* 2006;37:98-104.

17. Parsons MW, Barber PA, Chalk J, Darby DG, Rose S, Desmond PM, Gerraty RP, Tress BM, Wright PM, Donnan GA, Davis SM. Diffusion- and perfusion-weighted MRI response to thrombolysis in stroke. *Ann Neurol* 2002;51:28-37.

18. Sorensen AG, Copen WA, Ostergaard L, Buonanno FS, Gonzalez RG, Rordorf G, Rosen BR, Schwamm LH, Weisskoff RM, Koroshetz WJ. Hyperacute stroke: simultaneous measurement of relative cerebral blood volume, relative cerebral blood flow, and mean tissue transit time. *Radiology* 1999;210:519-527.

19. Butcher KS, Parsons M, MacGregor L, Barber PA, Chalk J, Bladin C, Levi C, Kimber T, Schultz D, Fink J, Tress B, Donnan G, Davis S, for the EPITHET Investigators. Refining the perfusion-diffusion mismatch hypothesis. *Stroke* 2005;36:1153-1159.

20. Grandin CB, Duprez TP, Smith AM, Oppenheim C, Peeters A, Robert AR, Cosnard G. Which MR-derived perfusion parameters are the best predictors of infarct growth in hyperacute stroke? Comparative study between relative and quantitative measurements. *Radiology* 2002;223:361-370.

21. Schellinger PD, Latour LL, Wu CS, Chalela JA, Warach S. The association between neurological deficit in acute ischemic stroke and mean transit time. Comparison of four different perfusion MRI algorithms. *Neuroradiology* 2006;48(2):69-77.

22. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet* 1991;337:1521-1526.

23. Rivers CS, Wardlaw JM, Armitage PA, Bastin ME, Hand PJ, Dennis MS. Acute ischaemic stroke lesion measurement on diffusion weighted imaging – important considerations in designing acute stroke trials with magnetic resonance imaging. *J Stroke Cereb Vasc Dis* 2007;16:64-70.

24. Ostergaard L, Sorensen AG, Kwong KK, Weisskoff RM, Gyldensted C, Rosen BR. High resolution measurement of cerebral blood flow using intravascular tracer bolus passages. Part II: Experimental comparison and preliminary results. *Magn Reson Med* 1996;36:726-736.

25. Bandera E, Botteri M, Minelli C, Sutton A, Abrams KR, Latronico N. Cerebral blood flow threshold of ischemic penumbra and infarct core in acute ischemic stroke. A systematic review. *Stroke* 2006;37:1334-1339.

26. Bardutzky J, Shen Q, Henninger N, Bouley J, Duong TQ, Fisher M. Differences in ischemic lesion evolution in different rat strains using diffusion and perfusion imaging. *Stroke* 2005;36:2000-2005.

27. Beaulieu C, de Crespigny A, Tong DC, Moseley ME, Albers GW, Marks MP. Longitudinal magnetic resonance imaging study of perfusion and diffusion in stroke: Evolution of lesion volume and correlation with clinical outcome. *Ann Neurol* 1999;46:568-578.

28. Derex L, Nighoghossian N, Hermier M, Adeleine P, Berthezene Y, Philippeau F, Honnorat J, Froment JC, Trouillas P. Influence of pretreatment MRI parameters on clinical outcome, recanalization and infarct size in 49 stroke patients treated by intravenous tissue plasminogen activator. *J Neurol Sci* 2004;225:3-9.

29. Barber PA, Parsons MW, Desmond PM, Bennett DA, Donnan GA, Tress BM, Davis SM. The use of PWI and DWI measures in the design of "proof-of-concept" stroke trials. *J Neuroimaging* 2004;14:123-132.

30. Rohl L, Geday J, Ostergaard L, Simonsen CZ, Vestergaard-Poulsen P, Andersen G, Le Bihan D, Gyldensted C. Correlation between diffusion-and perfusion-weighted MRI and neurological deficit measured by the Scandinavian Stroke Scale and Barthel Index in hyperacute subcortical stroke (< or = 6 hours). *Cerebrovasc Dis* 2001;12:203-213.

31. Shih LC, Saver JL, Alger JR, Starkman S, Leary MC, Vinuela F, Duckwiler G, Gobin YP, Jahan R, Villablanca JP, Vespa PM, Kidwell CS. Perfusion-weighted magnetic resonance imaging thresholds identifying core, irreversibly infarcted tissue. *Stroke* 2003;34:1425-1430.

32. Butcher K, Parsons M, Baird T, Barber A, Donnan G, Desmond P, Tress B, Davis S. Perfusion thresholds in acute stroke thrombolysis. *Stroke* 2003;34:2159-2164.

33. Chalela JA, Kang D-W, Luby M, Ezzeddine M, Latour LL, Todd JW, Dunn B, Warach S. Early MRI findings in patients receiving tissue plasminogen activator predict outcome: Insights into the pathophysiology of acute stroke in the thrombolysis era. *Ann Neurol* 2004;55:105-112.

34. Baron JC. How healthy is the acutely reperfused ischemic penumbra? *Cerebrovasc Dis* 2005;20 suppl 2:25-31.

35. Price CJ, Wang D, Menon DK, Guadagno JV, Cleij M, Fryer T, Aigbirhio F, Baron JC, Warburton EA. Intrinsic activated microglia map to the peri-infarct zone in the subacute phase of ischemic stroke. *Stroke* 2006;37:1749-53.

4 The practicalities of MR as an imaging modality in acute stroke

4.1 Feasibility of a simplified MR imaging protocol for patients with acute ischaemic stroke

4.1.1 Introduction

The most promising treatment for acute ischaemic stroke, in patients who present within three hours, is thrombolysis with recombinant tissue plasminogen activator, rt-PA. Currently rt-PA is licensed for use in patients with acute ischaemic stroke who meet strict eligibility criteria. It is not known which brain imaging method best identifies the patients that are most likely to benefit from (or be harmed by) thrombolysis, as has been discussed in earlier chapters of this thesis. CT scanning is widely available and quick to perform, but might not be sufficiently sensitive to tissue changes that could indicate either a greater chance of benefit or greater susceptibility to haemorrhage.

MR DWI is very sensitive to early ischaemic damage.[1] MR PWI demonstrates blood flow in and around the infarct.[2] Areas where there is 'mismatch' with evidence of perfusion deficit without tissue damage may be the area of the brain (i.e. the 'penumbra') likely to be 'salvaged' by reperfusion therapy[3,4] but as the systematic review in Chapter 2 revealed there is a paucity of data supporting this theory. There was no evidence that mismatch predicted clinical or tissue outcome or that it influenced the response of an individual to thrombolysis.

Perhaps other features of the DWI lesion need to be considered, e.g. degree of hyperintensity (whiteness) and 'haziness' of the lesion edge, might be important determinants of tissue injury. Magnetic resonance angiography (MRA) may also help -

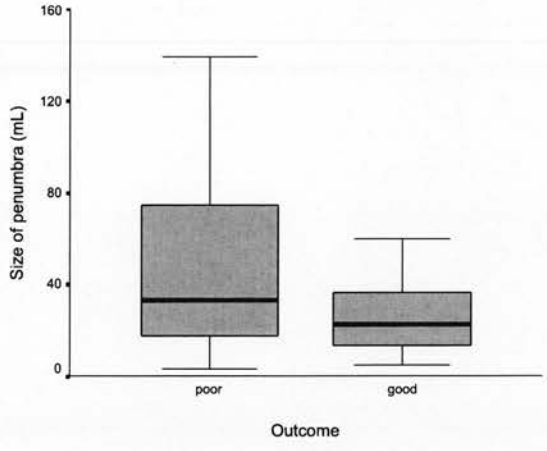
perhaps patients with a still-occluded major artery without much evidence of tissue damage on DWI will benefit most from rt-PA. MR imaging might help identify potential hazards in other ways. Microhaemorrhages (tiny areas of old asymptomatic haemorrhage) increase with age, are associated with periventricular white matter hyperintensities on T2 MR and may[5] or may not[6] be associated with a higher risk of bleeding with rt-PA.

The Third International Stroke Trial (IST-3) is evaluating the safety and efficacy of rt-PA in a wider variety of patients than is covered by the current licence. To enable as many centres as possible to randomise patients as quickly as possible, CT scanning is the specified pre-randomisation imaging technique. However, many sites are interested in evaluating MR PWI/DWI imaging for patient selection.

Thus, we needed to develop and test the methodology for a simple and efficient MR PWI/DWI protocol that yields sufficient information to improve patient selection, yet is not unduly time consuming or hazardous.[7] This protocol could then be employed in centres participating in IST-3 that have MR facilities. The MR would be performed after CT scanning but before randomisation. The data would then allow an assessment of the influence of mismatch and other MR features on the response to thrombolysis, in a prospective study, with appropriate randomised controls. If the MR imaging protocol we developed proved to be feasible in a multicentre study, and if the results were shown to be useful in clinical practice, it could be adopted widely.

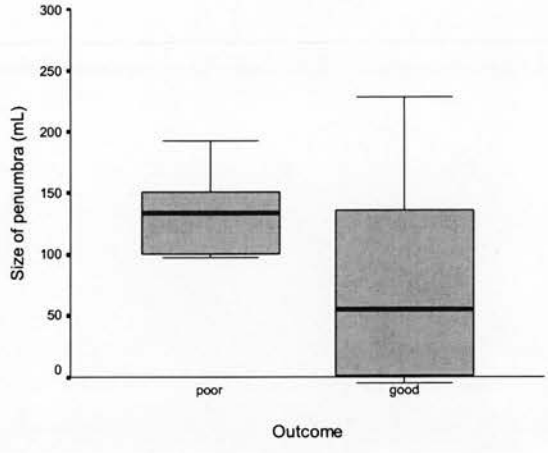
Prior to setting up the pilot study, 198 patients had been randomised into IST-3 (42 at the Western General Hospital, Edinburgh). An interim analysis of 60 patients with baseline PWI/DWI imaging in an observational study of the pathophysiological changes following acute ischaemic stroke on PWI/DWI imaging at the Western General Hospital, showed no association between the presence of a PWI/DWI mismatch (mean transit time - MTT or cerebral blood flow - CBF) and 3 month clinical outcome in patients not receiving rt-PA[8] (Figure 1); patients with early spontaneous improvement in

Figure 1



CBF maps: P=0.33

(Mann Whitney U)



MTT maps: P=0.25

(Mann Whitney U)

A study of the relationship between PWI/DWI mismatch and clinical outcome at 3 months in patients not treated with thrombolysis according to whether the PWI lesion is measured as CBF or MTT. Box and whisker plot of size of mismatch for patients divided into good and poor functional outcome. All included patients presented with acute ischaemic stroke.[8]

perfusion parameters had more rapid "normalization" of DWI changes.[9] Previous work in the Division of Clinical Neurosciences, Edinburgh and elsewhere, showed that spontaneous reperfusion of the infarct is associated with improved clinical outcome.[10] Whilst the influence these imaging features have on prognosis is of interest, the key question is whether there is a significant interaction with the treatment effect of rt-PA. This can only be studied in a randomised controlled trial, where the relevant MR parameters are measured before randomisation.

We therefore aimed to develop and test a short, simple streamlined MR protocol that could be widely adopted in centres participating in a randomised controlled trial of thrombolysis (IST-3). These data would then provide reliable evidence about which MR sequences were the most useful for identifying which patients were most likely to benefit from or be harmed by thrombolysis.

Research questions to be asked and hypotheses to be tested

The key hypothesis for a large-scale study is that MR imaging will help select those patients with acute ischaemic stroke who will benefit most from rt-PA. The ultimate aim of a sub-study of IST-3 is to address the following questions:

- Can routine MR be made more rapid, practical and safe in acute stroke?
- Does ischaemic lesion appearance on DWI (extent, intensity, or clarity) predict the amount of non-salvageable tissue?
- Is the benefit of rt-PA confined to those with a PWI lesion larger than the DWI lesion (DWI/PWI mismatch) or do those *without* mismatch benefit as well?
- Are patients with white matter hyperintensities or microhaemorrhages at greater risk of intracranial haemorrhage after rt-PA than those without?
- How do CT scan 'early infarct signs' and white matter hypodensities relate to MR 'early infarct signs' and white matter hyperintensities?

To answer these questions a multicentre study is required in order to attain a large enough sample. Therefore the research question concerning the pilot study was, in the context of IST-3, 'is it feasible to run an MR imaging sub-study at the Western General Hospital aiming to improve the safety of thrombolysis?' As this was outside the funding originally available for IST-3, I prepared and submitted a small project grant application (£15,000) to the Chief Scientist's Office to obtain funding for scans and various assessments of imaging (see Appendix 7).

4.1.2 Methods

Selection of MR sequences

We considered all of the MR sequences that might be included in the protocol, information that might be gleaned from each, and the implications for scanning time, requirement for post-processing, overall cost and feasibility. Then, by a process of discussion, sought to select the best scanning sequence to: limit scanning time, ensure that the sequences could be run on a wide variety of MR machines, ensure adequate data were collected to investigate mismatch, without undue cost or risk to the patient. During this process we also discussed potential MR sequences with IST-3 centres in Sweden (including one visit from Stockholm by a radiologist) and in Belgium (including face to face meetings, and communication by email and teleconference) to refine the protocol to match what other centres could reasonably be expected to do.

Based on these discussions and data presented earlier in this thesis, the plan was for the patients to have the following sequences: PWI/DWI, T_2, gradient echo and 3D time-of-flight MRA (TOF MRA):

- DWI (three gradient echo planar technique TR 10000ms, TE 98.8ms, 34 phases)
- PWI (intravenous gadolinium bolus tracking using various simple methods of analysis of the signal time curve and more complicated methods such as the modified Ostergaard technique to produce mean transit time (MTT), cerebral blood flow (CBF) and cerebral blood volume)[2,11]

- T2 weighted imaging (fast spin echo TR 6300ms, TE 102ms)
- Gradient echo imaging (TR 625ms, TE 15ms), and
- 3D time of flight MRA are all standard techniques, total acquisition time 12-15 minutes maximum (full details Appendix 8).

The MR protocol was to be repeated at 24-48 hours to identify haemorrhage, infarct expansion and perfusion changes in place of the routine IST-3 follow-up CT at 24-48 hours. A final follow up scan at 3 months was proposed to determine the volume of the late T_2 lesion. This has similarities with the EPITHET protocol and other studies like the recently completed DIAS 2.

There are no clearly defined validated guidelines equivalent to the "1/3 MCA rule for CT", on whether the appearance of the infarct on PWI/DWI should alter treatment decisions. Therefore we did not specify what PWI/DWI appearances should lead to inclusion or exclusion of the patient from the study. The only major and absolute exclusion was the presence of fresh intracranial haemorrhage. The justification for the approach was that DWI lesions may resolve, that animal studies have shown severely ischaemic tissue beyond the boundaries of the DWI-visible lesion, and that some patients with severe strokes and poor outcome do not have a DWI visible lesion at presentation. Even less is known about the PWI lesion.

Subject selection

All patients potentially eligible for IST-3 who presented at the Western General Hospital, between 9am and 5pm, Monday to Friday, were assessed and recorded. Those fitting the trial eligibility criteria (summary of IST-3 protocol Appendix 9), consenting to IST-3 and safe to MR, were then examined, following the imaging protocol mentioned above. Ethics approval had previously been sought for IST-3 (more detail in chapter 5) and this was reviewed and granted for this MR sub-study with four methods of consent possible – written, witnessed, assent and waiver of consent (see Appendices 10 & 11 for patient information leaflet and an example of a consent form).

In the protocol it was proposed that patients should have a CT followed by MR as outlined in the pathway (Appendix 12). This was specifically to test what additional information MR could add to CT and to be able to translate MR results to CT. As part of the protocol, coordination times and any delays were to be recorded (Appendix 13) as part of the planning for a larger study in order to find the optimum way of organising a comparative imaging study.

Clinical assessments

We planned detailed baseline clinical assessments of neurological deficit (National Institutes of Health Scale – NIHSS), blind to imaging at baseline by the stroke physician. Further clinical information was to be obtained at 7 days as per the IST-3 in-hospital follow-up form and in addition we planned to record the NIHSS. Six month final follow-up in IST-3 is by detailed postal questionnaire, mailed directly to the patient and conducted independently of the treating physician.

Assessment of the scans

As part of IST-3 the CT scans were to be read centrally for lesion site and extent and degree of hypodensity according to well-validated scoring methods by an expert panel as already established for the main trial (see www.neuroimage.co.uk).[12,13] The MR image analysis for a main study would need to be established and streamlined, but would include several methods, including comparing the MR read locally (i.e. by the attending physician) with a reading centrally, blinded to treatment allocation. Central analysis would be blinded to clinical details and would include simple subjective inspection of the PWI/DWI mismatch (for example, by the same coding template as for CT,[12] and whether the DWI lesion involves more than 1/3 of the MCA territory),[14] measurement of the volume of the DWI and PWI lesions and mismatch, and voxel by voxel analysis of subregions of the lesion on a workstation using co-registered images. The characteristics of the DWI lesion appearance were to be recorded (e.g. signal intensity – bright/pale and edge clarity – sharply defined/fuzzy edge) since these features may be the "DWI equivalent" of CT early infarct signs. PWI processing was to include CBF, cerebral

blood volume (CBV) and MTT.[11] The PWI/DWI 'mismatch' was be defined as a difference in the volume of the lesion of more than 20% between DWI and PWI (CBF and MTT). We planned to compare estimation by visual inspection with measured lesion volume analysis. On MRA, we aimed to compare the presence of major artery occlusion with PWI/DWI appearance, degree of reperfusion, and clinical outcome. Microhaemorrhages are round dots of low signal on gradient echo imaging usually less than 2mm in diameter. Small asymmetric dots of low signal where the lenticulostriate arteries perforate the brain substance in the inferior part of the basal ganglia are not microhaemorrhages. The presence and extent of microhaemorrhages were to be recorded. The proposal was that MRA be coded for vessel occlusion using the modified TIMI classification.[15]

Statistical analysis plan for the main study and this pilot

When the main IST-3 study has finished statistical analysis will include univariate and multivariate modelling to test for: a) independent associations between PWI/DWI lesion volumes, other aspects of their appearance, the mismatch, time to treatment, final infarct size and clinical outcome and the interaction with rt-PA; b) risk of intracerebral haemorrhage with improved perfusion, and microhaemorrhages and the interaction with rt-PA; and c) correlation between the CT appearance and PWI/DWI. Unblinding of treatment allocation would not be appropriate prior to the final main study completion, and at the time of planning, IST-3 was in the double blind phase with identical placebo (although it subsequently became an open label study). We planned to evaluate how each PWI parameter mapped to infarct extent at 24-48 hours[16] and how initial DWI lesion extent, perfusion changes, and rt-PA relate to infarct swelling. The primary objective of the pilot was to assess feasibility, so although we aimed to analyse the PWI/DWI data obtained as proposed, we have to accept the sample size is not large enough to reliably answer the primary questions as put forward earlier in the introduction.

Sample size for the pilot study

A sample size of 20 subjects was chosen since it was thought this was a reasonable number of patients to test feasibility and allow piloting of the analyses of the MR data, given the limited time available. A smaller sample than this would be too small to draw any meaningful conclusions. Although an ambitious target, it was felt that 20 patients could be recruited in a 12 month period from the Western General Hospital based on existing observational and trial data. Prior to starting this pilot study, around one patient a month was being recruited into IST-3, but with increasing awareness of the trial and of thrombolysis as a potential treatment for acute ischaemic stroke, it was felt that recruitment should increase.

4.1.3 Results

The funding was finally approved in December 2004, leaving only 11 months for recruitment. Over the study period, 68 patients with acute stroke were assessed for consideration for thrombolysis. Of those, 57 were not suitable for thrombolysis. In the majority of cases this was because they fell outside the 6 hour time window once a detailed history was taken or they woke with their symptoms making the time of onset impossible to ascertain. In a minority of cases there were specific contraindications to thrombolysis e.g. rapidly resolving symptoms or recent treatment with heparin and a clotting time exceeding that permitted for treatment. Eleven patients received thrombolysis, one with intra-arterial rt-PA and balloon angioplasty, four under the current licence and six were randomised in IST-3.

As it turned out, I was unable to recruit any of these patients into the proposed MR pilot study. There were several reasons for this that were beyond my control. Firstly, re-organisation of stroke services in Lothian led to lack of clarity over whether the WGH would continue as a hospital admitting acute medical emergencies and a reduction in the number of acute stroke cases sent urgently to the WGH; this was further compounded by a reduction in the capacity of the research team to assess those patients that did reach the

WGH early enough to be considered for the study, (so some potentially suitable patients may have been missed); and finally, by chance, most of the patients randomised into IST-3 (or treated under the licence) in the last year arrived and were treated out of normal working hours (when the research scanner does not operate).

Note: Further discussions about the Lothian-wide delivery of services for patients with acute stroke, and an increase in the number of clinical research staff have led to nine of the subjects for the pilot study being recruited at the time of writing. Of note five other patients were excluded because of specific contraindications to MRI.

4.1.4 Discussion

This pilot was needed to see if MR is practicable in acute stroke, in patients treated in the NHS, and to try to set up a streamlined way of investigating a larger group of patients in the future. A much larger sample is needed to answer the questions about the additional benefits (if any) of performing MR instead of CT in acute stroke patients being considered for thrombolysis. It is important that any imaging sequences are available in 'real time' if decisions have to be made regarding thrombolysis. Having images which require complicated and timely post processing is useless in the acute setting. The team worked very hard to establish this protocol and make sure that the radiographers maintained training. We achieved this despite many changeovers – the norm in the NHS. The simple fact was that there were not enough patients eligible for recruitment into the study, and those that were eligible often presented outside working hours. I was awarded a grant by the Chief Scientist Office (CSO), Scottish Executive, to carry out this pilot study. The CSO have granted a 'no cost extension' to the grant so that further patients can be recruited.

It is clear that, at the time this feasibility study was conducted, with the resources available, acute MR was not practicable in this group of patients. The results of previous, and subsequently published studies, suggest that similar problems are

experienced elsewhere. For example the EPITHET study has been running since 2001 to recruit 120 patients in 10 centres in Australia and Europe. It has required several extensions and struggled to reach its target. The DEFUSE study[17] recruited 74 patients in 7 centres over 4 years. If MR was easy, then more patients would be recruited more rapidly.

The difficulties I have experienced in recruiting patients highlights a key problem in acute stroke care in the UK. That is, that the majority of patients with stroke symptoms still do not arrive at hospital early enough to permit assessment and treatment within 6 hours of symptom onset. There are factors operating at every point in the system that handles patients with suspected acute stroke that hamper prompt treatment:[7,18] the patient and family do not recognise the symptoms of stroke; they fail to seek attention urgently; the emergency transport system does not always recognise acute stroke as an emergency condition, and there are major delays in triaging patients once they reach hospital – although a quarter reach hospital in 3 hours and half within 6 hours (despite referral by GP). There is then a median delay of 1 to 1.5 hours while the patient is assessed by junior medical staff before any brain scan is even requested. A major overhaul of the in-hospital system is needed to eliminate these avoidable delays. It leaves the scanning element with little time before the six hour treatment deadline (for IST-3) expires. The resource limitations are an additional factor, not enough medical staff available for prompt expert assessment of acute stroke, and not enough radiography and radiology staff to permit 24 hour use of MR. However, there would be little point in providing 24 hour MR availability if serious efforts are not made to remove the barriers that are apparent at earlier stages in the assessment process. Providing 24 hour MR now would simply add to the already significant waste of resources due to inefficient stroke assessment and treatment.

4.2 Survey of the availability of CT and MR for assessing patients with acute stroke in the UK

4.2.1 Introduction

As I have discussed throughout this thesis, brain imaging is one of the key elements in selecting a patient with acute stroke for thrombolysis. Imaging needs to be accessible 24 hours a day, require a minimal amount of time to perform the necessary sequences, be accurate in excluding stroke mimics and intracerebral haemorrhage, and ideally reliable in identifying the acute ischaemic lesion.

In the UK, the most commonly used and cost effective method used for imaging acute stroke patients is CT.[19] Over recent years it has become widely available and is often accessible 24 hours a day.[20] It is known that with an experienced viewer CT will identify all haemorrhages of sufficient volume to cause a clinically apparent stroke.[21] However, one of the problems for clinicians occurs when the patient presents with a clinical stroke syndrome but a 'normal' CT scan. Clinicians find, when considering patients for potentially risky treatments such as thrombolysis, that the absence of positive evidence of ischaemia is a barrier to the use of rt-PA: 'positive signs of infarction' add sufficient diagnostic information to the clinical features to help make a confident diagnosis of ischaemic stroke and would help remove this barrier. However, these CT signs e.g. loss of the insular ribbon and the hyperdense artery sign, are often subtle in patients presenting within the first few hours of stroke onset,[22] and hence easily missed.

MRI can provide more information than CT about patients with acute stroke. For example diffusion weighted imaging shows up more ischaemic stroke lesions than CT or conventional T1 or T2 MR sequences. It may be that advanced MR techniques can help us to select those patients who will do best with thrombolysis and other emerging

treatments. In some centres (chiefly USA and Germany) MR is already regarded by 'experts' as the imaging method of choice to select stroke patients for thrombolysis[23] and even in the UK, at least one centre has developed a policy of using MR as the first-line imaging method in patients with clinically suspected acute stroke.[24] However this centre focuses primarily on minor stroke thus avoiding the 20-30% of patients with moderate to severe stroke who are unable to tolerate MR.

As part of our assessment of the feasibility of MR to select patients for thrombolysis, I sought to assess the availability of MR for acute stroke in the UK. I therefore undertook a survey of all acute hospitals in the UK in 2005 to assess how many had MR scanners on site, and if they had one, to estimate how often (and how rapidly) patients with acute stroke had an MR scan.

4.2.2 Methods

I assembled a database of all hospitals in the UK (England, Wales, Scotland and Northern Ireland) that admitted acute stroke patients. The hospitals were identified from the list of those trusts participating in the recent National Sentinel Stroke Audit[20] and the Scottish Stroke Audit. I included both teaching hospitals and district general hospitals. At the time of the survey, some of the hospitals included had merged with others or had closed since those lists had been assembled. Once the hospitals were located, I sought a contact name for the lead stroke physician in each hospital. Where possible, this was the named stroke physician, or in other cases it was the clinician with an interest in stroke, who may have been a general physician, a geriatrician or a neurologist.

I developed a simple one page survey (Appendix 14) and sent it to the relevant clinician at each acute hospital, with a covering letter detailing the survey, enclosing a stamped addressed envelope for reply. The content and layout of the questionnaire, the covering letter, the mailing and reply arrangements were designed to maximise response rates in line with findings of a Cochrane systematic review.[25] I sought details on the presence or

absence of CT and MRI at each acute hospital. For centres with access to MR, I sought further details on MR capacity to scan patients with acute stroke (i.e. within six hours of symptom onset) within working hours and out of hours. The questionnaire included visual analogue scales for the questions on ease of access to MR, which were measured at equal intervals using a scale of 0 for 'impossible' to 12 for 'very easy'.

4.2.3 Quantitative results

Response rate

I sent the first mailing of the questionnaire to 268 hospitals. After the first posting, I received 224 (84%). Of those, two reported that the hospitals concerned had closed or were in the process of closing. One reported that it did not admit acute stroke patients. After the second posting, a further 24 replies were received, bringing the total number of responses to 248 (93%); this was very satisfactory.

Proportion with CT on site

Of the hospitals which responded to the survey, and were still admitting acute stroke patients, 240 (97%) had a CT scanner on site. Only eight hospitals did not have a CT, of which three were in remote areas of Scotland and required a journey of anything between 108 to 250 miles (usually by air) to their nearest CT or MRI. The remaining five hospitals with no CT or MRI were small units located, on average, 20 miles from their nearest centre with CT or MRI. One of these hospitals was in Northern Ireland, one in Wales and the remaining three in England.

Access to MR on site

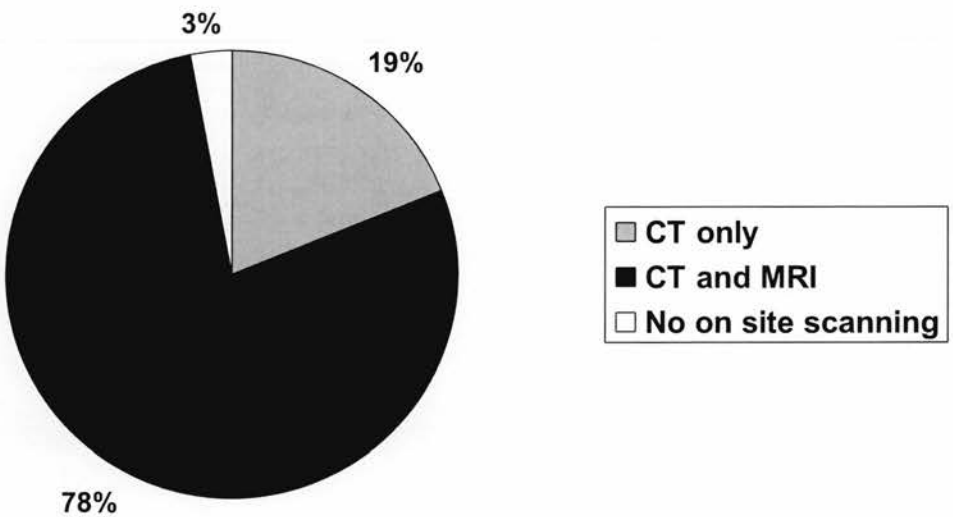
Of the respondents, 245 hospitals admitted acute stroke patients. Of those, 192 (78%) stated that they had MR facilities on site. Some hospitals reported that they had more than one MR scanner, although this information was not specifically requested. Of the hospitals which reported that they had MR, three had mobile units which were present at certain times, but were not available 24 hours a day. Of the 56 (23%) without MRI

facilities on site, one reported that it had a mobile unit visiting infrequently. The availability of imaging facilities is summarised in Figure 2. There were no hospitals that had an MRI scanner but no CT. As demonstrated, the majority of acute hospitals in the UK (78%) had both CT and MRI on site. 48 hospitals had on site CT, but no MRI facility. Of those, 46 gave details of the distance to their nearest MR. The average distance was 22.9 miles with a range of 0.5 miles to 80 miles.

Although more than three quarters of hospitals had access to MR within their hospital, availability of the scanner for patients with acute stroke was often problematic. Analysis of the visual analogue scales (questions 3 and 4 of the survey) showed that for patients presenting within 6 hours of stroke symptom onset, accessing MR at all times was far from easy (Figure 3). I arbitrarily defined 'difficult' access to MR as a visual analogue scale score of between 0 (impossible) and 5 (see Figure 3). With this definition, access was difficult in 73% of hospitals during working hours and in 95% for 'out of hours' access.

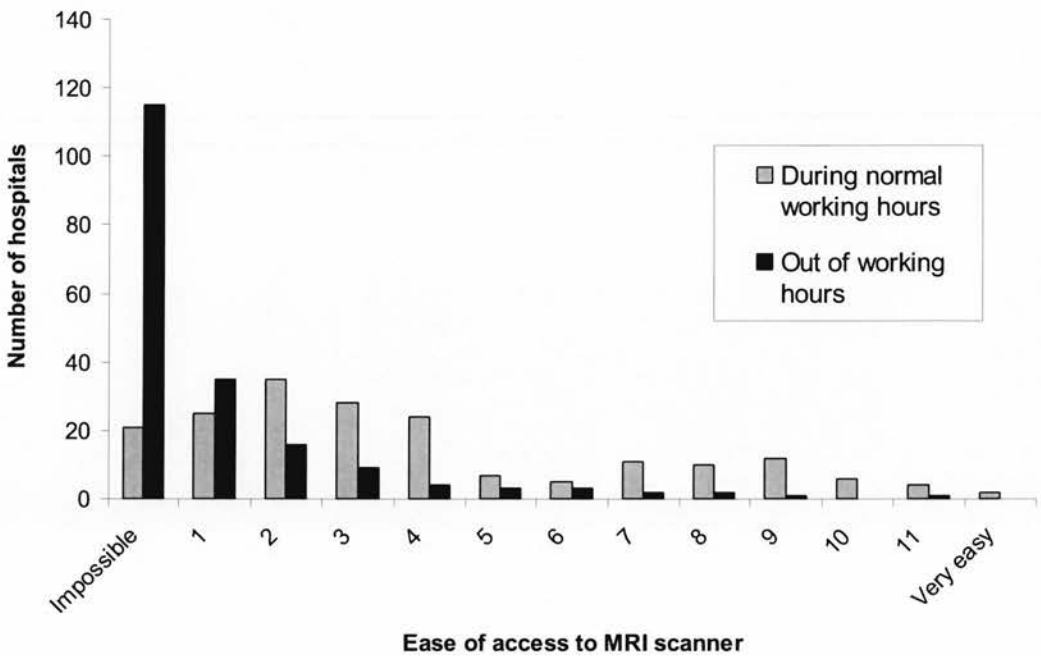
I wished to estimate how many acute stroke patients were being imaged with MR in the UK at the time of the survey (question 7 of survey). The results (Table 1) suggest that MR was rarely used as an imaging method in acute stroke patients. During the six months before the survey date only 21 (11%) hospitals (out of 192 with MRI facilities) reported that they had MR scanned any patients within 6 hours of stroke onset and 58 (30%) hospitals had scanned any patients within 12 hours of symptom onset. From the survey responses, I estimated that, per year in the whole UK, about 150 patients with acute stroke were scanned with MR within 6 hours of symptom onset, i.e. approximately 0.1% of all acute stroke cases.

Figure 2



Availability of on site brain scanning facilities for patients with acute stroke among 245 acute hospitals that admitted patients with acute stroke, in England, Wales, Scotland and N. Ireland in 2005.

Figure 3



Ease of access to MRI for patients with acute stroke presenting within 6 hours of symptom onset during normal working hours and out of hours, among 192 hospitals with on site MR.

Type of scanner and installation date

This question (question 5, Appendix 14) was the least well answered. Of the hospitals with MR, 90 (47%) physicians did not know the make of the MR scanner or declined to answer the question at all. Among those with known magnet strength, 75 (39%) had a 1.5T MR, 33 (17%) had <1.5T and 6 (3%) had 3.0T systems. Most of the more advanced 3.0T scanners were in teaching hospitals and in a few cases the responding physician commented that these were facilities specifically for research. The increasing recognition of MR as a scanning modality is reflected in the installation dates of the MR scanners in the hospitals surveyed. Only 39 (20%) of the MR scanners were installed before 2000; just over half, 103 (54%), of those acute hospitals with on site MR had their machines fitted in the last 5 years. In 50 (26%) cases the responder was not aware of the installation date of the MR at their hospital.

4.2.4 Qualitative results

The descriptive analysis of the comments from some of the physicians in response to the survey were of interest and highlight the quite considerable hurdle that would have to be overcome to introduce MR as a first line imaging technique in acute stroke. I have grouped them in themes below.

Shortage of radiology and radiography staff, other staffing problems

'We don't have enough trained radiographers to operate the MRI scanner 24hrs a day. CT however is available all the time at the discretion of the duty radiologist'

'In our hospital there are significant delays both at the scanning stage and then at the reporting stage'

'Our main problem is that we have six vacant consultant radiologist posts and neuro-radiology is off site. Under the circumstances we do get good support from radiology'

'Skilled staffing shortage'

'We have a fast MRI scanner - but poor access due to shortages of staff. Not available after 5pm'

'Our MRI department is new. It lacks staffing (consultant support)'

'Radiology registrars often defer scans overnight till next morning'

'We have a very severe shortage of radiologists and no immediate prospect of recruitment'

'We have neuroscience dept with neuroradiology and MRI scanner functional but only 2 of 3 neuroradiology posts filled'

'Radiology very reluctant [to adopt MR for stroke] as [they] argue that blood more easily seen on CT'

'Restraints mainly due to manpower and funding shortages'

'Also issues of reporting, neuroradiology reporting although much improved recently is still by no means perfect, but particularly out of hours is difficult'

'With sufficient funding to pay out of hours cover, staff are willing to come in but only for RESEARCH scanner. The MRI scanner is hugely overburdened'

'Radiology won't do out of hours CT for stroke'

'Major funding and staffing issues - also pressure of other imaging needs'

Pressure on scanner from other specialities; stroke not a priority

'Radiology service very over stretched. MRI seen as elective procedure. CT scanning routinely within 24 hours only agreed 2 years ago'

'Our MRI was provided via a lottery grant, largely based on its potential use in acute stroke and cardiology. Needless to say it is mostly used for knees and backs! Wouldn't perfusion CT be more practical?'

'More delays recently due to pressures from 2 week cancer rule'

'MRI scanners in use most days for cancer planning. On some days there are slots where it might be possible to slot stroke patients within 6 hours. However no out of hours MRI service is funded'

Local protocols for acute stroke do not include MR

'The (unwritten) policy is CT as first line but radiologists happy to discuss doing MRI as 2nd line if clinically indicated. I think unlikely to ever be 1st line imaging'

'Our acute stroke protocol includes a section on neuro-imaging. CT scanning is recommended in all acute cases. Indications for MRI scanning are included but not as an emergency investigation'

'MR tends to be used for younger patients'

'Preferred option in our hospital is CT. MRI during working hours could be made available assuming an appropriate case is made for an exception to CT'

'We routinely use CT structural and perfusion scans for acute stroke, and it is possible to do an angiogram without excessive delays in thrombolysis'

'We did previously use MRI on ALL patients, but waiting up to 10 days so reverted to CT unless posterior circulation/?MS/further clarification of CT signs/>10 days after onset, therefore by default most outpatients get MRI'

'CT access improving progressively over 10 years. Delayed formal reporting. CT is investigation of choice. MR 1st line for posterior circulation strokes – [MR] increasing for selected patients'

'24hr CT cover for acute stroke - if requested - otherwise next working day service'

'CT scanning is the first investigation and our X-ray dept provides an excellent service. They don't provide MRI scanning for acute stroke unless there is some doubt on CT'

'CT is still the main imaging modality for acute stroke. Not yet providing thrombolysis. CT usually available within 24 hours, though delays occur over weekends'

'CT scanning is used acutely with MR for uncertain images. MR used for O/P especially if >7-19 days'

'Trust does not at present provide thrombolytic therapy. Not all our patients have CT scanning within 6 hrs, 12 hrs. All patients have CT within 24 hours. Stroke association/BASP should concentrate on improving acute stroke care in all hospitals caring for stroke patients before addressing MRI provisions'

'New MRI installed mid 2004. No out of hours service. At present no coordinated acute stroke care and thus no thrombolysis on site - but looking to change'

'The problem is that we don't have the software for DWI or PWI in our MRI scanner'

General problems of access to scanning facilities

'We are not achieving CT scan within 24 hours. MR scanning within 6 hours would not be feasible for us with the present setup'

'CT access and capability is good (new scanner). MRI access is limited, and always delayed, impeding accurate assessment and impairing care'

'Very difficult to routinely get CT within 24 hours due to other pressures on scanners'

'No on site CT - this would be nice. I think it will be a long time before we have MRI!'

'It is very difficult to get patients scanned within 24 hours as per RCP guidelines if it is not urgent - this is for CT'

'We have access problems at the weekend which we are trying to resolve'

'Our MRI is PFI which makes it more complicated'

'We only scan about 60% of stroke patients within 48hrs (CT, that is), so are well off the current RCP guidelines'

'Acute emergencies i.e. unconscious/suspected big bleeds/SAH can be done within hours [using CT]. Routine strokes admitted via MAU daily take 24-48hrs [to get CT scan]. Delay mainly due to workload for the scanner. No scans on weekend

'Re Q3 - I suspect that it would be very difficult to get acute MRI - but I am unconvinced of the value and haven't requested them'

'No slots reserved for MRI scans for stroke patients'

'Getting CT scan within time may be, at times, difficult'

'CT scanning is very accessible for inpatients and selected outpatients. 200 on waiting list for O/P MRI, 24 weeks for routine CT'

'Have 2 MRI scanners but access, even to our neurologists, is poor and usually needs consultant to radiologist verbal referral for urgent scan'

'Very limited access [to MRI] for stroke patients. Waiting time 20 weeks'

'CT easier to obtain and less contraindications'

'Getting a timely CT scan is difficult enough'

'Lucky to get a CT at weekends - no chance of MRI!'

'We only have finance for three days of scanning/week. Within that limit our radiologists are very helpful'

'We have difficulty at times getting CT let alone MR, although often this is due to poor request mechanisms'

'Probably far more helpful to try and get a CT within 3 hours (of onset) before worrying about additional, somewhat marginal benefits of MRI within 3-6hours from onset. This, to most of us in DGH's is difficult enough!!'

'Our main priority at present is to get carotid doppler examination without much delay'

'Access to carotid imaging also a problem. Techniques for rarer causes of stroke - dissection, dural thrombosis - need to be incorporated into mainstream radiology'

'Despite national sentinel audit x3 and agreement on need for an acute stroke unit we do not yet have any stroke beds!! - PCT recognise the need but no funding available from PCT'

Specific comments on MR

'We have an extremely approachable MR service who have no problem doing urgent MR's'

'Difficult to get patients on and off [MR] table. Scanning sequence takes a long time. Some patients cannot lie still. Likely to cause disruption to service e.g. orthopaedic cases'

'45% of our patients have MRI'

'I support the move towards MRI for acute stroke imaging'

'No difficulty getting MRI in working hours'

'Usually we can access MR DWI etc easily but if good reason'

The comments suggest that there is still a problem achieving current RCP guidelines for CT scanning in much of the UK and there are obvious frustrations with the lack of funding to staff 24 hour a day, seven day a week imaging services.

4.2.5 Discussion

The results of the survey confirm that CT is almost universally available to stroke patients in the UK and must therefore - for now - remain the primary imaging method for patients with acute stroke. Although just over three quarters of UK hospitals have on

site MR facilities, access to this imaging modality appears to be very poor for acute stroke patients. This is probably due to a number of factors. Currently MR appointments are usually filled many weeks in advance and, with current work patterns, it is difficult to fit in emergency cases, such as patients with acute stroke. There is a huge demand from many other specialities for MR imaging, both medical and surgical. Thus until there is very strong evidence that MR is a cost-effective way to provide additional information to CT for the acute treatment of stroke patients, it will be difficult to bring about a major change in the primary imaging methods for stroke. As mentioned in Chapter 1 (section 1.3.4) there are practical difficulties with the MR imaging of 20-30% of patients with moderate to severe strokes (i.e. patients likely to be considered for thrombolysis) due to medical reasons (e.g. reduced conscious level, unable to lie flat, unable to protect airway) or MR contraindications (e.g. the presence of a pacemaker).

This survey demonstrates that although the majority of hospitals have access to MR, those in rural areas are still at a disadvantage. It also shows that access to MR is very difficult for acute stroke patients. If on going trials were to show that MR was a useful tool in selecting patients for acute treatments such as thrombolysis there would have to be a massive investment in equipment and even more so in highly trained staff in order to provide the service.

4.3 Summary

- Further data on MR imaging in acute stroke are needed so that we can determine how features visible on MR may help to improve the use of thrombolysis. Only by gathering such data in a randomised trial of thrombolysis can we hope to identify features that may suggest that a patient may benefit or be harmed by thrombolytic therapy.

- More data are needed on whether MR PWI/DWI mismatch influences response to thrombolysis from randomised control trials and we hope the protocol developed in the study in this chapter will prove feasible to be undertaken as a multicentre sub-study within the MRC funded IST-3.

- However, the experience at the WGH suggests that, even in a well-equipped acute stroke centre with MR available to patients with acute stroke, many factors act as barriers to the use of MR in this situation.

- Currently, in the UK, CT scanning is the primary imaging modality for acute stroke patients.

- The survey I performed has shown that, although many hospitals have on site MR facilities, acute stroke patients are not commonly scanned within 6 hours of symptom onset.

- If ongoing studies show that MR is a useful tool in selecting patients for thrombolytic therapy, a huge investment in staff, equipment and training will be needed if it is to be implemented throughout the UK.

Table 1: Summary of time taken to scan patients with MR (if MR was undertaken at all).

Approximate number of patients scanned	Number of hospitals scanning within this time* (time from symptom onset to MRI)		
	< 6 hours	**<12 hours**	**At anytime after stroke onset**
None	137	117	8
1-5	17	29	34
6-10	3	3	40
>10	1	5	59

* Of the 192 hospitals with MRI, 158 gave useable responses to access < 6 hours, 154 to access < 12 hours and 141 to access at anytime

References

1. Moseley ME, Kucharczuk J, Mintorovich J, Cohen Y, Kurhanewicz J, Derugin N. Early detection of regional cerebral ischaemia in cats: comparison of diffusion and T2 weighted MRI and spectroscopy. *Magn Res Med* 1990;14:330-346.

2. Sorensen AG, Copen WA, Ostergaad L, Buonanno FS, Gonzalez RG, Rordorf G et al. Hyperacute stroke: simultaneous measurement of relative cerebral blood volume, relative cerebral blood flow, and mean transit time. *Radiology* 1999;210:519-527.

3. Schlaug G, Benfield A, Baird AE, Siewart B, Lovblad KO, Parker RA et al. The ischaemic penumbra operationally defined by diffusion and perfusion MRI. *Neurology* 1999;53:1528-1537.

4. Keir SL, Wardlaw JM. Systematic review of diffusion and perfusion imaging in acute ischaemic stroke. *Stroke* 2000;31:2723-2731.

5. Kidwell C, Saver JL, Villablanca JP, Duckwiler G, Fredieu A, Gough K et al. Magnetic resonance imaging detection of microbleeds before thrombolysis. *Stroke* 2002;33:95.

6. Derex L, Hermier M, Adeleine P, Honnorat J, Berthezene Y, Froment JC et al. Usefulness of T2-weighted MRI sequences before intravenous t-PA for acute ischaemic stroke. Abstracts of the 7th International Symposium on thrombolysis and acute stroke therapy. Lyon, 27-28 May 2002.

7. Kwan J, Hand P, Sandercock. A systematic review of barriers to delivery of thrombolysis for acute stroke. *Age and Ageing* 2004;33:116-121.

8. Hand PJ, 2002. 'Brain attack'. A new approach to stroke and transient ischaemic attack. Thesis (MD). Edinburgh University.

9. Rivers CS, Armitage PA, Carpenter T, Hand PJ, Dennis MS, Wardlaw JM. MR diffusion and perfusion abnormalities in ischaemic stroke – patterns of sub-regional change and tissue recovery. *Cerebrovasc Dis* 2003;16(suppl 4):119.

10. Wardlaw JM, Dennis MS, Lindley RI, Warlow CP, Sandercock PAG, Sellar RJ. Does early reperfusion of a cerebral infarct influence cerebral infarct swelling in the acute stage or the final clinical outcome? *Cerebrovasc Dis* 1993;3:86-93.

11. Grandin CB, Duprez TP, Smith AM, Oppenheim C, Peeters A, Robert AR et al. Which MR-derived perfusion parameters are the best predictors of infarct growth in hyperacute stroke? *Radiology* 2002;223:361-370.

12. Barber P et al for the ASPECTS study group.Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. *Lancet* 2000;355:1670-1674.

13. Wardlaw JM, Sellar R. A simple practical classification of cerebral infarcts on CT and its interobserver reliability. *Am J Neuroradiol* 1994;15:1933-1939.

14. Silver B, Demaerschalk B, Merino JG, Wong E, Tamayo A, Devasenapathy A et al. Improved outcomes in stroke thrombolysis with pre-specified imaging criteria. *Can J Neurol Sci* 2001;28:113-119.

15. http://www.galileo1.knowledgemed.com/Cardiology/Terminology/TIMI.

16. Wardlaw JM, Keir SL, Bastin ME, Armitage PA, Rana AK. Is diffusion imaging appearance an independent predictor of outcome after ischaemic stroke? *Neurology* 2002;59:1381-1387.

17. Albers GW, Thijs VN, Wechsler L, Kemp S, Schlaug G, Skalabrin E, Bammer R, KakudaW, Lansberg MG, Shuaib A, Hamilton S, Moseley M, Marks MP, for the DEFUSE Investigators. Magnetic resonance imaging profiles predict clinical response to early reperfusion: The diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. *Ann Neurol* 2006;60:508-517.

18. Rowat AM, Dennis MS, Wardlaw JM. Hypoxaemia in acute stroke is frequent and worsens outcome. *Cerebrovasc dis* 2006;21:166-172.

19. Wardlaw JM, Keir SL, Seymour J, Lewis S, Sandercock PAG, Dennis MS, Cairns J, What is the best imaging strategy for acute stroke? Health Technol Assess 2004;8(1).

20. Prepared on behalf of the Intercollegiate Stroke Working Party Royal College of Physicians. National Sentinel Stroke Audit Report 2004.

21. Warlow CP, Dennis MS, van Gijn J, Hankey G J, Sandercock PAG, Bamford JM Wardlaw JM. What pathological type of stroke is it? Stroke: A practical guide to management (2^{nd} edition);5:151-222.

22. Wardlaw JM, Farrall AJ. Diagnosis of stroke on neuroimaging. *BMJ* 2004;328:655-656.

23. Hjort N, Butcher K, Davis SM, Kidwell CS, on behalf of the UCLA Thrombolysis Investigators, Koroshetz WJ, Rother J, Schellinger PD, Warach S, Ostergaard L. Magnetic resonance imaging criteria for thrombolysis in acute cerebral infarct. *Stroke* 2005;36:388-397.

24. Buckley BT, Wainwright A, Meagher T, Briley D. Audit of a policy of magnetic resonance imaging with diffusion weighted imaging as first-line neuroimaging for in-patients with clinically suspected acute stroke. *Clinical Radiology* 2003;58:234-237.

25. Edwards P, Roberts I, Clarke M, DiGuiseppie C, Pratap S, Wentz R, Kwan I. Increasing response rates to postal questionnaires: systematic review. *BMJ* 2002;324:1183-1185.

5 Issues surrounding consent processes for thrombolysis and related procedures

5.1 Consenting patients with acute ischaemic stroke for thrombolysis

5.1.1 Introduction

As discussed in chapter 1, for patients with acute ischaemic stroke, thrombolysis with recombinant tissue plasminogen activator (rt-PA), can reduce disability in survivors and is of net benefit, despite a 3% risk of fatal intracranial bleeding.[3] As mentioned previously in the USA and Europe, rt-PA is approved for use in acute ischaemic stroke in highly selected patients who present very early and can be assessed and treated within three hours of symptom onset. The American Heart Association (AHA) guidelines state that, when considering treatment in routine clinical practice with intravenous rt-PA, written consent is not a necessity, but patients and their relatives should be informed about the potential risks and benefits.[4] Ciccone has proposed a practical approach to consent in this setting.[5] A recent study by Rosenbaum et al highlighted that while such consent was often not documented, patients with diminished capacity seemed to have given consent.[6] A systematic review also highlighted difficulties in obtaining informed consent as a barrier to effective delivery of thrombolytic treatment.[7]

To investigate which forms of consent could be used I looked at data from IST-3. IST-3 is a large-scale trial (aiming to recruit up to 6000 patients) which seeks to determine whether a wider variety of patients might benefit from thrombolytic therapy, beyond the very restricted group defined by the current approval. In order to achieve this sample size, the trial methods had to be simple, flexible, yet ethically acceptable. The trial team therefore developed,[8] and obtained ethical approval for, a set of flexible consent

procedures that allowed patients with different types of stroke and different degrees of neurological impairment to be included. In this analysis, I aimed to examine how often each method of consent was employed and to explore the impact of the patient's initial neurological deficit on the method of consent employed. This analysis sought to identify ways to reduce the 'consent barrier' for use of thrombolysis both in trials and in routine clinical practice.

5.1.2 Methods

IST-3 is a multicentre randomised controlled trial of intravenous recombinant tissue plasminogen activator (rt-PA) in patients with acute ischaemic stroke. Patients, aged over 18, who can be assessed and have treatment started within six hours of symptom onset, are eligible for the trial. Consent or assent must be obtained before randomisation. The full trial protocol can be found at www.ist3.com.

We developed draft patient information leaflets and consent forms. To improve the quality of the informed consent process, we then subjected the draft forms to an iterative process of testing and further development that closely involved patients and potential patients.[8] The trial information leaflets include approximate percentage benefits and risks derived from the latest Cochrane review.[3] There are three methods of consent/assent, which may be employed to recruit patients into the trial. The UK multicentre research ethics committee has approved these. The first, and the ideal, is **written consent** from the patient themselves. However, if the patient is unable to write, for example if the dominant hand is affected, they are able to give **witnessed consent** if they have no problems with communication. If the patient is unable to give informed consent as a consequence of their stroke (e.g. due to aphasia), **assent** can be sought from the patient's relatives (in North America, this is known as surrogate consent). In some countries, under exceptional circumstances, a fourth method, **waiver of consent** is also permitted, usually on condition that an independent physician agrees that recruitment of

that individual into the trial is appropriate and that if the patient recovers, the option to withdraw consent may be offered (this is not exactly comparable to what is referred to as 'deferred consent'). When obtaining consent to enter a patient in the trial, the randomising clinician has a discussion with the patient and the family and the trial information leaflets are used as a guide to the conversation, employing simple language that is easy to understand. The method of consent is recorded in the hospital records and on the trial seven day follow up form. The presence or absence of the key neurological deficits is recorded at randomisation. A computer algorithm uses these data to assign a stroke syndrome to each patient: total anterior circulation (TACS), partial anterior circulation (PACS), lacunar (LACS) or posterior stroke syndrome (POCS). A separate algorithm, based on a validated prognostic model,[9] uses the baseline clinical data to calculate a predicted probability that the patient will be alive and independent at six months after the stroke.

Note: The introduction of the European Union directive on clinical trials, and its enactment in UK law led to some changes in terminology and minor changes to the documentation. These changes came into force after the patients included in this analysis were recruited. The term 'assent by relatives' has been replaced by 'consent by personal legal representative'. For simplicity, we have retained the term 'assent', for these analyses.

5.1.3 Results

We analysed data for the first 300 patients randomised in the trial. The method of consent employed was: written consent in 71 patients (24%), witnessed verbal consent in 30 (10%), assent by relative in 197 (66%) and waiver of consent in 2 (1%).

Table 1 shows the impact of individual neurological deficits on the method of consent. In patients with dysphasia, 92% were randomised into the trial with assent of a relative or by witnessed verbal consent. In patients with visuospatial disorders, most commonly

due to a non-dominant hemisphere stroke, the majority of patients were recruited by relatives assent (76%) or witnessed verbal consent (10%). Those without such a deficit were more likely to be able to give written consent. As expected, the hemisphere affected by the stroke has a clear influence: patients with left hemisphere lesions were less likely to be able to give written consent than patients with right hemisphere lesions 14% vs 36% respectively (difference 22%, 95% confidence interval 13 to 32%).

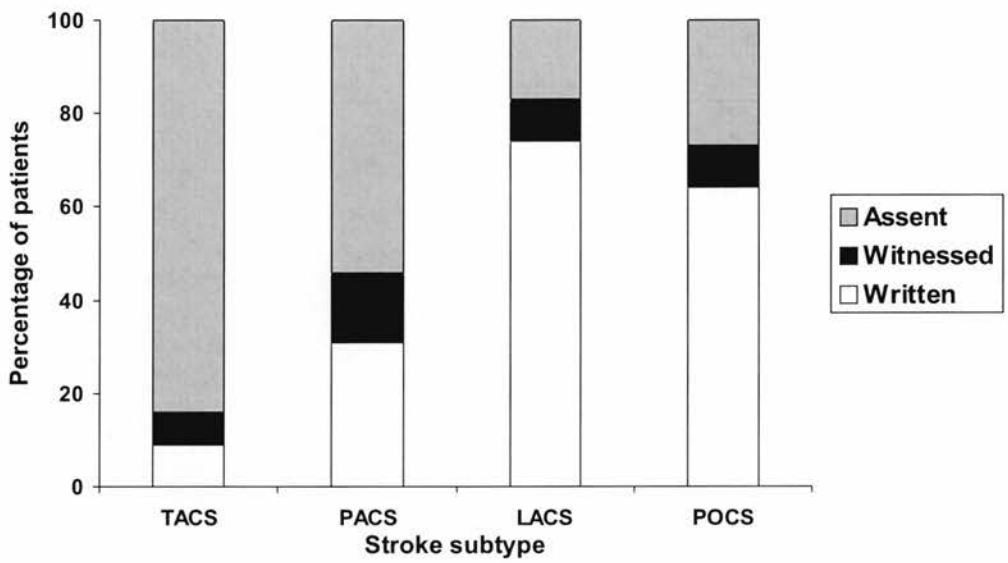
As demonstrated in Figure 1, those patients with most severe strokes (i.e. TACS) were consented with either relatives assent or witnessed verbal consent in the majority of cases. In patients with the milder PACS syndrome, about a third of patients were able to give written consent. The numbers in the LACS and POCS subtypes were small but written consent in these groups was common.

Figure 2 confirms the observations from Figure 1, that demonstrates a trend, that patients randomised into the trial with written consent, have less severe strokes and those consented with assent or waiver of consent had, on average, more severe strokes.

5.1.4 Discussion

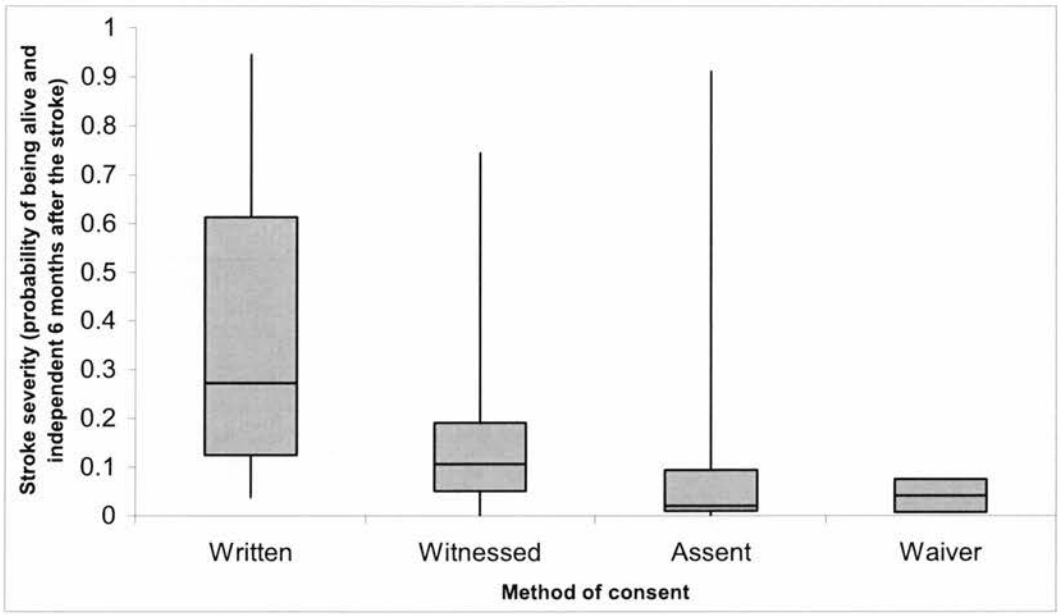
These analyses confirm that the consent procedures we developed were feasible and permitted patients with a range of neurological deficits to be recruited. In general, the more the severe the stroke (either determined by clinical stroke syndrome or predicted outcome), the less likely was written informed consent to be employed, as one would expect. The proportion of patients with TACS syndrome was greater in the assent group compared with the written consent group (Figure1). When stroke severity was assessed by the predicted probability of outcome, patients giving written consent were judged to have milder strokes (Figure 2).

Figure 1: Effect of stroke syndrome on method of consent



The percentage of patients within each stroke subtype and the type of consent used to recruit them into the trial depending on their stroke subtype: Total anterior circulation stroke (TACS), partial anterior circulation stroke (PACS), lacunar stroke (LACS) and posterior circulation stroke (PACS). Note: Only 2 cases had waiver of consent, both of which have been omitted from this figure. Both had TACS type strokes.

Figure 2: Effect of stroke severity on method of consent



Stroke severity is assessed by the predicted probability of the patient being alive and independent 6 months after their stroke. The predicted probability is calculated from their pre-treatment neurological deficit with a validated prognostic model. Hence, a probability of zero represents a very severe stroke with a low probability of good outcome and 1.0 a very mild stroke, with a very high probability of a good outcome. The patients have been grouped according to the method of consent used to recruit them into IST-3. It does not take into account the effect of post-randomisation treatment. In this plot, the box represents the interquartile range. The whiskers extend from the box to the highest and lowest values. The line across each box indicates the median. If it is assumed that the method of consent is an ordered categorical variable and a Jonckheere test is performed, then the trend is significant ($p<0.001$) with those giving written consent having a less severe stroke, as assessed by this measure.

The data also suggested that, the more severe the stroke deficit, the more likely it is that assent will be needed as the method of consent (Table 1). In particular, the data show that those with any type of higher cerebral dysfunction such as TACS patients e.g. dysphasia or a visuospatial disorder, could not take part in a trial such as IST-3, without the option of a flexible consent procedure. If the left hemisphere is affected by the stroke, then assent is more likely since patients are more likely to be dysphasic or - even if they do not have such a higher cerebral dysfunction - their dominant (writing) arm is likely to be affected making writing difficult or impossible.

If only the patients who are able to provide written informed consent were included in acute stroke trials, they would generate estimates of treatment effect applicable to a group with a good prognosis (irrespective of treatment allocation). The IST-3 consent procedures conform to legal requirements and allow a wider variety of patients to be included in the trial. These patients may have as much to benefit from thrombolysis treatment as patients with milder strokes. Indeed, previously fit and active elderly people who are affected by a severe stroke should surely have the opportunity to participate in research. According to the World Medical Association Declaration of Helsinki policy on the ethics of medical research involving human subjects it is stated "for a research subject who is legally incompetent, physically or mentally incapable of giving consent, or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorised representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons".[10] Research on emergency medical treatments is necessary on stroke patients who are unable to give consent due to the nature of their stroke. Without studying them, we would be unable to move forward and provide an evidence base for giving these groups of people such acute treatments in emergency settings, when time is limited and decisions have to be made very quickly.

When considering treatments whose benefits decline with increasing time from onset of symptoms, the need to avoid delay, reduces the time available to the patient and the family and the doctor for discussion and weighing up risks and benefits. Data from the recent MRC CRASH trial showed there were significant reductions in time to randomisation when waiver of consent was used compared with assent by relatives.[11] This reduction in time delay may be crucial in acute brain disorders to maximise the benefit from treatment and hence the likelihood of the trial producing a clear and positive result, if treatment is clearly effective. One way to do this may be to increase public understanding and awareness of conditions like acute stroke by improving public education in groups at risk of stroke. At least then people have a chance to think about potential situations that may arise in the future and what sort of risks of treatment they may find acceptable.

The requirements of the EU directive makes consent for trials in emergency situations possible under some circumstances. A relative or spouse may act as the patient's 'personal legal representative' and can give consent on their behalf. A 'professional legal representative' can also give consent, but it is not rapidly available at the moment when consent is required. This will be a major obstacle to evaluating interventions that could have substantial impact on mortality and disability.

These data confirm that the consent procedures developed for IST-3 have proved feasible and have enabled the balance of risk and benefit of thrombolytic therapy to be assessed in a randomised trial in a wider variety of patients than previously. This is an area where there is scope to develop still better tools to improve the process of informed consent in acutely ill people. A wider public debate to secure acceptance of waiver of consent in trials in emergency situations would also be appropriate.

5.2 Summary

- The issue of consent is very important to consider in trials of acute medicine, especially where there is little time available for people to consider treatment options.

- Data from this study show that different methods of consent are feasible in an acute stroke trial. This is important to allow a wide variety of patients with stroke to be recruited, who otherwise may not be eligible.

- Without flexible consent procedures, those with the most severe neurological deficit (who potentially have the most to gain), would be excluded from trial treatments.

- When considering the development of alternative forms of consent it is important to include the public in discussions and to incorporate their views as much as possible.

- Restrictive consent procedures are a major obstacle to evaluating interventions that could have substantial impact on mortality and disability.

Table 1

Method of consent and neurological deficit.

	Method of consent			
Neurological deficit at baseline	**Written consent n (%)***	**Witnessed verbal consent n (%)**	**Assent by relative n (%)**	**Waiver of consent n (%)**
Motor deficit only	18 (69)	2 (8)	6 (23)	0 (0)
Dysphasia	13 (7)	14 (8)	145 (83)	2 (1)
Visuospatial disorder	26 (14)	20 (10)	145 (76)	1 (1)
Lesion location (final diagnosis)†				
Right hemisphere	45 (36)	13 (10)	66 (54)	0 (0)
Left hemisphere	23 (14)	15 (9)	128 (76)	2 (1)
Cerebellar or brainstem	2 (67)	1 (33)	0 (0)	0 (0)
Not localisable‡	1 (20)	1 (20)	3 (60)	0 (0)
Total	**71 (24)**	**30 (10)**	**197 (66)**	**2 (1)**

*Percentages are of row totals

†Final diagnosis is determined at 7 days on the basis of all the neuroimaging data, ancillary investigations and the patients clinical course

‡Some patients had a clinical syndrome consistent with localisation in either hemisphere or the posterior fossa, but had no relevant visible lesion on brain imaging

References

1. Bateman BT, Meyers PM, Schumacher HC, Mangla S, Pile-Spellman J: Conducting stroke research with an exception from the requirement for informed consent. Stroke. 2003;34:1317-1323.

2. Demarquay G, Derex L, Nighoghossian, Adeleine P, Philippeau F, Honnorat J, Troullais P: Ethical issues of informed consent in acute stroke. Cerebrovasc Dis. 2005;19:65-68.

3. Wardlaw JM, del Zoppo G, Yamaguchi T, Berge E: Thrombolysis for acute ischaemic stroke (Cochrane Review). In: The Cochrane Library. Issue 4, 2003. Oxford, UK: Update Software, © Cochrane Library, John Wiley & Sons Ltd.

4. Adams HP Jr, Adams RJ, Brott T, del Zoppo GJ, Furlan A, Goldstein LB, Grubb RL, Higashida R, Kidwell C, Kwiatkowski TG, Marler JR, Hademenos GJ, Stroke Council of the American Stroke Association: Guidelines for the early management of patients with ischemic stroke: a scientific statement from the Stroke Council of the American Stroke Association. Stroke. 2003;34:1056-1083.

5. Ciccone A: Consent to thrombolysis in acute ischaemic stroke: from trial to practice. Lancet Neurology. 2003;2:375-378.

6. Rosenbaum JR, Bravata DM, Concato J, Brass LM, Kim N, Fried TR: Informed consent for thrombolytic therapy for patients with acute ischemic stroke treated in routine clinical practice. Stroke. 2004;35:e353-e355.

7. Kwan J, Hand P, Sandercock P: A systematic review of barriers to delivery of thrombolysis for acute stroke. Age and Ageing. 2004;33:116-121.

8. Koops L, Lindley RI: Thrombolysis for acute ischaemic stroke: consumer involvement in design of new randomised controlled trial. BMJ. 2002;325:415-417.

9. Counsell C, Dennis M, McDowall M, Warlow C: Predicting outcome after acute and subacute stroke. Development and validation of new prognostic models. Stroke. 2002;33:1041-1047.

10. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. Accessed 25th June 2005 http//www.wma.net/e/policy/b3.htm.

11. The CRASH Trial Management Group: Research in emergency situations: with or without relatives consent. Emerg Med J. 2004;21:703.

My contribution to this thesis

I applied for, and was awarded, a grant from the Chief Scientist Office (£15,000) to fund the IST-3 MR imaging sub-study and the UK MRI survey, outlined in chapter 4.

I performed the systematic review that formed the basis of chapter 2. I developed the rationale for the perfusion MRI study (chapter 3), coordinated the analysis and processed all the PWI lesions by drawing around the individual perfusion lesions for each patient in the study and collated the baseline details of the patients along with their clinical and imaging results. I entered the data into Excel and SPSS and analysed the data.

For the MRI pilot study (chapter 4) I coordinated discussions between interested centres to develop a suitable protocol, obtained ethical approval for the study and designed the information and consent forms for potentially eligible patients. I also designed the data collection forms. I reviewed suitable patients in the hospital and where possible recruited them into the study. I performed all the work for the survey of imaging facilities, including creating a comprehensive database of all acute hospitals in the UK.

I was involved in recruiting a large number of acute stroke patients during my time in Edinburgh, including into IST-3, to both the studies mentioned and several others. I was the IST-3 trial research fellow. As IST-3 research fellow I also produced several trial items not explicitly recorded in this thesis but all designed to streamline thrombolysis trial processes. This included the design and production of the image training set for the British Association of Stroke Physicians (http://www.dcn.ed.ac.uk/ist3/) now available to all IST-3 centres during start up, and a simple 'thrombolysis trolley' with all necessary materials easily available for use in IST-3 centres.

Work from chapters 2 and 3 formed the basis of platform presentations at the European Stroke Conference 2006 and the Joint World Congress on Stroke in 2006. The systematic review from chapter 2 and the comparison of PWI processing have been fully

published in the Journal of Neurology, Neurosurgery and Psychiatry and Stroke; and the study in chapter 5 has been published by Cerebrovascular Diseases (2006). The results of the MRI survey have been presented in poster format at the British Association of Stroke Physicians Meeting 2006 and the British Geriatrics Society Meeting in 2006 and accepted for publication in Cerebrovascular Diseases.

During my time in research I was a member of the group developing the programme for the European Stroke MSc; this involved attending meetings in Austria as well as in the UK.

This thesis was composed by myself, the research undertaken in Edinburgh, and has not been submitted for candidature for any other degree, postgraduate diploma or professional qualification.

Acknowledgements

I am grateful to the Health Foundation who funded my post as clinical research fellow for the Third International Stroke Trial (IST-3) and to the Chief Scientist Office (CSO) who awarded me the small project grant (CZG/1/116) to fund the MRI pilot study and the UK MRI survey. The CSO (C2B/4/14) and UK Stroke Association (TSA 02/01) also provided funding towards the PWI data collection.

I would like to thank my supervisors Professor Peter Sandercock and Professor Joanna Wardlaw for all their advice and encouragement. They have taught me an enormous amount about stroke and the principles of clinical research, as have Professor Martin Dennis, Professor Charles Warlow and Professor Richard Lindley. I am grateful to Dr Graeme Dewhurst who first introduced me to stroke medicine as a senior house officer and encouraged me to apply for the Fellowship in Edinburgh. There are a huge number of people who have helped me during my time in the Department of Neurosciences: Sarah Keir, Andrew Farrall, David Perry, Brenda Thomas, Caroline Jackson, Sheila Grant, Robin Flaig, Steff Lewis and Francesca Chappell. I am indebted to the help provided by staff at the SFC Brain Imaging Centre; in particular Trevor Carpenter, Mark Bastin and the radiographers. I would not have been able to see as many patients with acute stroke without the help of Anne Rowat and research fellow colleagues. To all those mentioned, and many who I have not, many thanks for making my time spent in Edinburgh so enjoyable.

Publications

1. Kane I, Whiteley W, Sandercock P, Wardlaw J. Availability of CT and MR for assessing patients with acute stroke in the UK. *Cerebrovasc Dis* 2008;25:375-377.

2. Kane I, Carpenter T, Chappell F, Rivers C, Armitage P, Sandercock P, Wardlaw J. Comparison of ten different Magnetic Resonance perfusion imaging processing methods in acute ischaemic stroke. Effect on lesion size, proportion of patients with diffusion/perfusion mismatch, clinical scores and radiological outcomes. *Stroke* 2007;38:3158-3164.

3. Kane I, Sandercock P, Wardlaw J. Magnetic resonance diffusion perfusion diffusion mismatch and thrombolysis in acute ischaemic stroke: A systematic review of the evidence to date. *J Neurol Neurosurg Psychiatry* 2007;78:485-491.

4. Kane I, Lindley R, Lewis S, Sandercock P. Impact of stroke syndrome and stroke severity on the process of consent in the Third International Stroke Trial. *Cerebrovasc Dis* 2006;21:348-352.

A copy of each of the published articles is contained in Appendix 15, with permission.

Appendices

Appendix 1: Electronic search strategies

Glossary of search terms

/	MEDLINE subject heading (MESH)
mp.	Title, abstract, heading word, trade name, manufacturer name
.tw	Identifies the word specified in the title or abstract
ti.	Identifies word specified in title
$	Identifies any word beginning with the text preceding it
or	In the search parameter specified, the article only has to be found in one of the search terms
and	In the search specified, the article must be found in all search terms

Expanded search strategy for stroke.

Table1. EMBASE

	Search History
1	cerebrovascular disease/
2	cerebrovascular accident/
3	stroke/
4	vertebrobasilar insufficiency/
5	carotid artery disease/
6	exp carotid artery obstruction/
7	brain infarction/
8	brain stem infarction/
9	cerebellum infarction/
10	brain ischaemia/
11	transient ischemic attack/
12	exp occlusive cerebrovascular disease/
13	(stroke$ or apoplexy$ or cerebral vasc$ or cerebrovasc$ or cva or transient isch$ or tia$).tw
14	(brain or cerebr$ or cerebell$ or verebrobasil$ or hemisphere$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation).tw.
15	(isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$).tw.
16	14 and 15
17	Or/1-13,16
18	fibrinolytic therapy/
19	fibrinolysis/
20	blood clot lysis/
21	fibrinolytic agent/
22	plasmin/ or plasminogen/ or exp plasminogen activator/
23	exp thromboembolism/dt
24	recanalization/ or recanali#ation.tw.
25	(thromboly$ or fibrinoly$ or clot lysis).tw.
26	(plasminogen or plasmin or tpa or t-pa or rtpa or rt-pa).tw.
27	(anistreplase or streptodornase or streptokinase or urokinase or pro?urokinase or rpro?uk or lumbrokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphylokinase or streptase or alteplase or tenecteplase or TNK).tw.
28	18 or 19 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29	17 and 28
30	*nuclear magnetic resonance imaging/
31	29 and 30
32	nuclear magnetic resonance imaging/
33	(magnetic resonance imaging or mri).tw.
34	32 or 33

35	29 and 34
36	35 not 31
37	diagnostic imaging/ or diffusion tensor imaging/ or diffusion weighted imaging/
38	29 and 37
39	38 not (31 or 36)
40	(1994$ or 1995$ or 1996$ or 1997$ or 1998$ or 1999$ or 200$).em.
41	31 and 40
42	36 and 40
43	39 and 40

Table 2. MEDLINE

	Search History
1	cerebrovascular disorders/
2	exp brain ischemia/
3	carotid artery diseases/ or carotid artery thrombosis/
4	exp cerebrovascular accident/
5	exp hypoxia-ischemia, brain/
6	cerebral arterial diseases/ or intracranial arterial diseases/
7	exp "intracranial embolism and thrombosis"/
8	(stroke$ or apoplexy$ or cerebral vasc$ or cerebrovasc$ or cva or transient isch$emic attack$ or tia$).tw.
9	(brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation).tw.
10	(isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$).tw.
11	9 and 10
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 11
13	thrombolytic therapy/
14	fibrinolysis/
15	exp plasminogen activators/
16	fibrinolytic agents/ or plasmin/ or plasminogen/
17	(thromboly$ or fibrinoly$ or clot lysis).tw.
18	(plasminogen or plasmin or tPA or t-PA or rtPA or rt-PA).tw.
19	(anistreplase or streptodornase or streptokinase or urokinase or pro?urokinase or rpro?uk or lumbrokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphylokinase or streptase or alteplase).tw.
20	exp "intracranial embolism and thrombosis"/dt or thromboembolism/dt
21	thrombosis/dt [drug therapy]
22	or/13-21
23	12 and 22
24	*magnetic resonance imaging/
25	23 and 24
26	magnetic resonance imaging/
27	mri.tw.
28	26 or 27
29	23 and 28
30	29 not 25

Appendix 2

Systematic review data collection form

- Author _____ Publication date _____
- Ref ID _____ Study design _____
- Sample size _____ Univariate / multivariate analysis _____
- What MR lesions measured_____

_____

_____

_____

_____

_____

- How? a) workstation_____

_____

b) quantification_____

_____

_____

_____

States patients attempted to image but not able to complete or imaged but discarded: incomplete / not analysed / not a stroke

- Number who died or not followed up. Stated n= ; Not stated
- Thrombolysis given? Agent and route:_____
- Proportion getting thrombolysis_____

MR DETAILS

- Onset to MR scan_____

_____

- Time to perform sequences _____
- Magnet Strength_____
- Was DWI/PWI mismatch defined and how_____

_____

_____

- What proportion of patients had mismatch or not?_____

_____

- Where the radiologists blind to clinical and previous imaging data Y / N

Explicit / implied / not

- Was IOV given Y / N

CLINICAL DATA

- At baseline_____
- At follow up_____

_____

- Who saw patient?_____
- Were they blind to other info at baseline? Explicit /implied /not
- Were they blind to baseline clinical details and imaging at follow up?

Explicit /implied /not

Did they give IOV? Y / N

Appendix 3: NIHSS

NIH Stroke Scale **(Please circle the most appropriate response for each section. See supplementary notes attached. If untestable please state reason. Add the scores for each item to get the total, and do not count untestable items)**		
1a Level of *Consciousness* **(LOC)**	0	Alert – *keenly responsive*
	1	Drowsy – *arousable by minor stimulation to obey, answer, or respond*
	2	Stuporous – *requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped)*
	3	Comatose – *responds only with reflex motor or autonomic effects or totally unresponsive*
1b LOC Questions	0	Answers both correctly
	1	Answers one correctly
	2	Incorrect
		Patient asked to state the month & his/her age.
1c LOC Commands	0	Obeys both correctly
	1	Obeys one correctly
	2	Incorrect
		Patient is asked to close & open eyes, grip & release normal hand
2. Best Gaze	0	Normal
	1	Partial gaze palsy – *gaze is abnormal in one or both eyes, no forced deviation/total gaze paresis*
	2	Forced deviation – *or total gaze paresis not overcome by oculocephalic maneouvre*
3. Visual Fields	0	No visual loss
	1	Partial hemianopia or visual inattention
	2	Complete hemianopia
	3	Bilateral hemianopia – *including cortical blindness*
4. Facial Palsy	0	Normal
	1	Minor - *flattened nasolabial fold, asymmetry on smiling*
	2	Partial – *total or near total paralysis of lower face*
	3	Complete - *absent facial movement in upper and lower face on one or both sides*
5. Best Motor RIGHT ARM	0	No drift – *holds limb at 90 degrees for full 10 seconds*
	1	Drift - *drifts down but does not hit bed*
	2	Some effort against gravity
	3	No effort against gravity
	4	No movement
	x	Untestable (only for amputation or shoulder joint fusion – please state which)
6. Best Motor LEFT ARM	0	No drift – *holds limb at 90 degrees for full 10 seconds*
	1	Drift - *drifts down but does not hit bed*
	2	Some effort against gravity
	3	No effort against gravity
	4	No movement
	x	*Untestable* (only for amputation or shoulder joint fusion – please state which)
7. Best Motor RIGHT LEG	0	No drift – *holds limb at 45 degrees for full 5 seconds*
	1	Drift - *drifts down but does not hit bed*
	2	Some effort against gravity
	3	No effort against gravity
	4	No movement
	x	*Untestable* (only for amputation or hip joint fusion – please state which)
8. Best Motor LEFT LEG	0	No drift – *holds limb at 45 degrees for full 5 seconds*
	1	Drift - *drifts down but does not hit bed*
	2	Some effort against gravity
	3	No effort against gravity
	4	No movement
	x	*Untestable* (only for amputation or hip joint fusion – please state which)
9. Limb Ataxia	0	Absent
	1	Present in 1 limb
	2	Present in 2 or more limbs
	x	*Untestable* (only for amputation or joint fusion – please state which)
10. Sensory	0	Normal
	1	Partial loss - *patient feels pinprick is less sharp or is dull on affected side*
	2	Dense loss - *patient is unaware of being touched on face, arm, leg*
11. Best Language *(see materials provided)*		No dysphasia
	0	Mild to moderate dysphasia - *obvious loss of fluency or comprehension, without significant limitation in ideas expressed or form of expression. Conversation about provided material difficult or impossible but examiner can identify items from patient's response.*
	1	
	2	Severe dysphasia - *all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener who carries burden of communication. Examiner cannot identify items provided from patient response.*
	3	Mute - *no usable speech or auditory comprehension.*
12. Dysarthria	0	Normal articulation
	1	Mild to moderate dysarthria - *patient slurs some words, can be understood with some difficulty.*
	2	Unintelligible or worse - *speech is so slurred as to be unintelligible (absence of or out of proportion to dysphasia) or is mute/anarthric*
	x	Untestable *(intubation or other physical barrier to producing speech – please state)*
13. Neglect	0	No neglect
	1	Partial neglect - *Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities*
	2	Complete neglect - *Profound hemi-inattention (e.g. does not recognise own hand or orients to only one side of space) or hemi-inattention to more than one sensory modality (e.g. visual + tactile).*

Appendix 4: Scandinavian Stroke Scale

Function	Score	Prognostic Score	Long Term Score
Consciousness			
– Fully consciousness	6	____	
– Somnolent, can be awaked to full consciousness	4		
– Reacts to verbal command, but is not fully consciousness	2		
Eye movement			
– No gaze palsy	4	____	
– Gaze palsy present	2		
– Conjugate eye deviation	0		
Arm, motor power*			
– Raises arm with normal strength	6	____	____
– Raises arm with reduced strength	5		
– Raises arm with flexion in elbow	4		
– Can move, but not against gravity	2		
– Paralysis	0		
Hand, motor power*			
– Normal strength	6		____
– Reduced strength in full range	4		
– Some movement, fingertips do not reach palms	2		
– Paralysis	0		
Leg, motor power*			
– Normal strength	6	____	____
– Raises straight leg with reduced strength	5		
– Raises leg with flexion of knee	4		
– Can move, but not against gravity	2		
– Paralysis	0		
Orientation			
– Correct for time, place, person	6		____
– Two of these	4		
– One of these	2		
– Completely disorientated	0		
Speech			
– No aphasia	10		____
– Limited vocabulary or incoherent speech	6		
– More than yes/no, but no longer sentences	3		
– Only yes/no or less	0		
Facial Palsy			
– None/dubious	2		____
– Present	0		
Gait			
– Walks 5 m without aids	12		____
– Walks with aids	9		
– Walks with help of another person	6		
– Sits without support	3		
– Bedridden/wheelchair	0		
Maximal Score		**22**	**48**

* Motor power is assessed only on the affected side.

Appendix 5: The modified Rankin scale (mRS)

Clinical status	Score
No symptoms	0
Minor symptoms which do not interfere with lifestyle	1
Some restriction to lifestyle, but look after themselves	2
Significant restriction to lifestyle, preventing total independence	3
Severe handicap preventing independent existence, but not requiring constant attention	4
Severe handicap, totally dependent, requiring attention day and night	5
Dead	6

Appendix 6: The Barthel Index

Activity	**Score**
FEEDING	
0 = unable	
5 = needs help cutting, spreading butter etc or requires modified diet	
10 = independent	_____
BATHING	
0= dependent	
5 = independent (or in shower)	_____
GROOMING	
0 = needs help with personal care	
5 = independent face/hair/teeth/shaving (implements provided)	_____
DRESSING	
0 = dependent	
5 = needs help but can do about half unaided	
10 = independent (including buttons, zips, laces etc)	_____
BOWELS	
0 = incontinent (or needs to be given enema)	
5 = occasional accident	
10 = continent	_____
BLADDER	
0 = incontinent, or catheterised and unable to manage alone	
5 = occasional accident	
10 = continent	_____
TOILET USE	
0 = dependent	
5 = needs some help, but can do something alone	
10 = independent (on and off, dressing, wiping)	_____
TRANSFERS (BED TO CHAIR AND BACK)	
0 = unable, no sitting balance	
5 = major help (one or two people, physical), can sit	
10 = minor help (verbal or physical)	
15 = independent	_____
MOBILITY (ON LEVEL SURFACES)	
0 = immobile or < 50 yards	
5 = wheelchair independent, including corners > 50 yards	
10 = walks with help of one person (physical or verbal) > 50 yards	
15 = independent (but may use any aid; eg stick) > 50 yards	_____
STAIRS	
0 = unable	
5 = needs help (verbal, physical, carrying aid)	
10 = independent	_____
TOTAL (0 – 100)	_____

Appendix 7: CSO Application

Chief Scientist Office Form 2

Grant application Form	**CSO reference number:**

Please complete this form in 12 point font size

Project title (not more than 25 words):

Practical, streamlined and optimal use of imaging in acute stroke.

Duration of project *(months)*:**12**

Summary of costs:

Staff	Indirect costs *(if applicable)*	Consumables	Travel	Ex. items	Equipment	**Total**
Not applicable	**Not applicable**	**£14450**	**Not applicable**	**Not applicable**	**Not applicable**	**£14450**
NHS support costs **Not applicable**						

Principal investigator:

Name and title	Position	Institution
Dr I A Kane	**Stroke Research Fellow**	**University of Edinburgh**

Project summary *(not more than 150 words)*:

The most promising treatment for acute ischaemic stroke, in those who present early, is thrombolysis with recombinant tissue plasminogen activator (rt-PA). Currently rt-PA is licensed for use in patients with acute ischaemic stroke who meet strict eligibility criteria. It is not known which brain imaging method best identifies the patients that are most likely to benefit from (or be harmed by) thrombolysis. CT scanning is widely available and quick to perform, but may be insensitive. Magnetic resonance (MR) diffusion weighted imaging (DWI) is sensitive to early ischaemic damage. MR perfusion imaging (PWI) demonstrates blood flow in and around the infarct. The difference between these two may represent the 'salvageable' brain. Under the umbrella of the Third International Stroke Trial, our aim is to test the methodology for a simple and efficient MR DWI/PWI protocol that yields sufficient information to improve patient selection, yet is not unduly time consuming or hazardous.

1. Application for a research grant in: *(please tick)*

	Full grant	Small grant
Biomedical & Therapeutic Research		✔
Health Services Research		

2. Project category: *(please tick)*

New project	✔
Re-submission	
Supplementary funding	

3. Keywords *(please see suggested list Appendix H)*:

Stroke	**Neuroradiology**	**Imaging**	**Emergency medicine**	**Geriatric medicine**

4. Dates:

Proposed start date	**May 2004**
Proposed finish date	**May 2005**

5. Applicants' details:

Title and full name *(Principal applicant)*	**Dr IA Kane**		
Full address	**University of Edinburgh** **Division of Clinical Neurosciences** **Bramwell Dott Building** **Western General Hospital** **Crewe Road** **Edinburgh. EH4 2XU**		
Telephone no./ext. **0131 537 3228**	Fax no. **0131 332 5150**	E-mail **ingrid.kane@ed.ac.uk**	Hours per week **10**
Organisation **University of Edinburgh**	Department **Division of Clinical Neurosciences**	Position **Stroke Research Fellow**	

6. Co-applicants:

Title and full name *(Co- applicant)*	**Professor JM Wardlaw**		
Full address	**University of Edinburgh** **Division of Clinical Neurosciences** **Bramwell Dott Building** **Western General Hospital** **Crewe Road** **Edinburgh. EH4 2XU**		
Telephone no./ext. **0131 537 3110**	Fax no. **0131 332 5150**	E-mail **joanna.wardlaw@ed.ac.uk**	Hours per week **4**
Organisation **University of Edinburgh**	Department **Division of Clinical Neurosciences**	Position **Professor and Honorary Cons. Neuroradiologist**	
Title and full name *(Co-applicant)*	**Professor PAG Sandercock**		
Full address	**University of Edinburgh** **Division of Clinical Neurosciences** **Bramwell Dott Building** **Western General Hospital** **Crewe Road** **Edinburgh. EH4 2XU**		
Telephone no./ext. **0131 537 2927**	Fax no. **0131 332 5150**	E-mail **peter.sandercock@ed.ac.uk**	Hours per week **1**
Organisation **University of Edinburgh**	Department **Division of Clinical Neurosciences**	Position **Professor of Medical Neurology**	
Title and full name *(Co- applicant)*			
Full address			
Telephone no./ext.	Fax no.	E-mail	Hours per week
Organisation	Department	Position	

7. Ethical approval:

Attached	✔	Not required		Requested	

Animals:

Attached		Not required	✔	Requested	

Confidentiality and data protection are the responsibility of the investigators.

8. Support:

This project has been submitted within the past year to:
No previous submission

This project is currently being submitted to:
No current submission

Other research grants currently held *(organisation, project title, funding and period of support):*
None by the PI. The co-applicants hold several grants which provide supporting infrastructure for the present proposal, as follows:
The Health Foundation. The Third International Stroke Trial: Thrombolysis for acute ischaemic stroke. Dr RI Lindley (PI), Professor PAG Sandercock, Professor JM Wardlaw, Professor MS Dennis, Professor CP Warlow. £656.977 1st Dec 2002 – 31st Nov 2005.

Is there any overlap between this application and the other grants that you hold or are applying for? *(organisation, project title, funding and period of support):*
No.

9. Commercial exploitation:

Is the proposed research likely to lead to patentable or other commercially exploitable results? *(please give details)*
No

10. Financial support requested:

Chief Scientist Office

	Financial year (1 April - 31 March)				
	Year 1	Year 2	Year 3	Year 4	Total
Staff	-	-	-	-	
Indirect costs	-	-	-	-	
Equipment	-	-	-	-	
Consumables	**£14450**	-	-	-	**£14450**
Travel	-	-	-	-	
Other	-	-	-	-	
Total					**£14450**

NHS support costs	Financial year (1 April - 31 March)				
	Year 1	Year 2	Year 3	Year 4	Total
Service support					
Blood tests, X-rays, etc.	-	-	-	-	
In-patient stays	-	-	-	-	
Extra nursing	-	-	-	-	
Other *(please specify)*	-	-	-	-	
Infrastructure					
R&D offices (peer review)	-	-	-	-	
Allocation of clinician time to R&D	-	-	-	-	
Purchase/hire of equipment	-	-	-	-	
Employment of additional staff	-	-	-	-	
Total					**£0.00**

11. Declaration and authorisation:

Applicants:
I have read the standard conditions of grant set out in Appendix B of "All you need to know about grants for research and training from the Chief Scientist Office" and agree to abide by them and any amendments which may subsequently be issued. To my knowledge the project described here represents the ideas, concepts and writings of myself and co-investigators and is not a modification of projects submitted by others elsewhere.

Signature of applicants	Name (Capitals)	Date

This application should be submitted by/through (i) the Head of Department and (ii) the officer who will be responsible for administering any grant that may be awarded.

I confirm that I have read this application and that, if successful, the work will be accommodated and administered in this Department/Institution. The staff gradings and salaries proposed are correct and in accordance with the normal practice of this Institution. I accept responsibility for the conduct of this project and funds awarded for it and shall immediately inform the Chief Scientist Office if there is any indication of scientific misconduct or misuse of grant funds.

Head of Department:

Signature	Date
Title and full name (block capitals) PROFESSOR PETER SANDERCOCK	Department DIVISION OF CLINICAL NEUROSCIENCES

Finance Office of Administering Institution:

Signature	Date
Title and full name (block capitals)	Position held
Address Postcode	
Telephone no./ext.	Fax no.

When NHSScotland support costs are requested, the R&D Officer must sign the following:

This project application has been discussed with me and I note the NHS Scotland support costs associated with the application.

Signature	Date
Title and full name (block capitals)	Position held
Address Postcode	
Telephone no./ext.	Fax no.

1. Title:
Practical, streamlined and optimal use of imaging in acute stroke.

2. Introduction:
In the UK, about 150,000 people have a stroke each year. About 30% die within 6 months and another 30% need help thereafter for everyday activities.[1] Eighty percent of strokes are ischaemic and most ischaemic strokes are due to a blocked (thrombosed) artery.

Recombinant tissue plasminogen activator (rt-PA) is licenced for use in patients with acute ischaemic stroke who meet highly specific clinical criteria and who can be treated within three hours of symptom onset.

There is debate about which brain imaging technique best identifies which patients are most likely to benefit from (or be harmed by) thrombolysis. CT scanning, a widely available imaging method, has been used as the standard in previous trials, but may be insensitive.[2] Magnetic resonance (MR) diffusion weighted imaging (DWI) is very sensitive to early ischaemic damage.[3] MR perfusion imaging (PWI) demonstrates blood flow in and around the infarct.[4] The difference between these two ('mismatch') may be the 'salvageable' brain (i.e. the 'penumbra' or potential benefit),[5,6] but the degree of abnormality on DWI[7,8] or PWI[9] indicating thrombolysis-salvageable tissue is unclear. Indeed DWI/PWI 'mismatch' did not predict outcome after rt-PA in one observational study.[10] Perhaps other features of the DWI lesion need to be considered, e.g. degree of hyperintensity (whiteness) and 'haziness' of the lesion edge, might be important determinants of tissue injury. Magnetic resonance angiography (MRA) may also help - perhaps patients with a still-occluded major artery without much DWI lesion will benefit most from rt-PA. MR imaging might help identify *potential hazards* in other ways. Microhaemorrhages (tiny areas of old asymptomatic haemorrhage) increase with age, are associated with periventricular white matter hyperintensities on T2 MR and may[11] or may not[12] be associated with a higher risk of bleeding with rt-PA. Unfortunately, MR takes longer and is more difficult and may be less safe to use in acutely ill patients than CT (11% become significantly hypoxic while in the MR scanner).[13] It is not clear that the extra information from MR ('benefit') outweighs the 'hazards' of delay to treatment (further tissue loss, performing plain X-rays to exclude metallic foreign bodies in aphasic patients), potential risk to patients (hypoxia), or the organisational implications for provision of imaging services. Despite numerous studies, issues remain controversial as to which imaging techniques are best in acute stroke (see abstracts, AHA 29th International Stroke meeting, February 2004, several of which directly contradict each other as to practicality and benefits of MR).

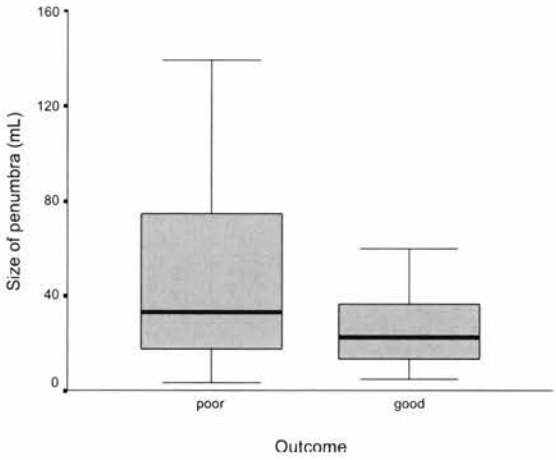
The Third International Stroke Trial (IST-3) is evaluating the safety and efficacy of rt-PA in a wider variety of patients than is covered by the current licence. To enable as many centres as possible to randomise patients as quickly as possible, CT scanning is the specified pre-randomisation imaging technique. However many sites are interested in performing MR DWI/PWI imaging to try to improve patient selection, but the Steering Committee are concerned that this could delay the start of treatment unduly.

Thus, we need to develop and test the methodology for a simple and efficient MR DWI/PWI protocol that yields sufficient information to improve patient selection yet is not unduly time consuming or hazardous.

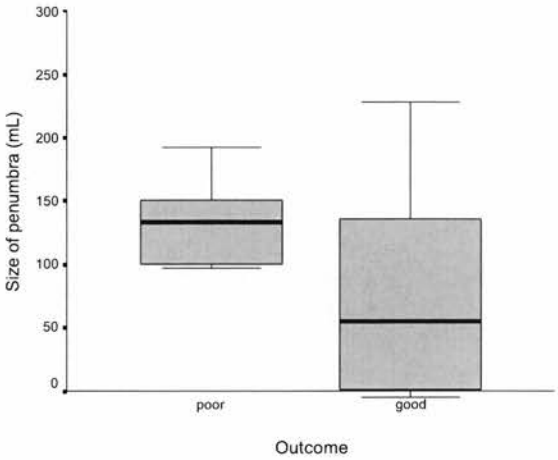
3. Results of any pilot studies:
To date, 198 patients have been randomised into IST-3 (42 from the Western General Hospital). Our observational study of the pathophysiological changes following acute ischaemic stroke on DWI/PWI imaging at the Western General Hospital is nearing completion (CSO ref CZB/4/14). Interim analysis at 60 patients with baseline DWI/PWI imaging showed no association between the

presence of a DWI/PWI mismatch (mean transit time - MTT or cerebral blood flow - CBF) and 3 month clinical outcome in patients not receiving rt-PA (Figure 1); patients with early spontaneous

Figure 1: relationship between PWI/DWI mismatch and clinical outcome at 3 months according to whether the PWI lesion is measured as CBF or MTT.



CBF maps: P=0.33



MTT maps: P=0.25

improvement in perfusion parameters had more rapid "normalization" of DWI changes.[14] Our, and others previous work showed that spontaneous reperfusion of the infarct is associated with improved clinical outcome.[15] Whilst the influence these imaging features have on prognosis is of interest, the key question is whether there is a significant interaction with the treatment effect of rt-PA. This can only be studied in a randomised controlled trial, where the relevant MR parameters are measured before randomisation.

Some such thrombolysis trials using DWI/PWI are ongoing: DIAS/DEDAS is using very restrictive MR features including DWI/PWI mismatch to *select* patients for desmoteplase therapy; EPIPHET in Australasia (29 patients recruited to date - S Davis personal communication) is recording MR DWI/PWI in up to 120 patients randomised to rt-PA or placebo three to six hours after stroke, but selecting patients on clinical/CT criteria; ROSIE, in the USA, is selecting patients with a perfusion deficit on MR and radiologically measuring reperfusion after ReoPro and Retevase treatment. None of these studies will be able to assess reliably whether or not there is an interaction with treatment effect and, to our knowledge, these studies are not examining the role of microhaemorrhages or white matter lesions. To address issues such as practicality and safety, as well as prognostic value, larger studies are needed.

To date there has been little comparative work on CT and CT perfusion versus MR. However, new CT technology makes these sorts of studies more feasible, therefore ultimately there will need to be some comparisons between the various imaging techniques.

4. Aims:

1. To develop, test and streamline an MR imaging protocol in Edinburgh (n=20) and devise methods for making large acute MR imaging studies conducted within a randomised controlled trial of thrombolysis possible.
2. To survey all acute stroke centres in the UK to identify those that could do MR imaging in acute stroke. This will determine available technology, estimate recruitment within a centre, the number of centres needed to complete a definitive study, and implications for healthcare of routine MR prior to thrombolysis.
3. To establish a network of interested IST-3 centres in and outside the UK, pilot the local image analysis methods and transfer of raw MR DWI/PWI data for archiving and analysis to the Neurosciences Trials Unit in Edinburgh.
4. To determine if a study large enough to be informative is practicable under the umbrella of IST-3.

5. Research questions to be asked and hypotheses to be tested:

The key hypothesis for a large-scale study is that MR imaging will help select those patients with acute ischaemic stroke who will benefit most from rt-PA. The ultimate aim is to address the following questions, but before this can be done a pilot study is needed to gain information on safety and feasibility. The questions are:

- Can routine MR be made more rapid, practical and safe in acute stroke?
- Does ischaemic lesion appearance on DWI (extent, intensity, or clarity) predict the amount of non-salvageable tissue?
- Is the benefit of rt-PA confined to those with a PWI lesion larger than the DWI lesion (DWI/PWI mismatch) or do those *without* mismatch benefit as well?
- Are patients with white matter hyperintensities or microhaemorrhages at greater risk of intracranial haemorrhage after rt-PA than those without?
- How do CT scan 'early infarct signs' and white matter hypodensities relate to MR 'early infarct signs' and white matter hyperintensities?

To answer these questions a multicentre study is required in order to attain a large enough sample. Therefore the research question concerning this application is:

- In the context of IST-3, is it feasible to run an MR imaging substudy aiming to improve the safety of thrombolysis?

6. Plan of investigation:

Study at the Western General Hospital

Subject selection

All patients potentially eligible for IST-3 who present at the Western General Hospital, between 9am and 5pm, Monday to Friday, are assessed and recorded. Those fitting the trial eligibility criteria (full protocol available at www.ist3.com), consenting to IST-3 and safe to MR, will then be examined with the following protocol (see appendix). Several patients have already been randomised at the Western General Hospital into IST-3 following MR rather than CT, but we need to obtain more systematic experience in a standardised fashion.

MRI protocol

It is proposed that patients will have a CT followed by MR as outlined in the pathway (Appx 2). As part of the protocol, coordination, times and any delays will be recorded as part of the planning for a larger study in order to find the optimum way of organising a comparative imaging study. Patients will have DWI/PWI, T_2, gradient echo and 3D time-of-flight MRA (TOF MRA). The DWI (three gradient echo planar technique TR 10000ms, TE 98.8ms, 34 phases), PWI (intravenous gadolinium bolus tracking using various simple methods of analysis of the signal time curve and more complicated methods such as the modified Ostergaard technique to produce mean transit time (MTT), cerebral blood flow (CBF) and cerebral blood volume);[4,9] T2 weighted imaging (fast spin echo TR 6300ms, TE 102ms), gradient echo imaging (TR 625ms, TE 15ms), and 3D time of flight MRA are all standard techniques, total acquisition time 12-15 minutes maximum. The MR protocol will be repeated at 24-48 hours to identify haemorrhage, infarct expansion and perfusion changes in place of the routine IST-3 follow-up CT at 24-48 hours.

There are no clearly defined, validated guidelines equivalent to the "1/3 MCA rule for CT", on whether the appearance of the infarct on DWI/PWI should alter treatment decisions. It is therefore not our intention to specify what DWI/PWI appearances (on the basis of very limited information) should lead to inclusion or exclusion of the patient from the study. The only major and absolute exclusion is the presence of fresh intracranial haemorrhage. The justification for the approach is that DWI lesions may resolve, that animal studies show severely ischaemic tissue beyond the boundaries of the DWI-visible lesion, and that some patients with severe strokes and poor outcome do not have a DWI visible lesion at presentation. Even less is known about the PWI lesion.

The CT scans will be read centrally for lesion site and extent and degree of hypodensity according to well-validated scoring methods by an expert panel as already established for the main trial (see www.neuroimage.co.uk).[16,17] The MR image analysis for a main study needs to be established and streamlined, but will include several methods, including comparing the MR read locally (i.e by the attending physician) with a reading centrally, blinded to treatment allocation. Central analysis will be blinded to clinical details and will include simple subjective inspection of the DWI/PWI mismatch (for example, by the same coding template as for CT,[16] and whether the DWI lesion involves more than 1/3 of the MCA territory),[18] measurement of the volume of the DWI and PWI lesions and mismatch, and voxel by voxel analysis of subregions of the lesion on a workstation using co-registered images. The characteristics of the DWI lesion appearance will be recorded (e.g. signal intensity – bright/pale and edge clarity – sharply defined/fuzzy edge) as these features may be the "DWI equivalent" of CT early infarct signs. PWI processing will include CBF, cerebral blood volume (CBV) and MTT.[9] The DWI/PWI 'mismatch' will be defined as a difference in the volume of the lesion of more than 20% between DWI and PWI (CBF and MTT). We will compare estimation by visual inspection with measured lesion volume analysis. On MRA, we will compare presence of major artery occlusion with DWI/PWI appearance, degree of reperfusion, and clinical outcome. Microhaemorrhages are round dots of low signal on gradient echo imaging usually less than 2mm in diameter. Small asymmetric dots of low signal where the lenticulostriate arteries perforate the brain substance in the inferior part of the basal ganglia are not microhaemorrhages. MRA will be coded for vessel occlusion using the modified TIMI classification.[19]

Detailed baseline clinical assessments of neurological deficit (National Institutes of Health Scale – NIHSS), blind to imaging will be obtained at baseline by the stroke physician. Further clinical information will be obtained at 7 days as per the IST-3 in hospital follow-up form including the NIHSS. Six month final follow-up in IST-3 is by detailed postal questionnaire, mailed directly to the patient and conducted independently of the treating physician.

Ultimately, statistical analysis will include univariate and multivariate modelling to test for a) independent associations between DWI/PWI lesion volumes, other aspects of their appearance, the mismatch, time to treatment, final infarct size and clinical outcome and the interaction with rt-PA; b) risk of intracerebral haemorrhage with improved perfusion, and microhaemorrhages and the interaction with rt-PA; and c) correlation between the CT appearance and DWI/PWI. We will evaluate how each PWI parameter maps to infarct extent at 24-48 hours[8] and how initial DWI lesion extent, perfusion changes, and rt-PA relate to infarct swelling. In the pilot study we will apply simple statistics to the survey results and analyse the DWI/PWI data obtained as proposed, but the sample size is not large enough to answer the primary questions posed in the first part of section 5.

Survey of UK stroke centres

All UK stroke centres will be contacted to see what advanced stroke imaging they have available and, if there are no on-site facilities, where the nearest available MR scanner is located in relation to their hospital. We have contact details from the 1999 Stroke Association survey, coupled with details from the Scottish Stroke Care Audit and the British Association of Stroke Physicians to ensure complete coverage. The proposed questionnaire (developed from previous experience of a survey of radiologists in Scotland which achieved 100% response rate) is in Appendix 1, but requires piloting prior to posting to all stroke centres. By collating the information obtained from the study at the Western General with the UK survey, an estimate of the percentage of all UK stroke patients who could potentially undergo MR DWI/PWI imaging will be made.

7. Timetable of work

The MR imaging sequences are well established. Pilot then circulate the questionnaire, collate responses and chase non-responders. IST-3 is currently in its expansion phase. Months 1-12 – patient recruitment, baseline and repeat imaging and collection of clinical details. Throughout the proposed study period data will be entered and images analysed as patients accrue.

8. Existing facilities

IST-3 has secure funding from the Health Foundation until December 2005, providing costs of trial co-ordination, patient randomization and a clinical research fellow. We have a research dedicated MR scanner with stroke research as a major remit, a PhD student working on methods of DWI/PWI image analysis in stroke, a post-doctoral research fellow working on MR perfusion analysis, and a well-developed CT imaging substudy already in progress for IST-3 (www.neuroimage.co.uk).

9. Justification of requirements

The project requires funding to cover the cost of the MR scans for the patients. The cost per scan (£300 not including contrast) is required to cover the running of the scanner (maintenance, essential core staffing, consumables, archiving, data processing and analysis). Contrast for PWI costs £50 per scan. However, this is cost effective as it is a heavily discounted rate (normal cost £350 per scan), considerable infrastructure for analysis is already in place, and it would be much more expensive to initiate such a study with no dedicated research scanner and the cost of the research fellow is already covered. Additional costs are for stationery and postage for the UK survey (£450).

10. Research outcomes and implementation

The outcomes of the proposed study will provide guidance on how to streamline MR imaging in acute ischaemic stroke and whether a larger study is feasible. If feasibility is confirmed then the aim will be to expand this study out to other IST-3 centres as a well validated protocol, to answer the further research questions proposed regarding MR imaging. Together with the survey of UK stroke centres, we can determine the feasibility of using MR in ischaemic stroke pre thrombolysis in the UK. If we can better determine the likelihood of salvageable tissue using MR techniques then it may be that a broader range of patients could be considered for thrombolysis, for example the large group who wake with stroke and in whom exact time of symptom onset is not known. This has important implications for the provision of imaging services in Scotland. Scotland has, on average, better MR provision than the rest of the UK so increasing demand for MR in acute stroke is likely to impact here first. Scotland is also ahead of the rest of the UK for CT provisions and access for stroke, so is well placed to address the use of MR.

11. Dissemination

Information from this pilot study will be disseminated through the IST-3 collaboration with the aim of developing a protocol that can be used in an international multi centre study. Findings will be published in peer-reviewed journals, presented at national and international stroke meetings, and incorporated into guidelines where appropriate.

12. Key references

1. Murray CJ, Lopez AD. Global Burden of Disease Study. Lancet 1997;349:1498-1504.
2. Von Kummer R, et al. Early CT diagnosis of hemispheric brain infarction. Springer-Verlag, Berlin, 1995.
3. Moseley ME, Kucharczuk J, Mintorovich J, Cohen Y, Kurhanewicz J, Derugin N. Early detection of regional cerebral ischaemia in cats: comparison of diffusion and T2 weighted MRI and spectroscopy. Magn Res Med 1990;14:330-346.
4. Sorensen AG, Copen WA, Ostergaad L, Buonanno FS, Gonzalez RG, Rordorf G et al. Hyperacute stroke: simultaneous measurement of relative cerebral blood volume, relative cerebral blood flow, and mean transit time. Radiology 1999;210:519-527.
5. Schlaug G, Benfield A, Baird AE, Siewart B, Lovblad KO, Parker RA et al. The ischaemic penumbra operationally defined by diffusion and perfusion MRI. Neurology 1999;53:1528-1537.
6. Keir SL, Wardlaw JM. Systematic review of diffusion and perfusion imaging in acute ischaemic stroke. Stroke 2000;31:2723-2731.
7. Fiehler J, Foth M, Kucinski T, Knab R, von Bezold M, Weiller C et al. Severe ADC decreases do not predict irreversible tissue damage in humans. Stroke 2002;33:79-86.
8. Wardlaw JM, Keir SL, Bastin ME, Armitage PA, Rana AK. Is diffusion imaging appearance an independent predictor of outcome after ischaemic stroke? Neurology 2002;59:1381-1387.

9. Grandin CB, Duprez TP, Smith AM, Oppenheim C, Peeters A, Robert AR et al. Which MR-derived perfusion parameters are the best predictors of infarct growth in hyperacute stroke? Radiology 2002;223:361-370.
10. Nighoghossian N, Hermier M, Adeleine P, Derex L, Philippeau F, Dugor JF et al. MR imaging prediction of stroke outcome. A pre-post thrombolytic therapy study. Abstracts of the 7th International Symposium on thrombolysis and acute stroke therapy. Lyon, 27-28 May 2002.
11. Kidwell C, Saver JL, Villablanca JP, Duckwiler G, Fredieu A, Gough K et al. Magnetic resonance imaging detection of microbleeds before thrombolysis. Stroke 2002;33:95.
12. Derex L, Hermier M, Adeleine P, Honnorat J, Berthezene Y, Froment JC et al. Usefulness of T2-weighted MRI sequences before intravenous t-PA for acute ischaemic stroke. Abstracts of the 7th International Symposium on thrombolysis and acute stroke therapy. Lyon, 27-28 May 2002.
13. Rowat AM, Hand PJ, Janneke H, Wardlaw JM. Hypoxia in the acute phase of stroke during MR brain imaging. Abstracts of the 27th International Stroke Conference. San Antonio, 7-9 February 2002.
14. Rivers CS, Armitage PA, Carpenter T, Hand PJ, Dennis MS, Wardlaw JM. MR diffusion and perfusion abnormalities in ischaemic stroke – patterns of sub-regional change and tissue recovery. Cerebrovasc Dis 2003;16(suppl 4):119.
15. Wardlaw JM, Dennis MS, Lindley RI, Warlow CP, Sandercock PAG, Sellar RJ. Does early reperfusion of a cerebral infarct influence cerebral infarct swelling in the acute stage or the final clinical outcome? Cerebrovasc Dis 1993;3:86-93.
16. Barber P et al for the ASPECTS study group.Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. Lancet 2000;355:1670-1674.
17. Wardlaw JM, Sellar R. A simple practical classification of cerebral infarcts on CT and its interobserver reliability. Am J Neuroradiol 1994;15:1933-1939.
18. Silver B, Demaerschalk B, Merino JG, Wong E, Tamayo A, Devasenapathy A et al. Improved outcomes in stroke thrombolysis with pre-specified imaging criteria. Can. J. Neurol. Sci. 2001;28:113-119.
19. http:/galileo1.knowledgemed.com/Cardiology/Terminology/TIMI.

13. Relevant additional material

1. Appendix 1: proposed pathway for patients involved in the practical advanced imaging brain study.
2. Appendix 2: Questionnaire for the UK survey of stroke centres.
3. The IST-3 protocol can be viewed at http://www.ist3.com

Appendix 1

Name of your hospital

Do you have an acute stroke unit/ stroke rehab unit / combined stroke unit?
(please circle most appropriate answer)

Do you have a CT scanner on site YES / NO

The following questions relate to **on site** MRI scanning facilities. If you have no MRI at your hospital please move directly to question 6.

1. Do you have an on site MRI scan YES / NO

2. If yes, is there 24-hour access to the MRI scanner YES / NO

3. Is the scanner available for acute stroke patients YES / NO

4. Can you MR scan acute stroke patients within 5 hrs of symptom onset? YES / NO
   If yes, go to question 5

5. How many patients filling the criteria in Q4 are scanned per month? I_____I

6. If you do not have a scanner on site – where is the nearest available MRI?

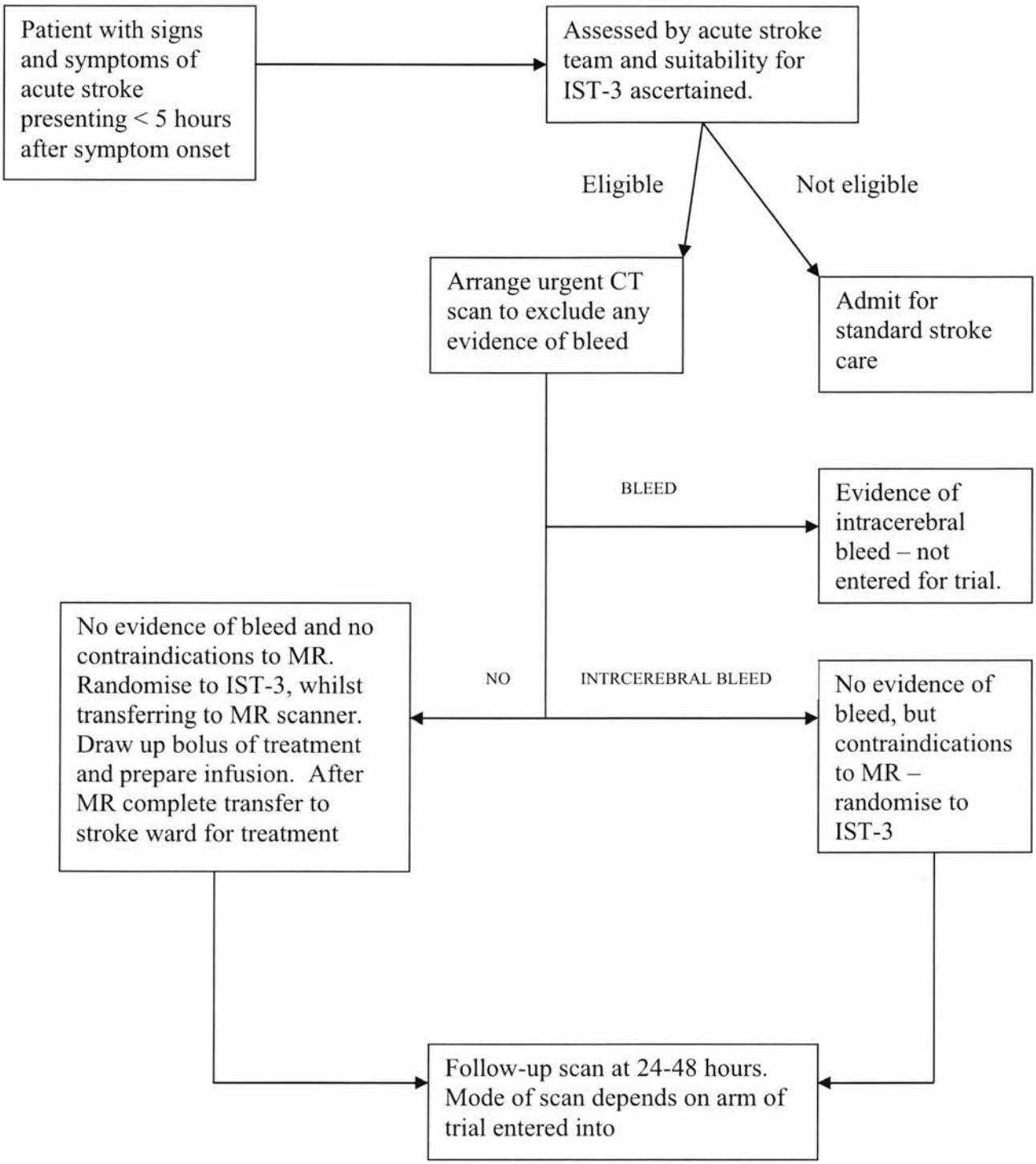
   - Location
   - Approximate distance from your hospital

If you have any other information, which you feel may be useful, please note it here

Many thanks for taking the time to answer this questionnaire.

Dr Ingrid Kane
IST-3 Stroke Research Fellow
Division of Clinical Neurosciences
Edinburgh University

Appendix 2



Note: if, at anytime, the MR scanner is unavailable for any reason the patient will undergo CT scanning and, if there is no evidence of intracerebral haemorrhage, they will be randomised to IST-3 as per the usual protocol. If any patients are eligible to receive thrombolysis under the strict current licence they can still be entered into the MR arm of the study prior to receiving treatment.

Details of financial support requested:
Staff details

Name	Grade	Spine point	Incremental date	Starting salary £	Superann. + NI (comb) £	Total year (notional) £
Research staff						
-	-	-	-	-	-	
-	-	-	-	-	-	
Technical staff						
-	-	-	-	-	-	
-	-	-	-	-	-	
Other staff						
-	-	-	-	-	-	
-	-	-	-	-	-	
Total						**£0.00**

Details of financial support requested

Staff costs (annual costs of staff listed above)	*Effort on project*		*Financial year 1 April - 31 March*				
	%	months	Year 1 £	Year 2 £	Year 3 £	Year 4 £	Total £
Research staff							
	-	-	-	-	-	-	
	-	-	-	-	-	-	
Technical staff							
	-	-	-	-	-	-	
	-	-	-	-	-	-	
Other staff							
	-	-	-	-	-	-	
	-	-	-	-	-	-	
Total annual costs							**£0.00**

Details of financial support requested (continued)

Consumables (please specify details of items)	*Financial year 1 April - 31 March*				
	Year 1 £	Year 2 £	Year 3 £	Year 4 £	Total £
MR scans (includes archiving and analysis) (40 in total) Contrast for MR scans (40 in total)	**£12000 + £2000**	-	-	-	**£14000**
Stationery for survey Stamps for survey	**£150 + £300**	-	-	-	**£450**
Total annual costs					**£14450**

Travel (please specify details – not conference attendance)	*Financial year 1 April - 31 March*				
	Year 1 £	Year 2 £	Year 3 £	Year 4 £	Total £
	-	-	-	-	
	-	-	-	-	
Total annual costs					**£0.00**

Exceptional items (please specify details of items)	*Financial year 1 April - 31 March*				
	Year 1 £	Year 2 £	Year 3 £	Year 4 £	Total £
	-	-	-	-	
	-	-	-	-	
Total annual costs					**£0.00**

Equipment (please give details of items and country of manufacture)	Date of purchase	Purchase price	VAT £	Total £
	-	-	-	
	-	-	-	
Total				**£0.00**

Section 3

Curriculum vitae of applicant(s)/proposed staff (if known): maximum 1 page per applicant.
(This form can be copied as necessary. *DO NOT ATTACH SEPARATE CV.*)

Surname	*Initials*	*Age*	*Title*
KANE	I A	33	DR

Degrees, etc.

BSc in Physiology and Basic Medical Sciences (2.1)	1993
MBBS (Lond)	1996
MRCP (UK)	2000

Posts held (with dates)

May 2003 -	Stroke Research Fellow, Edinburgh University
Oct 2001-May 2003	SpR in Geriatrics and General Medicine (SW Thames)
Feb 2000-Aug 2000	Staff grade General Medicine, St Richards Hospital
Feb 1998-Aug 2000	SHO General Medicine, St Richards Hospital
Aug 1997-Feb 1998	SHO Accident and Emergency, West Middlesex University Hosp
Feb 1997-Aug 1997	HO General Surgery, Worthing Hospital
Aug 1996-Feb 1997	HO General Medicine, West Middlesex University Hospital

Relevant recent publications (with title and reference)

Kane I, Sandercock P. Thrombolysis for acute ischaemic stroke. Stroke Review 2003; 7(4): 95-99

Curriculum vitae of applicant(s)/proposed staff (if known)
(this form can be copied as necessary)

Surname	*Initials*	*Age*	*Title*
WARDLAW	JM	45	PROFESSOR
Degrees, etc.			
BSc(Hons), Physiology First Class	University of Edinburgh		1979
MBChB (Hons), Medicine	University of Edinburgh		1982
MRCP			1986
DMRD			1987
FRCR			1988
MD			1994
FRCP			1998
Posts held (with dates)			
2002 – present	Professor and Honorary Consultant Neuroradiologist, Edinburgh		
1998 – 2002	Reader and Honorary Consultant Neuroradiologist, Edinburgh		
April '94 – Sept '98	Senior Lecturer and Honourary Consultant Neuroradiologist, Edin		
Feb '92 – Mar '94	Consultant Neuroradiologist, INS, Glasgow		
Oct '90 – Jan '92	MRC Research Fellow (Senior Registrar) in Neuroradiology, Edin.		
1988 – 90	Senior Registrar Radiology, Edinburgh		
1985 – 88	Registrar Radiology, Edinburgh		
1983 - 85	SHO General Medicine, Edinburgh		
1982 – 83	Pre Registration HO, Edinburgh		
Relevant recent publications (with title and reference)			
Wardlaw JM, Keir SK, Bastin ME, Armitage PA, Rana AK. Is diffusion imaging appearance an independent predictor of outcome after ischemic stroke? *Neurology* 2002;59:1381-1387.			
Rana AK, Wardlaw JM, Armitage PA, Bastin ME: Apparent diffusion coefficient (ADC) measurements may be more reliable and reproducible than lesion volume on diffusion-weighted images from patients with acute ischaemic stroke – implications for study design. *Magn. Reson. Imag* 2003;21:617-624.			
Wardlaw JM, West TM, Sandercock PAG, Lewis SC, Mielke O, The International Stroke Trials Collaborative Group: Visible infarction on computed tomography is an independent predictor of poor functional outcome after stroke, and not of haemorrhagic transformation. *JNNP* 2003;74:452			
Wardlaw JM, Sandercock PAG, Berge E. Thrombolytic therapy with recombinant tissue plasminogen activator for acute ischaemic stroke. Where do we go from here? A cumulative meta-analysis. *Stroke* 2003;34:1437-1442.			
Wardlaw JM, del Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2003. Oxford: Update Software. CD000213			
Keir SL, Wardlaw JM: Systematic review of diffusion and perfusion imaging in acute ischaemic stroke. *Stroke* 2000;31:2723-2731.			
Wardlaw JM, Keir SL, Seymour J, Lewis S, Sandercock PAG, Dennis MS, Cairns J. What is the best imaging strategy for acute stroke? *Health Technol Assess* 2004;8(1).			
Keir SL, Wardlaw JM, Bastin ME, Dennis MS: In which patients is diffusion-weighted MR imaging most useful in routine stroke care? *Journal of Neuroimaging* 2004			

Surname	*Initials*	*Age*	*Title*
SANDERCOCK	P A G	52	PROFESSOR

Degrees, etc.

BA	University of Oxford (1st Class)	1972
BM, BCh	University of Oxford	1975
DM	University of Oxford	1985
FRCPE	Royal College of Physicians, Edinburgh	1991
FmedSci	Fellow Academy of Medical Sciences	2002

Posts held (with dates)

Professor of Neurology	University of Edinburgh	1999 -
Reader in Neurology	University of Edinburgh	1992-1999
Senior Lecturer in Neurology	University of Edinburgh	1987–1992
Lecturer and Hon Senior Registrar	Liverpool University	1985–1987
Registrar in Neurology	Manchester Royal Infirmary	1979–1981
Registrar in General Medicine	North Staffordshire Hospital	1978–1979
Rotating Senior House Officer	North Staffordshire Hospital	1977-1978

Relevant recent publications (with title and reference)

Collaborative meta-analysis of randomised trials of antiplatelet for prevention of death, myocardial infarction, and stroke in high risk patients. Antithrombotic Trialists' Collaboration. BMJ 2002; 324:71-86.

International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. Molyneux A, Kerr R, Stratton I, Sandercock PAG, Clarke M, Shrimpton J, Holman R. The Lancet 2002; 360:1267-1272.

A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS. Sandercock PAG, Berge E, Dennis M, Forbes J, Hand P, Kwan J, Lewis S, Lindley R, Neilson A, Thomas B, Wardlaw J. Health Technology Assessment 2002; Vol 6: No.26.

Visible infarction on computed tomography is an independent predictor of poor functional outcome after stroke, and not of haemorrhagic transformation. Wardlaw JM, West TM, Sandercock PAG, Lewis SC, Mielke O for the International stroke Trials Collaborative Group. J Neurol Neurosurg Psychiatry 2003; 74:452-458.

Thrombolytic therapy with recombinant tissue plasminogen activator for acute ischemic stroke: where do we go from here? A cumulative meta-analysis. Wardlaw J, Sandercock PAG, Berge E. Stroke 2003; 34(6):1437-42.

Is breakdown of the blood-brain barrier responsible for lacunar stroke, leukoaraiosis, and dementia? Wardlaw J, Sandercock PAG, Dennis M, Starr J. Stroke 1003; 4(3):806-12.

What is the best imaging strategy for acute stroke? Wardlaw JM, Keir SL, Seymour J, Lewis S, Sandercock P, Dennis MS, Cairns J. Health Technol Assess 2004;8(1):1-192.

Report on previous CSO grant(s)

For each and every CSO grant which you or any of your co-applicants have held as principal applicant and which has begun or terminated over the past five academic years, please give the information requested below (this form should be copied for each grant).

Project title **Validation of a Prognostic Model for Stroke Risk**		
Project number (if known) ***K/MRS/50/C2457***		
Start date **1st May 1996**	*Finish date* **30th July 2000**	*Date reported* **February 2001**
Grantholders **Dr JM Wardlaw, Dr MS Dennis**		
Current perception of significance		
The purpose of this work was to improve identification of patients at greatest risk of stroke after a TIA, amaurosis fugax or minor stroke, so that preventive measures like carotid endarterectomy may be targetted more effectively. We also examined the prediction of vascular death and myocardial infarction. We collected clinical and radiological data on over 4000 TIA/stroke patients. Our statistical models can identify the 75% of patients who are very unlikely to have a stroke, MI or vascular death, and the small proportion of patients at 40-50% risk of stroke, MI or vascular death in the two years after presentation, although they, like others,are not so specific. Compared with previously described models in the literature, ours performed better predicted MI and vascular death as well as stroke, and was derived in a realistic, modern cohort of patients typical of vascular clinics (as opposed to those from highly selected trial data). We therefore believe that it will make a significant contribution to the body of knowledge on targeting stroke prevention and impact on neurovascular clinics and daily patient management, as well as in new research to identify other risk factors.		
Scientific papers directly resulting from this grant		
- Wardlaw JM, Lewis SC, Dennis MS, Counsell C, McDowall M: Is Visible Infarction of Computed Tomography Associated With an Adverse Prognosis in Acute Ischaemic Stroke? *Stroke* 1998;29:1315-1319. - Mead G, Lewis SC, Wardlaw JM, Dennis MS: Should computed tomography appearance of lacunar stroke influence patient management? *JNNP* 1999;67:682-4. - Mead GE, Wardlaw JM, Lewis SC, McDowall M, Dennis MS: The influence of randomised trials on the use of anticoagulation for atrial fibrillation. *Age Ageing* 1999;28:441-446. - Oliver TB, Lammie GA, Wright AR, Wardlaw J, Patel SG, Peek R, Ruckley CV, Collie DA: Atherosclerotic Plaque at the Carotid Bifurcation: CT Angiographic Appearance with Histopathologic Correlation. *AJNR* May 1999;20:897-901. - Mead GM, Wardlaw JM, Lewis SC, McDowall M, Dennis MS: Can simple clinical features be used to identify patients with severe carotid stenosis on Doppler ultrasound? *JNNP* 1999;66:16-19. - Lammie GA, Wardlaw JM, Allan PA, Ruckley CV, Peek R: What simple markers of atheromatous plaque activity can be reliably detected using ultrasound? *Eur J Ultrasound* 2000;11:77-86. - Mead GE, Lewis SC, Wardlaw JM: Interobserver variability in Doppler ultrasound influences referral of patients for carotid surgery. *Eur J Ultrasound* 2000;12:137-143. - Mead GE, Wardlaw JM, Lewis SC, McDowall M, Dennis MS: The influence of randomised trials on the use of anticoagulation for atrial fibrillation. *Age Ageing* 1999;28:441-446. - Mead G, Lewis SC, Wardlaw JM, Dennis MS: Should computed tomography appearance of lacunar stroke influence patient management? *JNNP* 1999;67:682-4. - Mead GE, Wardlaw JM, Dennis MS, Lewis SC, Warlow CP: Relationship between pattern of intracranial artery abnormalities on transcranial Doppler and Oxfordshire Community Stroke Project clinical classification of ischaemic stroke. *Stroke* 2000;31:714-719. - Mead GM, Lewis SC, Wardlaw JM, Dennis MS, Warlow CP: Severe ipsilateral carotid stenosis and middle cerebral artery disease in lacunar ischaemic stroke: innocent bystanders? *J Neurol* 2002;249:266-271. - Lewis SC, Wardlaw JM: Which Doppler velocity is best for assessing suitability for carotid endarterectomy? *European Journal of Ultrasound* 2002;15:9-20. - Mead G. Lewis S, Wardlaw JM, Dennis MS: Comparison of risk factors in patients with transient and prolonged eye and brain ischemic syndromes. Stroke 2002;33:2383-2390.		

Report on previous CSO grant(s)

For each and every CSO grant which you or any of your co-applicants have held as principal applicant and which has begun or terminated over the past five academic years, please give the information requested below (this form should be copied for each grant).

Project title **Pathophysiological studies of human acute ischaemic stroke using advanced brain imaging**		
Project number (if known) **CSO CZB/4/14**		
Start date **1st Feb 2001**	*Finish date* **31st Jan 2004**	*Date report due* **March 2004**
Grantholders **Dr JM Wardlaw, Dr MS Dennis, Dr ME Bastin**		
Current perception of significance		
We aim to improve understanding of the relationship between the appearance of the brain on advanced MR imaging and brain perfusion and clinical features and outcome to improve identification of penumbral tissue after acute ischaemic stroke.		
There is great interest in applying advanced imaging in acute ischaemic stroke but most of the previous work has not been very critically performed. We are collecting a series of patients who will have sequential MR imaging to follow the pattern of change in imaging appearance and symptoms to identify salvageable/ unsalvageable tissue. We aim to recruit 60 with complete imaging and have already recruited 35 of whom 10 have completed imaging.		
57 patients had been recruited. 46 patients have undergone serial scanning. 11 have not had further scanning because of refusal (5), the stroke was actually due to a haemorrhage (3), or death (3). 30 patients have reached the 3 month follow-up point so far.		
Scientific papers directly resulting from this grant		
So far only abstracts have been produced: - Hand PJ, Rivers CS, Rowat AM, Bastin ME, Dennis MS, Wardlaw JM. Does DWI lesion volume predict outcome after stroke? 11th European Stroke Conference, Geneva, Switzerland, May 29th – June 1st 2002 (Oral Session – Neuroimaging I), *Cerebrovasc Dis* 2002;13(suppl 3):57. - Hand PJ, Kwan J, Sandercock PAG, Wardlaw JM, Dennis MS. Improving the clinical assessment of patients eligible for thrombolysis. 7th International Symposium on Thrombolysis in Acute Ischaemic Stroke, Lyon, May 2002. - P.A. Armitage, C.S. Rivers, T.K. Carpenter, M.E. Bastin, P.J. Hand, J.M. Wardlaw. MR perfusion imaging: problems resulting from a lack of contrast agent in infarcted regions. 12th European Stroke Conference, May 2003, Valencia, *Cerebrovascular Dis* in press. - O'Brien P, Stratton S, Seller RS, Wardlaw JM. Fogging" on MR after ischaemic stroke - how often does it occur and does it matter? 12th European Stroke Conference, May 2003, Valencia, *Cerebrovascular Dis* in press. - Rivers CS, Armitage PA, Carpenter T, Hand PJ, Dennis MS, Bastin ME, Wardlaw JM. MR diffusion and perfusion abnormalities in ischaemic stroke – patterns of sub-regional change and tissue recovery. 12th European Stroke Conference, May 2003, Valencia, *Cerebrovascular Dis* in press. - Rivers CS, Armitage PA, Carpenter T, Bastin ME, Hand PJ, Dennis MS, Wardlaw JM The effect of ischaemic lesion swelling on serial MR diffusion and perfusion measurements in stroke. 12th European Stroke Conference, May 2003, Valencia, *Cerebrovascular Dis* in press. - Carpenter TK, Armitage PA, Bastin ME, Wardlaw JM. Artefacts in MR Perfusion parametric images in ischaemic stroke – effects of variation in bolus arrival time. 12th European Stroke Conference, May 2003, Valencia, *Cerebrovascular Dis* in press.		

Report on previous CSO grant(s)

For each and every CSO grant which you or any of your co-applicants have held as principal applicant and which has begun or terminated over the past five academic years, please give the information requested below (this form should be copied for each grant).

Project title: **Cochrane Stroke Group**	
Project number (if known): **CSO CZB/4/142**	
Start date: **1st July 2003**	*Finish date:* **30th June 2006**
Final report date and CSO Committee Grade (excellent, good, satisfactory, unsatisfactory) **Six month report completed.**	
Grantholders: **Professor PAG Sandercock**	
Current perception of significance:	
Scientific papers directly resulting from this grant:	

R&D Project Details Pro forma – Information for the National Research Register

1. Methodology:
(please tick)

	Full grant	Small grant
Clinical trial		
Randomised trial		✔
Other *(please specify in free text)*		

2. Sample group description *(the notional population from which the sample is drawn for the purposes of your study)*

The population is drawn from those presenting within 6 hours of developing the symptoms of acute ischaemic stroke, who fit the eligibility criteria for thrombolysis under the Third International Stroke Trial (see www.ist3.com). They must have no contraindications to MR imaging.

3. Outcome measure description *(endpoints or factors used to evaluate health status, such as survival discharge status or quality of life. Can also be a symptom e.g. reduction in blood pressure.)*

The outcomes of the proposed study will provide guidance on how to streamline MR imaging in acute ischaemic stroke and whether a larger study is feasible. If feasibility is confirmed then the aim will be to expand this study out to other IST-3 centres as a well validated protocol, to answer the further research questions proposed regarding MR imaging. Together with the survey of UK stroke centres, we can determine the feasibility of using MR in ischaemic stroke pre thrombolysis in the UK.

4. Project related web site *(the address for a web site which contains further related information for an individual project)*

www.ist3.com

Appendix 8

Protocol for IST-3 Imaging Study – DCN Guidelines

Position subject in head coil

All sequences can be found in the head section of the SITE protocol list. All the parameters below are set up in each sequence and SHOULD NOT be changed.

This MRI protocol will be repeated at 24-48 hours to identify haemorrhage, infarct expansion and perfusion changes.

Switch on research mode

Select

1. 3 Plane localizer: Run as normal clinical sequence (11 s).

2. Axial T_2 FSE **[IST-3 MRI]**: Run with 26 **axial slices** (2:44 minutes).

FOV (cm)	Phase FOV	Matrix	Slices	Thick. (mm)	Space (mm)	TR (ms)	TE (ms)	NEX
24 × 24	1	256 × 256	26	5.0	1.0	6300	102.0	1

3. Axial T_1 GRE **[IST-3 MRI]**: Run with the same slice locations as the axial T_2 FSE sequence (2:02 minutes).

FOV (cm)	Phase FOV	Matrix	Slices	Thick. (mm)	Space (mm)	TR (ms)	TE (ms)	NEX
24 × 24	1	256 × 192	26	5.0	1.0	625	15.0	1

4. DW-EPI **[IST-3 MRI]**: Run TWICE with the same slice location as the axial T_2 FSE sequence. Make sure 'recon all' button is selected in diffusion window (2 × 48 s).

FOV (cm)	Phase FOV	Matrix	Slices	Thick. (mm)	Space (mm)	TR (ms)	TE (ms)	NEX
24 × 24	1	128 × 128	26	5.0	1.0	12000.0	97.4	1

5. DSC PW-EPI **[IST-3 MRI]**: Perform dynamic susceptibility contrast perfusion-weighted MRI with 15 axial slices chosen to overlay the centre of the stroke region, but coincident with slices imaged in the T_2 FSE sequence. The delay between start of imaging and injection of contrast should be 10 s (1:26 s).

FOV (cm)	Phase FOV	Matrix	Slices	Thick. (mm)	Space (mm)	TR (ms)	TE (ms)	Phases
24 × 24	1	128 × 128	15	5.0	1.0	2500.0	30	34

6. 3D TOF MRA COW **[IST-3 MRI]**: Run TOF MRA only **if the patient is cooperative and there is time** (5:05 minutes).

FOV (cm)	Phase FOV	Matrix	Slices	Thick. (mm)	Space (mm)	TR (ms)	TE (ms)	NEX
24 × 18	0.75	256 × 224	50	1.8	0	36	6.9	1

Appendix 9

ELIGIBILITY

- **ANY patient** with a mild, moderate, or severe deficit, due to **acute stroke,** in whom:

  1. There is a clear time of onset of **< 6 hours** since symptoms first noticed.
  2. CT or MRI brain scan has **excluded** intracranial haemorrhage.
  3. In the doctor's opinion, there is no clear indication for treatment, or clear contraindication to rt-PA (recombinant tissue plasminogen activator).

- Reasons for **not** entering patients in the trial may include:
  1. *small likelihood of worthwhile benefit, such as:*
     - ❑ symptoms considered likely to resolve **completely** within the **next few hours** (i.e. a TIA)
     - ❑ patient already dependent on others prior to the onset of the present stroke
     - ❑ prognosis likely to be very poor no matter what treatment(s) are given (e.g. coma)
     - ❑ patient has another serious life-threatening illness which is likely to lead to death within the next few months,
     - ❑ patient is female and has childbearing potential (unless it can be assured that pregnancy is not possible), or is currently breast feeding.
  2. *high risk of adverse effects of treatment, such as:*
     - ❑ persistent, severe elevation of blood pressure.
     - ❑ known abnormal coagulation or platelet dysfunction.
     - ❑ trauma (e.g. collapse at time of stroke) or major surgery, or gastrointestinal or urinary tract haemorrhage within the previous 21 days.
     - ❑ arterial puncture at a non-compressible site within the previous 7 days.

- Patients who have been taking aspirin or other anti-platelet agents before the trial are eligible.
- The final decision for trial eligibility rests with the responsible doctor, if unsure phone the trial's 24-hour helpline (details below).

BEFORE YOU MAKE THE RANDOMISATION PHONECALL

- Measure NIHSS
- Check blood glucose (must be 3.0 – 20 mmol/L)
- Obtain patient consent, or relative assent, for entry into IST-3 using patient or relative information provided
- Complete the Randomisation Notepad
- Telephone the 24 hour randomisation service **+44 (0) 131 537 2797**
- At the end of the call you will be allocated either rt-PA (the calculated dose for the bolus and one-hour infusion will be provided) or conventional treatment.

TELEPHONE RANDOMISATION

If allocated rt-Pa

Give bolus immediately over 1-2 minutes by hand, randomisation
followed by the remainder infusion over the next 60 of the
minutes
Complete the treatment record form as you give the trial treatment
record,
Do not give antiplatelet or anticoagulant therapy in first 24 hours after the infusion
All other management is at the discretion of the responsible clinician
Repeat brain scan 24-48 hours after randomisation

IF NOT allocated rt-PA

Repeat brain scan 24-48 hours after

Management of the patient is at the discretion

responsible clinician
Aspirin can be given
Fill in the patient treatment and monitoring

including the blood pressure readings

Appendix 10

NHS Lothian

The Lothian University Hospital NHS Trust
Western General Hospital

PATIENT INFORMATION

THE MAGNETIC RESONANCE IMAGING STUDY IN ACUTE STROKE

You have been admitted to the Western General Hospital because you have had a stroke. We would like you to consider being a part of a study on Magnetic Resonance Imaging (MRI) in patients who have had a stroke within the last 6 hours. It will provide valuable information about what exactly is happening in the brain when people have a stroke and therefore help us give the right kind of treatment.

You will first be seen by the doctor who will ask you questions about the symptoms that brought you to hospital, then you will have full examination.

As soon as possible after the examination we will organise for you to have an MRI. This scan uses magnetism but will not cause any harm to you. Many other hospitals around the world use the magnetic scan routinely. We do ask you to lie still for around 10-15 minutes. The machine is slightly noisy so you will have earplugs to protect your ears. You will be able to communicate with us during the scanning. If you feel uncomfortable or claustrophobic, the scan can be stopped at any time. If you know you are

claustrophobic, please tell us and we will not do the MR scan.

This scan is important because it gives us more detailed pictures of the brain, including what sort of damage may have happened to cause your stroke. We think that in the future, this more detailed information will help us decide what sort of treatment is best for patients like you. In order to record blood flow in your brain you will need a small injection into a vein in your arm through the needle, which usually gets put in, while you are in the admission unit. This scan will be in addition to a CT (computed tomography) scan of your brain which is a routine treatment in this hospital. We are trying to establish what extra information MR scans give on patients like you.

In order to monitor what happens to your stroke, we would like to repeat the magnetic resonance scan in 24-48 hours and three months after your stroke. In three months time you will also have a full examination by the doctor to assess how well have you recovered from the stroke.

You may decide to withdraw from the study at any time. This will make no difference to the care you receive from the stroke team in the hospital and outpatients. If you decide to take part in this study you will be asked to sign a consent form. Even when you sign a consent form you are still free to withdraw from the study at any time without having to give a reason and without affecting your future care.

Your GP will receive information about your involvement in the study.

Any information that you give us as well as the results of the scans will be treated as confidential and will only be available to the doctors looking after you and research staff involved in this project.

This study has been funded by the Chief Scientist Office and has been approved by the Lothian Research and Ethics Committee.

If you would like to obtain further information about the study from somebody who is not directly involved you could speak to Dr Zeman who can be contacted through the Western General switchboard No 0131 537 1000.

If you have any questions about the study even after you leave the hospital, please feel free to contact Dr Kane at the Western General Hospital (switchboard no. 0131 537 1000, bleep 5160).

Appendix 11

MAGNETIC RESONANCE IMAGING STUDY IN ACUTE STROKE

PATIENT'S CONSENT FORM

The Magnetic Resonance Imaging Study in Acute Stroke has been explained to me and I have read the information leaflet about it. I have had time to consider the study and have had all my questions about it answered. ☐

I understand that I am free to withdraw at any time from any part of the study, without giving a reason, and without it adversely affecting my future medical care. ☐

I agree to take part in the above study. ☐

Signed:.....(patient's signature)

Name:.....(patient's name)

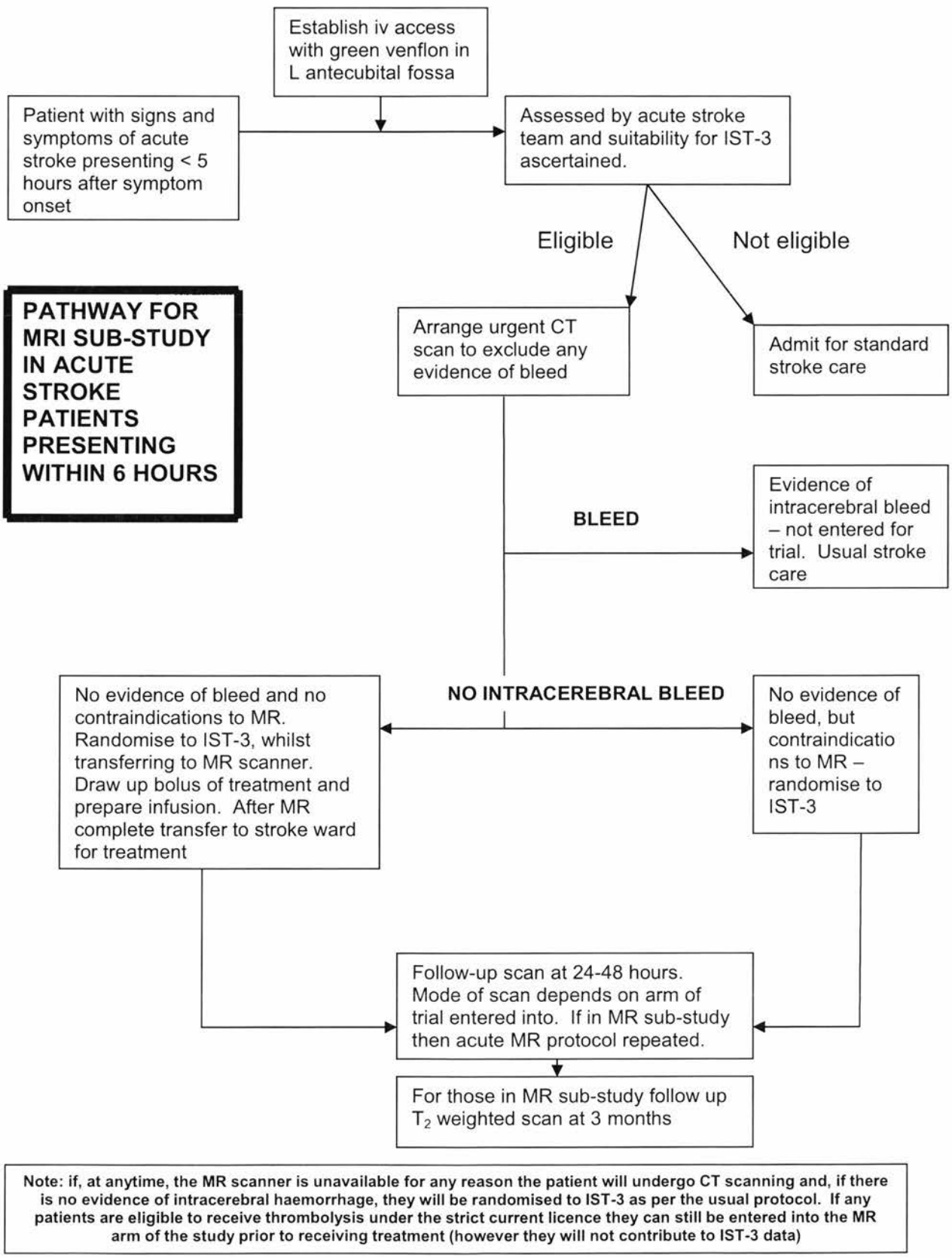
Date:.....

Signed: .....(signature of the investigator)

Name: .....(name of the investigator)

Date: .....

Appendix 12



Note: if, at anytime, the MR scanner is unavailable for any reason the patient will undergo CT scanning and, if there is no evidence of intracerebral haemorrhage, they will be randomised to IST-3 as per the usual protocol. If any patients are eligible to receive thrombolysis under the strict current licence they can still be entered into the MR arm of the study prior to receiving treatment (however they will not contribute to IST-3 data)

Appendix 13

Practical, streamlined and optimal use of imaging in acute stroke.

Date: __/__/__

Patient details:

Time of symptom onset: __: __
Time of arrival at ARU: __: __
Time of assessment: __: __
Time of CT: __: __
Total time in CT: _____
Time of MRI: __: __
Total time in MRI: _____
Time of randomisation: __: __
Treatment: control / rt-PA / rt-PA (licensed)

Clinical diagnosis: Left / Right (side of brain)
TACS
PACS
LACS
POCS

Brief history:

Drug treatment on admission:

O2 administered: Y / N
Rate: l/min
Prior to MR?
In MR?

Baseline NIHSS:

Any other details e.g. delays prior to MR; skull or CXR required

Total scan acquisition time in MR (mins):

Observer with patient in MR: Y / N
Scan completed: Y / N If N, main reason:

Appendix 14

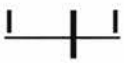
UK survey of availability of MR scanning for patients with acute stroke

Name of your hospital:

1. Do you have a CT scanner on site? YES / NO

2. Do you have an MRI scanner on site? YES / NO

The following questions relate to the **on site** MRI scanning facilities at your hospital. If you do NOT have an MRI scanner at your hospital please move directly to question **6**.

3. Is it possible to obtain an MR scan on an acute stroke patient within 6 hours of symptom onset in normal working hours?
   Please indicate using scale below, by marking on the line e.g. 

   Very easy — Impossible

4. Is it possible to get out of hours access to the MR scanner for stroke patients?
   Please indicate using scale below, by marking on the line e.g.

   Very easy — Impossible

5. If you know the details of your MR scanner, please circle relevant options.

   Make: GE Phillips Siemens Not known

   Magnet strength: <1.5T 1.5T 3.0T Not known

   Approx. year installed: Before 2000 2000-2005 Not known

6. If you do NOT have a scanner on site – where is the nearest available MRI?
   - Location _____
   - Approximate distance from your hospital _____

7. In the last 6 months, how often (approx) have you obtained an MR scan for stroke **within 6 hrs of symptom onset** _____, **within 12hrs** _____, **after any time**_____.

If you have any other information about access to imaging for acute stroke, which you feel may be useful, please note it here

Appendix 15

1. Kane I, Whiteley W, Sandercock P, Wardlaw J. Availability of CT and MR for assessing patients with acute stroke in the UK. *Cerebrovasc Dis* 2008;25:375-377.

2. Kane I, Carpenter T, Chappell F, Rivers C, Armitage P, Sandercock P, Wardlaw J. Comparison of ten different Magnetic Resonance perfusion imaging processing methods in acute ischaemic stroke. Effect on lesion size, proportion of patients with diffusion/perfusion mismatch, clinical scores and radiological outcomes. *Stroke* 2007;38:3158-3164.

3. Kane I, Sandercock P, Wardlaw J. Magnetic resonance diffusion perfusion diffusion mismatch and thrombolysis in acute ischaemic stroke: A systematic review of the evidence to date. *J Neurol Neurosurg Psychiatry* 2007;78:485-491.

4. Kane I, Lindley R, Lewis S, Sandercock P. Impact of stroke syndrome and stroke severity on the process of consent in the Third International Stroke Trial. *Cerebrovasc Dis* 2006;21:348-352.

Cerebrovascular Diseases

Published online: March 14, 2008

Cerebrovasc Dis 2008;25:375–377
DOI: 10.1159/000120688

Availability of CT and MR for Assessing Patients with Acute Stroke

I. Kane[a], *W.N. Whiteley*[b], *P.A.G. Sandercock*[b], *J.M. Wardlaw*[b]

[a]Department of General Medicine, St. Richard's Hospital, Chichester, [b]Division of Clinical Neurosciences, University of Edinburgh, Edinburgh, UK

Background

Brain imaging is essential for the selection of stroke patients for thrombolysis. The imaging method must be available rapidly at all times, quick to perform, and able to exclude intracerebral haemorrhage and mimics of stroke [1]. Computerised tomography (CT) scanning is already widely available [2–4] and cost-effective [5]. However, signs on CT indicating ischaemic stroke are subtle within the first few hours of symptom onset and can be hard to see in people with leukoaraiosis or previous stroke [6].

Magnetic resonance imaging (MRI) may provide more information than CT in patients with acute stroke. For example, diffusion-weighted imaging (DWI) MR may be more sensitive than CT at detecting ischaemic stroke in patients with mild symptoms [7], and gradient echo more sensitive for showing old haemorrhages in patients who present several days after their stroke [8]. There is increasing pressure that MR should be the method of choice to select patients with acute stroke for thrombolysis [9] and the first-line imaging method for all stroke [10] (though there are practical difficulties in performing MR in about 20% of stroke patients) [11, 12].

At least 2 acute stroke trials in progress are assessing the use of MRI DWI to select patients [13, 14]. If it is established that MR improves selection for thrombolysis, we sought to identify whether the UK would be in a position to provide this imaging modality for patients with acute stroke. We therefore surveyed all acute hospitals in the UK admitting patients with acute stroke to assess their access to MRI.

Methods

We assembled a database of the 268 hospitals in the UK that admitted acute stroke patients, from the National Sentinel Stroke Audit [2] and the Scottish Stroke Audit [4]. We sent a short questionnaire to the lead stroke clinicians at each hospital, with a covering letter and stamped addressed envelope in February 2005. For centres with access to MRI, we sought further details on the capacity of their MRI machines both in and out of normal working hours. The questionnaire included visual analogue scales to assess the ease of access to MRI, which were measured with a scale from 0 for 'impossible' to 12 for 'very easy'. We arbitrarily defined 'difficult' as a score between 0 and 5. We sent a reminder to those who failed to respond on the first occasion.

Results

The total number of replies was 248/268 (93% of the total number of admitting hospitals). The survey was complete by the end of 2005.

Access to CT

Of the hospitals admitting acute stroke patients, 240 (97%) had a CT scanner on site. Only 8 had neither CT nor MRI, of which 3 were in rural areas (174–402 km to their nearest scanner). The remaining 5 hospitals with no CT or MRI were very small units about 32 km from their nearest scanner.

Access to MRI

Most hospitals that admitted patients with acute stroke had MRI facilities on site (192/245; 78%). Of the 192 hospitals with MR, 3 used mobile units which were not available 24 h a day. All the hospitals that had MR also had CT (fig. 1).

Forty-eight hospitals had on-site CT but no MRI. Of the 46 respondents, the average distance to an MRI machine was 37 km (range 0.8–129).

Although more than three quarters of hospitals had MRI in their hospital, access for stroke patients was difficult. Seventy-three percent of hospitals found MRI access difficult during working hours and 95% out of hours.

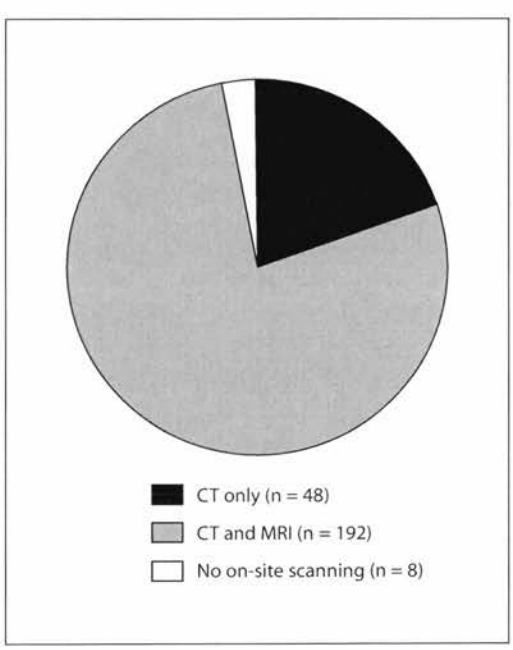


Fig. 1. UK availability of scanning facilities for acute stroke.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1015–9770/08/0254–0375$24.50/0

Accessible online at:
www.karger.com/ced

Table 1. Number of hospitals carrying out MRI scans on acute stroke patients within the previous 6 months

Estimated number of patients scanned	<6 h after stroke (number of hospitals)	<12 h after stroke (number of hospitals)	At any time after stroke onset (number of hospitals)
None	137	117	8
1–5	17	29	34
6–10	3	3	40
>10	1	5	59
Totals	158	154	141

Few patients had MRI within 6 h of stroke (table 1). Within the 6 months preceding the survey, only 21/192 (11%) hospitals with MR on site had performed MR on any patients within 6 h of stroke onset and 58/192 (30%) had scanned any patients within 12 h of stroke.

Discussion

CT scanning was available in almost all UK hospitals admitting patients with acute stroke. Although 78% of such hospitals had access to MRI, it was rarely available sufficiently quickly to be of value in the management of patients with acute stroke. Making a number of assumptions about patterns of acute stroke care, we estimated that for the year 2005 in the whole of the UK about 300 patients with acute stroke had MRI within 6 h of stroke; about 0.2% of all new strokes in the UK. This may be an underestimate, but even if we have erred by a factor of 10 (which would not accord with our experience), the total would still only be 2%. We believe this estimate of MRI service provision to be realistic in view of the excellent response rate (93%). The Royal College of Physicians Sentinel Stroke Audit [2] tends to confirm this and found that although 88% of stroke units had access to MRI scanning, it was only available urgently in 53%. This contrasts with 91% of units having access to emergency CT scanning.

Does this survey indicate that stroke patients in the UK are disadvantaged? For routine use of thrombolysis, perhaps not. Immediate CT scanning for acute stroke is a highly cost-effective CT strategy [15]. In patients who are candidates for thrombolysis, CT within the first few hours of stroke with a structured interpretation is as good as MR with DWI in identifying early ischaemic change [12], though in milder stroke, MRI may be more sensitive [16]. Both CT and MR can assess cerebral perfusion in the acute phase, and it remains unclear which will be the best test for selecting patients for thrombolytic therapy.

Although this survey demonstrates that there is wide provision of MRI equipment in the UK, the proportion of scanners per head of population is still less than in the best resourced areas of Europe or North America [17]. Many UK centres now have access to MRI and at least 1 UK centre has audited the use of MR as first-line imaging for suspected stroke [18]. We have not found any comparable nationwide surveys of access to MR for patients with acute stroke in other countries, although MR is reported to be difficult to access in some countries [19]. However, access to imaging for stroke patients depends on more than the mere presence of an MR scanner. Stroke competes with many other diseases, which often affect a younger population who are perceived to be needier. Demands on CT and MR are substantial, with radiology departments dealing with many competing priorities. Better access to MRI (and CT) for stroke patients requires not only more machines but also extended operating hours and increased funding for support by clinical radiologists (currently a shortage specialty). If the UK, one of the most prosperous countries in Europe (ranked fourth in the world by GDP), has yet to provide rapid access to MR for all patients with acute stroke, how can less wealthy countries be expected to provide MR for all?

Therefore, in many countries, CT may well continue to be the 'workhorse' imaging modality in acute stroke, since it is universally available – without delay – to patients with acute stroke; for a trained reader, it is as sensitive as DWI MR; and perfusion CT imaging may prove to be as effective as MR perfusion for selecting patients for thrombolysis. On the other hand, for milder strokes, strokes presenting late and other areas of cerebrovascular disease, MR still has advantages over CT and does not involve ionizing radiation, so the drive to increase the availability of MR around the world for patients with stroke should continue.

Competing Interests and Funding

This survey was funded by the Chief Scientist Office of the Scottish Executive.

References

1 Koehrmann M, Juettler E, Huttner HB, Nowe T, Schellinger PD: Acute stroke imaging for thrombolytic therapy – an update. Cerebrovasc Dis 2007;24:161–169.
2 Intercollegiate Stroke Working Party: National Sentinel Stroke Audit Report 2004. London, Royal College of Physicians, 2005.
3 National Audit Office (UK): Reducing Brain Damage. Faster Access to Better Stroke Care. London, Stationary Office, 2005.
4 Scottish Stroke Care Audit: National Report on Stroke Services in Scottish Hospitals. Edinburgh, Scottish Stroke Care Audit, 2006.
5 Wardlaw JM, Keir SL, Seymour J, Lewis S, Sandercock PA, Dennis MS, et al: What is the best imaging strategy for acute stroke? Health Technol Assess 2004;8:iii, ix-x, 1–180.
6 Wardlaw JM, Farrall AJ, Perry D, von Kummer R, Mielke O, Moulin T, et al: Factors influencing the detection of early CT signs of cerebral ischemia: an internet-based, international multiobserver study. Stroke 2007;38:1250–1256.
7 Keir SL, Wardlaw JM, Bastin ME, Dennis MS: In which patients is diffusion-weighted magnetic resonance imaging most useful in routine stroke care? J Neuroimaging 2004;14:118–122.
8 Wardlaw JM, Keir SL, Dennis MS: The impact of delays in computed tomography of the brain on the accuracy of diagnosis and subsequent management in patients with minor stroke. J Neurol Neurosurg Psychiatry 2003;74:77–81.
9 Hjort N, Butcher K, Davis SM, Kidwell CS, Koroshetz WJ, et al; UCLA Thrombolysis Investigators: Magnetic resonance imaging criteria for thrombolysis in acute cerebral infarct. Stroke 2005;36:388–397.
10 Chalela JA, Kidwell CS, Nentwich LM, Luby M, Butman JA, Demchuk AM, et al: Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: a prospective comparison. Lancet 2007;369:293–298.
11 Hand PJ, Wardlaw JM, Rowat AM, Haisma JA, Lindley RI, Dennis MS: Magnetic resonance brain imaging in patients with acute stroke: feasibility and patient-related difficulties. J Neurol Neurosurg Psychiatry 2005;76:1525–1527.
12 Barber PA, Hill MD, Eliasziw M, Demchuk AM, Pexman JHW, Hudon ME, et al: Imaging of the brain in acute ischaemic stroke: comparison of computed tomography and magnetic resonance diffusion-weighted imaging. J Neurol Neurosurg Psychiatry 2005;76:1528–1533.

13 Butcher KS, Parsons M, MacGregor L, Barber PA, Chalk J, Bladin C, et al: Refining the perfusion-diffusion mismatch hypothesis. Stroke 2005; 36:1153–1159.
14 Furlan AJ, Eyding D, Albers GW, Al-Rawi Y, Lees KR, Rowley HA, et al: Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS): evidence of safety and efficacy 3 to 9 hours after stroke onset. Stroke 2006;37:1227–1231.
15 Wardlaw JM, Seymour J, Cairns J, Keir S, Lewis S, Sandercock P: Immediate computed tomography scanning of acute stroke is cost-effective and improves quality of life. Stroke 2004;35:2477–2483.
16 Chalela JA, Kidwell CS, Nentwich LM, Luby M, Butman JA, Demchuk AM, et al: Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: a prospective comparison. Lancet 2007;369:293–298.
17 Goldstein LB, Hey LA, Laney R: North Carolina Stroke Prevention and Treatment Facilities Survey: statewide availability of programs and services. Stroke 2000;31:66–70.
18 Buckley BT, Wainwright A, Meagher T, Briley D: Audit of a policy of magnetic resonance imaging with diffusion-weighted imaging as first-line neuroimaging for in-patients with clinically suspected acute stroke. Clin Radiol 2003;58:234–237.
19 Leys D, Ringelstein B, Kaste M, Hacke W: Facilities in European hospitals treating stroke patients. Stroke 2007;38:2895–2991.

Dr. William Whiteley
Department of Clinical Neurosciences, University of Edinburgh
Western General Hospital
Edinburgh EH4 2XU (UK)
Tel. +44 78 1111 3610, Fax +44 131 3325 150
E-Mail william.whiteley@ed.ac.uk

Cerebrovasc Dis 2008;25:377–380
DOI: 10.1159/000120689

Reversible Posterior Encephalopathy Syndrome Followed by MR Angiography-Documented Cerebral Vasospasm in Preeclampsia-Eclampsia: Report of 2 Cases

Kiyomi Tsukimori [a], *Hirofumi Ochi* [b], *Yasuo Yumoto* [a], *Satomi Iwasaki* [a], *Satoshi Hojo* [a], *Tomoyuki Noguchi* [c], *Norio Wake* [a]

Departments of [a] Gynecology and Obstetrics and [b] Neurology, Neurological Institute and [c] Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Introduction

Posterior reversible encephalopathy syndrome (PRES) is a rare complication of preeclampsia-eclampsia [1]. The characteristic neuroradiological findings are multifocal and often symmetric, increased T2 or diffusion-weighted signal intensity lesions in the posterior dominant white and gray matter [2]. Diffusion tensor imaging (DWI) changes support the hypothesis that vasogenic edema is the pathophysiological mechanism underlying this syndrome [2]. Several reports, however, associate PRES with cytotoxic edema, ischemic stroke, and angiographic vasospasm [3–6]. These findings suggest an interrelationship between PRES and cerebral vasospasm. We report two preeclamptic-eclamptic patients with clinical and neuroradiological features of PRES. In these patients, MR angiography (MRA) showed reversible vasospasm of large- and medium-sized cerebral arteries. The vasospasm was not present initially, and was preceded by the development of vasogenic edema.

Case Reports

Patient 1

A 28-year-old Japanese woman, gravida 2, para 0, with a twin pregnancy, suddenly developed a severe headache and vomiting at 35 weeks and 5 days of gestation. She had no evidence of cardiac, pulmonary, renal or cerebrovascular disease. Her blood pressure was 178/80 mm Hg, with proteinuria of 7.8 g/24 h. Neurological examination was normal. Hematological, renal and liver function tests were also normal. A diagnosis of preeclampsia was made. She was started on intravenous magnesium sulfate for seizure prophylaxis, and an emergent cesarean delivery was performed for breech presentation. Two male infants weighting 2,302 and 1,948 g were delivered, and both did well.

Four hours postoperatively, the patient grew disoriented and became obtunded. Her blood pressure was 170/110 mm Hg. A complete blood count showed no major abnormalities with a platelet count of 160,000/μl. Her electrolytes and renal function tests were normal. Brain magnetic resonance imaging (MRI) showed multifocal areas of edema with hyperintense signals on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images in the bilateral frontal, parietal, and occipital gray and white matters, basal ganglia, brainstem and bilateral cerebellum (fig. 1a). These areas showed predominantly high signals on DWI that corresponded to high signal intensities on an ADC map. These findings represented vasogenic edema. However, some of the diffusion-hyperintense lesions in the bilateral basal ganglia and left cerebellum showed low-signal intensities on the ADC map. This was consistent with cytotoxic edema. An MRA at this time did not show any significant abnormalities except for an aneurysm at the right internal carotid-ophthalmic artery (fig. 1b). The patient was treated with sodium nitroprusside, nicardipine, magnesium sulfate, glycerol, and the free radical scavenger edarabone. The next day, she recovered consciousness without neurological sequelae. On postpartum day 4, her headache had resolved and her blood pressure stabilized at 120/70 mm Hg.

A follow-up MRI on postpartum day 4 showed resolution of the high signal areas on FLAIR and T2-weighted images (fig. 1c); however, MRA revealed multifocal irregular narrowing of the bilateral anterior cerebral arteries (ACAs), middle cerebral arteries (MCAs), and posterior cerebral arteries (PCAs). This was consistent with vasoconstriction (fig. 1d). An extensive workup for cerebral vasculitis was negative. Additionally, microbiological, autoimmune and thrombophilia studies showed no abnormalities. On postpartum day 13, the patient's blood pressure had returned to normal without any medications, and she had no proteinuria. All neuroradiological abnormalities had resolved on a repeat brain MRI and MRA preformed on postpartum day 13. The patient had recovered completely with no neurological deficits on postpartum day 22, and was discharged.

Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Stroke Association℠

A Division of American Heart Association

Comparison of 10 Different Magnetic Resonance Perfusion Imaging Processing Methods in Acute Ischemic Stroke: Effect on Lesion Size, Proportion of Patients With Diffusion/Perfusion Mismatch, Clinical Scores, and Radiologic Outcomes

Ingrid Kane, Trevor Carpenter, Francesca Chappell, Carly Rivers, Paul Armitage, Peter Sandercock and Joanna Wardlaw

Stroke 2007;38;3158-3164; originally published online Nov 1, 2007;
DOI: 10.1161/STROKEAHA.107.483842
Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0039-2499. Online ISSN: 1524-4628

Comparison of 10 Different Magnetic Resonance Perfusion Imaging Processing Methods in Acute Ischemic Stroke

Effect on Lesion Size, Proportion of Patients With Diffusion/Perfusion Mismatch, Clinical Scores, and Radiologic Outcomes

Ingrid Kane, MRCP; Trevor Carpenter, PhD; Francesca Chappell, MSc; Carly Rivers, PhD; Paul Armitage, PhD; Peter Sandercock, FRCPE, FMedSci; Joanna Wardlaw, FRCR, FRCP, FMedSci

Background and Purpose—Several methods are available to assess the magnetic resonance perfusion lesion in acute ischemic stroke. We tested 10 of these to compare perfusion lesion sizes and to assess the relation to clinical scores and final infarct extent.

Methods—We recruited patients with acute ischemic stroke, performed diffusion- and perfusion-weighted imaging, and recorded stroke severity at baseline, final infarct size on T2-weighted imaging at ≥1 month, and Rankin Scale score at 3 months. We calculated 10 perfusion parameters (6 of mean transit time, MTT; 3 of cerebral blood flow; 1 of cerebral blood volume; 7 relative and 3 quantitative), measured the perfusion-weighted imaging lesion and diffusion/perfusion mismatch volumes, and compared each with clinical and radiologic outcomes.

Results—Among 32 patients, the median perfusion lesion volume varied from 0 to 14 882 voxels ($P<0.0001$); the proportion of patients with mismatch varied from 9% to 72% ($P<0.05$), depending on the perfusion parameter. Five measures of relative MTT were associated with baseline National Institutes of Health Stroke Scale score; 1 (arrival time fitted) was also associated with clinical outcome. Final infarct size was most strongly associated with MTT measures, including arrival time fitted. There was no advantage of quantitative perfusion measures and no relation between mismatch presence/absence and infarct expansion with any of the 10 perfusion measures.

Conclusions—Perfusion lesion size differs markedly depending on the parameter calculated. Relative perfusion parameters performed as well as quantitative ones. Some parameters (mainly representing MTT measures) were correlated with clinical scores; others were correlated with final infarct size; and arrival time fitted was correlated with both. These findings should be validated in other datasets. A consensus is required on which perfusion measurement and processing methods should be used. (***Stroke*. 2007;38:3158-3164.)**

Key Words: cerebral perfusion ■ diffusion imaging ■ magnetic resonance ■ stroke

Magnetic resonance (MR) perfusion-weighted imaging (PWI) in combination with diffusion-weighted imaging (DWI) is thought to identify ischemic, potentially salvageable tissue in acute ischemic stroke. Therefore, PWI and DWI are used increasingly in clinical trials[1] and to guide clinical decision making in patients with acute ischemic stroke.[2,3]

The most commonly used method for acquiring the PWI data, dynamic susceptibility contrast imaging, is performed by rapid imaging immediately before and then for up to 1.5 minutes after an intravenous injection of a gadolinium-based MR contrast agent.[4] PWI data so acquired may then be analyzed in several different ways to yield relative or quantitative values (Figure 1 and Table 1).[5,6] Relative values require less complex data processing and are often immediately accessible from the scanner console (eg, time to peak, TTP; full-width, half-maximum, FWHM). However, relative measurements do not usually account for the arterial input function (AIF) and thus may introduce large errors.[7–9] Quantitative perfusion parameters (eg, quantitative cerebral blood flow, qCBF, or cerebral blood volume, CBV)[4] overcome some but not all[10,11] of the limitations of relative parameters but require off-line processing including deconvolution; therefore, they take longer to produce the perfusion image.[10] A recent literature summary of a stroke imaging center survey indicated that different PWI parameters were used in different centers.[3] Does this variation matter?

Received January 28, 2007; final revision received May 8, 2007; accepted May 14, 2007.

From the Division of Clinical Neurosciences (I.K., T.C., F.C., P.A., P.S., J.W.), Western General Hospital, Edinburgh, Scotland, and the Clinical Trials Research Unit (C.R.), Leeds, England.

The first 2 authors contributed equally to this work.

Correspondence to Prof Joanna M. Wardlaw, Division of Clinical Neurosciences, Bramwell-Dott Building, Western General Hospital, Crewe Road, Edinburgh, EH4 2XU, Scotland. E-mail joanna.wardlaw@ed.ac.uk

***Stroke* is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.107.483842**

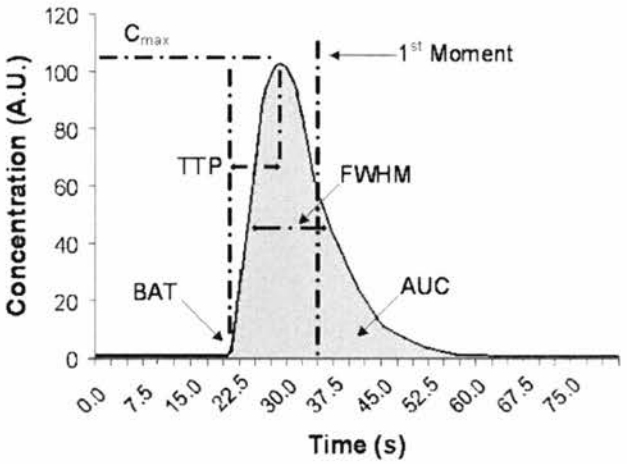


Figure 1. Contrast-time curve showing the different parameters used to estimate perfusion (concentration in arbitrary units, AU). FWHM first moment="balancing point" of curve along the time axis; Cmax (also known as peak height), TTP (also known as Tmax after deconvolution), and BAT=bolus arrival time. AUC indicates area under the curve.

PWI lesions that reflect CBF are generally smaller than those that reflect mean transit time (MTT).[12–16] Different ways of estimating a single PWI parameter like MTT may yield differently sized PWI lesions.[17] Comparisons of how well different relative and/or quantitative PWI lesions predict infarct growth yield differing results,[17–19] possibly due to differences in patient case mix or the timing of scanning, as well as to variations in the combinations of PWI processing methods used.

What effect does this PWI lesion variability have on any relation between the presence or size of the PWI lesion or DWI/PWI mismatch and the neurologic severity of the stroke at baseline? Of previous studies reporting correlations between perfusion parameters and stroke severity at presentation, 2[20,21] reported that TTP, a relative measure of MTT, was correlated with baseline National Institutes of Health Stroke Scale (NIHSS) score; 2[15,22] suggested a correlation between qMTT and baseline NIHSS; and 1[23] suggested a correlation between qMTT and the Scandinavian Stroke Scale score.

If imaging is to guide clinical trials or routine practice, then it is important to know which baseline PWI lesion(s) best relates to the final infarct extent and clinical outcome. These 2 outcomes may have different baseline predictors, which may differ from PWI lesions that are correlated with baseline neurologic deficit. Several studies that compared acute PWI lesions and radiologic outcomes used outcome time points that were too early to determine the "final" infarct extent (24 hours to ≈1 week after stroke).[18,24] Three studies that examined later time points only compared perfusion values, not lesion extent, but found associations between measures of MTT and 60- or 90-day T2 findings.[20,21,25] A correlation between the acute PWI lesion and functional clinical outcome was found between TTP and modified Rankin Scale (mRS) score,[21] relative (r) MTT and mRS,[26] and qMTT and the Barthel Index.[23]

In view of these differences, we compared 10 different ways of processing the PWI data to quantify variation in PWI lesion size and DWI/PWI mismatch and to explore the association between each PWI parameter and the NIHSS score on admission, the mRS score at 3 months, the final infarct size on T2-weighted imaging at least 1 month after stroke, and infarct growth between baseline and final T2-weighted imaging.

Methods

Patients

We recruited patients presenting with their first-ever acute ischemic stroke who were able to undergo MRI as soon after stroke onset as possible and within an absolute maximum of 24 hours (the scanner was only available during normal working hours). A trained stroke physician assessed all patients as soon as possible, assigned a stroke subtype according to the Oxfordshire Community Stroke Project classification,[27] and determined the stroke severity according to the NIHSS. Blinded to baseline features and imaging, we measured functional outcome at 3 months by the mRS. We included all ischemic stroke subtypes.

Image Acquisition

We performed all imaging on a GE Signa LX 1.5-T MRI scanner (General Electric, Milwaukee, Wis) with a birdcage quadrature coil and a standardized protocol for acute stroke (described previously).[14] The spin-echo echoplanar imaging diffusion-tensor axial sequences and dynamic susceptibility contrast echoplanar imaging PWI had 15 axial slices each of 5-mm thickness with an interslice gap of 1 mm and an imaging matrix 128×128 encompassing a 240×240 mm field of view. Additionally for PWI, a gadolinium-based contrast agent (10 mL of 1 mol/L Gadovist or 20 mL of 0.5 mol/L Omniscan) was injected, with imaging starting 10 seconds after the start of contrast injection, continuing for 85 seconds, and collecting 34 volumes of 15 axial slices with an echo time of 30 ms and a repetition time of 2.5 seconds. Final follow-up T2-weighted imaging was performed at ≥1 month.

Image Processing

We performed all image processing blinded to clinical and any other imaging data. We coregistered the individual DWI and PWI data by using the open-access software FLIRT (www.fmrib.ox.ac.uk/fsl). We obtained the DWI lesion volumes by manually tracing around the edge of the hyperintense lesion on a workstation (previously described).[14]

To produce the PWI images, we discarded the first acquisition volume (as is standard) and converted the remaining signal time course in each voxel to a concentration-time curve. We fitted a γ variate function to the concentration data in every voxel that showed enhancement >3 times the SD of the precontrast points. Voxels not meeting the >3 times SD criterion were given a negative value in the perfusion maps, can represent either cerebrospinal fluid or other tissue not accessible to contrast (eg, center of the infarct), and were excluded unless a lesion volume completely encircled negative voxels, in which case these voxels were included in the calculation of the lesion volume.

We defined the AIF from the fitted data by averaging the concentration-time data from voxels corresponding to the lumina of both internal carotid arteries on the first volume of the registered data (to limit effects of any carotid stenosis). We chose this approach for several reasons: to be more relevant to an acute situation, wherein the only knowledge of infarct location (before DWI/PWI data processing) may come from the symptoms; to characterize brain blood supply as a global "normalizing" factor (the internal carotid arteries being before the circle of Willis represent the available blood supply minus the contribution from the basilar artery); and last because the internal carotid arteries are aligned perpendicular to the plane of imaging and hence avoid problems associated with partial volume. Care was taken to ensure that the regions drawn within the internal carotid arteries corresponded to the lumen (2 or 3 voxels per vessel).

Table 1. Volumes of PWI Lesions and Mismatch Tissue and No. of Patients With a PWI Lesion and PWI/DWI Mismatch by PWI Processing Method Used

	Definition	Mean (Median) PWI Lesion Volume	No. With No PWI Lesion	No. With Mismatch (%)	Median Volume of Mismatch*
ATF	Estimated delay in arrival of contrast in a voxel obtained from the curve fitting procedure; μ rMTT	15 106 (5747)	11	18 (56)	715
PTF	Estimate of the time of maximum contrast concentration obtained from the fitted parameters; μ rMTT	21 185 (12478)	7	21 (66)	7690
TTP	Peak time fitted minus arrival time fitted; μ rMTT	22 802 (14882)	9	20 (63)	8213
FWHM	Width of the concentration-time curve at the point halfway to the peak concentration; μ rMTT	32 260 (13405)	7	23 (72)	8748
First moment (ie, rMTT)	First moment of the concentration-time curve; μ rMTT	23 177 (13996)	7	23 (72)	9684
Cmax	Maximum value of the fitted concentration-time curve; μ rCBF and MTT	5993 (0)	17	7 (22)	−1224
rCBF	rCBV/rMTT	4162 (0)	17	5 (16)	−1278
qMTT	qCBF/qCBV	22 167 (8620)	13	18 (56)	3853
qCBF	Maximum value of the scaled estimate of the voxel residue response	12 783 (0)	17	13 (41)	−492
CBV	Area under the concentration-time curve; μ rCBV or qCBV	2446 (0)	19	3 (9)	−1849

Mean and median PWI volumes are shown to overcome the "0" medians. Lesion volumes are expressed in voxels. μ indicates proportional to.
*Negative values indicate that the median DWI lesion is larger than the median acute PWI lesion.

We calculated maps of rCBV, rMTT, rCBF, arrival time fitted (ATF), peak time fitted (PTF), TTP, and FWHM of the concentration-time curve and the maximum value of the fitted concentration-time curve (Cmax). We normalized the parameter value in each voxel by the sample mean of the parameter value in the voxels used to define the AIF. Normalizing the rCBV value by the rCBV sample mean of the voxels used to define the AIF results in qCBV; hence, this parameter is not mentioned later. We produced maps of qCBF and qMTT by deconvolving the peak voxel concentration-time curves with the concentration-time curve of the AIF to obtain a scaled estimate of the voxel residue response.[4,28] The deconvolution was performed by singular value decomposition,[4,28] with the addition of a block-circulant discretization scheme to remove the dependency on arrival time in the calculated qMTT maps. The value of qCBF was estimated by using the peak height of the residue function.[29] We did not cross-calibrate the PWI data with an assumed value for CBF for normal white matter or use data for the patient's white matter to provide an assumed normal value, because in this older patient population, white matter is unlikely to be standard. We then scaled the individual perfusion maps at a constant level chosen to encompass the range of parameter values across all subjects to yield a consistent image presentation per parameter across all subjects. The thresholded maps were then converted to Analyze format.

An experienced stroke neuroradiologist outlined any PWI lesions visible on printed color maps (Figure 2) by identifying areas of signal that indicated reduced cerebral perfusion (reduced CBF, abnormal CBV, or increased MTT) compared with the normal perfusion distribution, taking account particularly of any differences between the 2 hemispheres or in the anteroposterior distribution and gray/white matter differences. We did not include areas of increased CBF or CBV in the "perfusion deficit." Each PWI parameter was outlined separately, blinded to all clinical, other imaging, and other PWI data. We then traced the lesion outline onto the Analyze format images by using Analyze version 7.8 and derived PWI lesion volumes by counting the number of voxels within the lesion on all slices on which it was visible. All PWI lesions for a single patient were traced in Analyze in the same session but while blinded to all other information. We defined the DWI/PWI mismatch as the acute PWI lesion volume minus the acute DWI lesion volume and infarct expansion as any increase in size from the acute DWI lesion to the final T2 lesion.

Statistical Analysis

The data were not normally distributed (Kolmogorov-Smirnov test). We compared the median PWI lesion and the PWI/DWI mismatch volumes with the Friedman test (multiple nonparametric related measurements). We compared the proportion of patients with or without DWI/PWI mismatch by PWI processing method by the χ^2 test. We compared the different PWI volumes to DWI lesion volumes and NIHSS score at baseline and T2-weighted imaging final infarct volume and functional outcome (mRS score) at 3 months by linear regression. We used each PWI parameter in turn as the dependent variable, with DWI lesion volume, NIHSS score, T2-

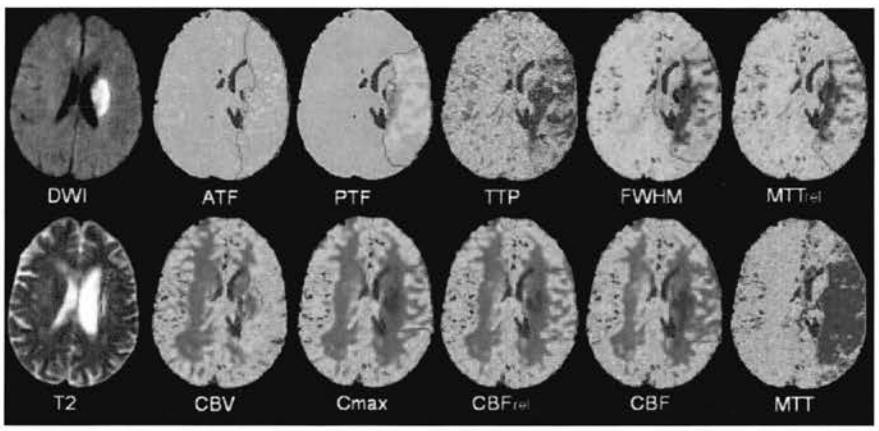


Figure 2. Admission DWI and PWI (10 different perfusion maps generated by the 10 different perfusion processing methods) and 1-month T2-weighted image for the same brain slice from 1 patient. See Table 2 for abbreviations and definitions.

weighted final infarct volume, and mRS score as the independent variables. We transformed the PWI lesion volume data by taking the cube root to minimize the effect of outliers. We used Fisher's exact test to investigate any correlation between the presence or absence of mismatch at baseline and the presence or absence of infarct expansion on the final T2 image. All analyses were performed in SPSS version 13 for Windows.

Results

We recruited 32 patients (13 female, 19 male), whose mean age was 70 years (range, 36 to 93 years). The median time to MRI was 7.3 hours (range, 1.4 to 24 hours). The time to imaging was <6 hours from symptom onset in 12 of 32 (38%), 6 to 12 hours in 8 (25%), and between 12 and 24 hours in 12 (37%). According to the Oxfordshire Community Stroke Project classification,[27] there were 3 lacunar stroke (LACS), 19 partial anterior circulation stroke (PACS), and 10 total anterior circulation stroke (TACS). The median baseline NIHSS score was 7 (range, 1 to 25).

The PWI lesion size varied markedly with the method of calculating the PWI lesion (Table 1 and Figure 2). The median PWI lesion volume varied from 0 voxels (Cmax, rCBF, CBV) to 14 882 voxels (TTP) (Friedman test 121.5, $P<0.0001$). Overall, measurements reflecting MTT (eg, TTP and PTF) produced larger PWI lesions, and measures of CBF gave smaller lesion volumes, with CBV giving the smallest PWI lesions (Table 1). The number of patients with no PWI lesion by at least 1 method (Table 1) varied from 7 of 32 (22%; rMTT, FWHM, PTF) to 19 of 32 (59%; CBV) (χ^2, $P<0.001$). As a consequence of variation in PWI lesion size, the median volume of tissue mismatch varied from 0 (actually, −1849 voxels, CBV) to the smallest positive value of 715 voxels (ATF) to the largest of 9684 voxels (rMTT) (Friedman test 123.8, $P<0.0001$). Four of the perfusion parameters (CBV, rCBF, qCBF, and Cmax) had negative median mismatch values because the median DWI lesion was larger than the PWI lesion. The proportion of patients with mismatch varied considerably (Table 1) from 3 of 32 (9%, CBV) to 23 of 32 (72%; rMTT, FWHM) ($\chi^2=48$, $P<0.0001$).

Only 1 PWI measure, ATF (Table 2), was associated with both baseline clinical severity (NIHSS) and clinical outcome (mRS at 3 months), with a regression slope of 0.209 ($P=0.006$) and 0.049 ($P=0.035$), respectively. No other PWI measures were associated with clinical outcome. Four other PWI measures (Table 2) were associated with baseline NIHSS: PTF, TTP, FWHM, and rMTT. All were relative measures of MTT. Eight PWI measures (Table 2) were associated with radiologic outcome (final T2 infarct size): 5 of MTT (ATF, PTF, TTP, rMTT, and FWHM in order of strength of association), 2 of CBF (rCBF and qCBF), and 1 of CBV (CBV).

Figure 3 shows the variation in the median PWI volumes and the median acute DWI and final T2 lesion volumes. There was no significant relation between the presence or absence of mismatch at baseline and infarct expansion at ≥1 month for any of the PWI parameters by Fisher's exact test (all probability values were >0.183).

Discussion

Different PWI parameters produce very different estimates of abnormal perfusion in the same data from the same patient and hence, very different estimates of the volume of "tissue at risk." If patients with DWI/PWI mismatch only were to receive thrombolysis, then selection based on TTP would result in 20 of 32 (63%) patients receiving treatment, whereas selection on the basis of Cmax would result in only 7 of 32

Table 2. Association Between PWI Lesion Size (in Voxels) and Baseline Clinical Score (NIHSS), Functional Outcome at 3 Months (mRS), and Final Infarct Extent on T2-Weighted MRI Imaging (≥1 Month After Symptom Onset)

	Slope of Linear Regression Line With		
Perfusion Method	Baseline NIHSS	3-Month mRS	T2 Final Infarct Size at ≥1 Month
ATF	0.209 (0.006)	0.049 (0.035)	0.330 (0.002)
PTF	0.210 (0.005)	0.042 (0.068)	0.292 (0.007)
TTP	0.193 (0.006)	0.040 (0.066)	0.286 (0.004)
FWHM	0.180 (0.006)	0.021 (0.313)	0.214 (0.025)
First moment (ie, rMTT)	0.206 (0.005)	0.042 (0.067)	0.303 (0.004)
Cmax	0.147 (0.133)	0.018 (0.549)	0.263 (0.059)
rCBF	0.206 (0.057)	0.035 (0.285)	0.324 (0.036)
qMTT	0.050 (0.456)	0.017 (0.407)	0.162 (0.089)
qCBF	0.098 (0.195)	0.029 (0.202)	0.236 (0.025)
CBV	0.236 (0.066)	0.042 (0.278)	0.392 (0.032)

Significant associations are highlighted in boldface type; *P* values are in parentheses.

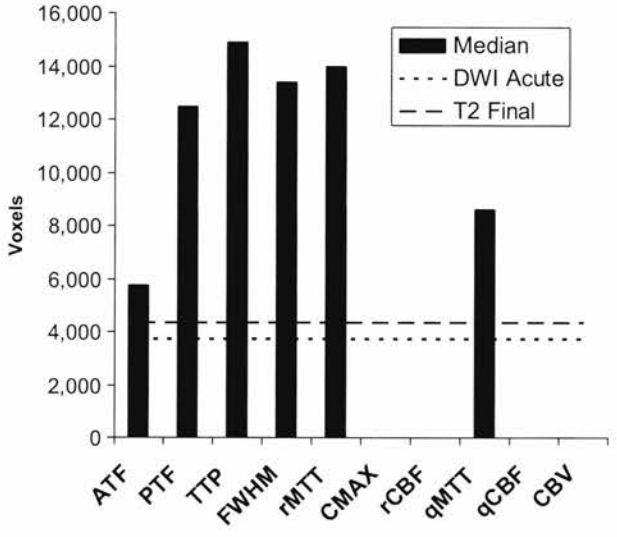


Figure 3. Variation in median perfusion lesion size (voxels) for the 10 different PWI processing methods. The median baseline DWI (DWI acute) and final infarct extent (T2 final) lesion volumes are also indicated. Note the median lesion volumes for Cmax, rCBF, qCBF, and CBV were 0 due to the large proportion of patients with no visible PWI lesion.

(22%) patients being so treated. Such a variation is not acceptable if PWI is to be used to guide treatment in routine clinical practice. However, both of these parameters are commonly quoted in the literature. In this dataset, ATF was the only parameter that was correlated with both clinical (baseline and follow-up) and radiologic parameters, but this finding should be replicated in other datasets. This work also highlights the need to standardize PWI, including the PWI parameter measured, the analysis approach, and the software used.

Nonquantitative PWI parameters have the advantage that they are quick to measure on the scanner console but may introduce unacceptable variability between patients. Quantitative PWI parameters reduce the difference in lesion volume between the PWI parameters but would still result in discrepancies in the number of patients treated: 18 of 32 (56%) with qMTT, 13 of 32 (41%) with qCBF, and 3 of 32 (9%) with qCBV, and require complex off-line processing to produce perfusion parameter maps. There were even differences between relative and quantitative parameters purporting to reflect only MTT or only CBF: with rCBF, 5 of 32 (16%) of patients had mismatch, and with qCBF, 13 of 32 (41%) patients had mismatch; with any of the rMTT measures, 18 of 32 to 23 of 32 (56% to 72%) had mismatch, and with qMTT, 18 of 32 (56%) had mismatch. However, relative measures were better correlated with clinically relevant outcomes.

Our overall important finding was that 5 MR perfusion parameters reflecting MTT (ATF, PTF, FWHM, rMTT, and rCBF) were associated with clinical scores of acute stroke severity, of which 1, also reflecting MTT (though on average producing smaller lesions than noted earlier, ATF), was associated with functional outcome. The correlation of large MTT lesions with baseline NIHSS score presumably means that these PWI lesions are a better indicator of the extent of neurologically "shut-down" tissue (viable and nonviable) at the time of imaging, although they overestimate functional outcome because they include both oligemic but not shut-down tissue as well as "tissue at risk," which recovers.

A wider range of PWI parameters was correlated with final T2 lesion extent, but how useful is this? ATF, PTF, TTP, and rMTT were most closely associated with final T2 lesion extent and FWHM, rCBF, qCBF and CBV less so. However, the final T2 lesion extent may not reflect the total damage within the brain. Histologic evidence of damage may occur outside the T2-visible lesion.[30,31] Functional outcome is more relevant to stroke services and patients. The true final damage being greater than just the T2-visible lesion might explain why, in this study, the correlations between baseline PWI lesion and functional outcome were strongest for rMTT measures.

Our results confirm previous observations that TTP and qMTT are correlated with baseline NIHSS score,[15,20–22] but previous studies compared fewer PWI lesions than in the present study. The maximum PWI parameters compared in previous studies were 9,[18] 6,[12] 4,[17,19] and 3,[13,16] but these studies did not quantify the difference in visible lesion volume or the impact of that difference on DWI/PWI mismatch. Thus, in general, relative measures of MTT were correlated with both baseline stroke severity and clinical functional outcome. These are relatively quick to perform and easy to obtain (no deconvolution required) and therefore are practical in the acute setting.

The fact that we were unable to demonstrate a correlation between the presence/absence of mismatch and the presence/absence of infarct expansion suggests that the presence of mismatch per se is not an ideal criterion to use when selecting patients for acute stroke treatments. About half of the patients without mismatch (either on rMTT or rCBF) may develop infarct growth,[14,32] so the mismatch concept may not identify all "tissue at risk"—DWI-abnormal tissue may recover, and most PWI parameters probably overestimate tissue at risk.

We used visual assessment of the PWI lesions because visual assessment is the fastest method for detecting the acute lesion in the clinical setting. We did not use thresholding/automated lesion edge detection because no consistent threshold has yet been identified.[33] Furthermore, it was unclear how a threshold with NIHSS score or 3-month functional outcome should be derived. The threshold that matches the boundary of the final T2 lesion is relatively straightforward to determine but may not represent the final tissue damage and is of less clinical relevance. However, manual outlining introduces observer variation. Some might disagree on where the boundaries should be drawn. For example, in Figure 2, it would appear that the ATF has produced a large lesion compared with other MTT lesions, whereas Figure 3 indicates that, on average, the ATF produced the smallest of the MTT-like lesions. Similarly, Figure 2 suggests that the CBF lesions are quite large, whereas Figure 3 indicates that, on average, the CBF, CBV, and Cmax lesions were very small or nonexistent. Figure 2 is only intended to illustrate the variation in lesion appearance among the 10 parameters and was chosen because the CBF and CBV lesions were visible, so these may not be truly representative of the average in this cohort. This is a

further reason for validation of these findings in other datasets.

We did not use cross-calibration (scaling to a fixed value of presumed normal white matter) so as to preserve information in the perfusion maps about the underlying perfusion status of all tissue. Although scaling to presumed normal white matter may allow the different PWI parameter images to be scaled directly into the same windowing, in the typical elderly stroke population, the background white matter is often abnormal, so applying an arbitrary scaling factor might not improve image accuracy or interpretability. It might also skew the scaling of some parameters so as to actually reduce the visibility of some lesions. Instead, we normalized the individual perfusion parameter maps to the average value of that parameter in the region used to define the AIF because AIF (eg, maximum contrast value, area under the curve) is linearly associated with the corresponding tissue parameters Cmax, rCBV, etc. Thus, normalization by the average parameter value within the AIF region of interest attempts to counteract variation in the calculated relative perfusion parameters due to the differing arrival rate of contrast in the brain between patients, thereby more effectively achieving standardization, as would scaling to presumed normal white matter.

We included data for all patients in the statistical analysis, whether there was a PWI lesion present or not, to be able to determine the relative predictive values of the different PWI processing methods, including those that less frequently produce a PWI lesion. Choosing a PWI parameter that has a high probability of not producing a visible lesion, while not knowing what the absence of a lesion means, is unlikely to be helpful. We did not use an explicit correction for multiple comparisons, but the effect of doing so can be seen by ignoring probability values >0.01 in Table 2. Other publications did not make clear whether all patients, or just those with visible PWI lesions, were included, which may explain previous discrepancies. Excluding patients without PWI lesions would result in a very skewed comparison; eg, in our series, some PWI parameters (eg, TTP) might contribute 23 of 32 patients, whereas others like rCBF or CBV might only contribute 13 of 32. Excluding patients without PWI lesions would provide no information on the relevance of a PWI-negative examination. In the acute situation, with limited time for multiple postprocessing attempts, one needs to use the PWI parameter that is most likely to inform decision making.

There is an urgent need to standardize methods for processing perfusion data. This includes deciding on not only which PWI lesion to measure but also how to measure it and which software should be used. Manufacturer processing algorithms may differ and could produce variations in lesion size between scanners, even when each center is producing maps of the same PWI lesion. Therefore, there is a need to standardize software also. Perhaps there is a need for a standard PWI test dataset that could be used to calibrate different software. This might at least reduce some of the variation between PWI lesions. Relative measures of MTT, which are quick to perform and are associated with stroke severity and functional outcome, may be more useful than PWI parameters that are related closely to radiologic surrogates. Similar variation may arise if computed tomography perfusion data are processed in different ways with different manufacturer's software. Similar studies should be performed with computed tomography perfusion as a matter of urgency, as computed tomography perfusion is rapidly increasing in popularity and is much more accessible than MRI.

Sources of Funding

This study was funded by the Scottish Executive's Chief Scientist Office (reference No. C2B/4/14), the Health Foundation (Dr I. Kane), the Row Fogo Charitable Trust (Dr. Armitage), the UK Stroke Association (reference No. TSA 02/01), the Royal Society of Edinburgh/Lloyds TSB Foundation (studentship for Dr C. Rivers), and the Cohen Charitable Trust (Dr Carpenter). The work was conducted at the SFC Brain Imaging Research Centre, University of Edinburgh (www.dcn.ed.ac.uk/bic).

Disclosures

None.

References

1. Hacke W, Albers G, Al Rawi Y, Bogousslavsky J, Davalos A, Eliasziw M, Fischer M, Furlan A, Kaste M, Lees KR, Soehngen M, Warach S. The Desmoteplase in Acute Ischemic Stroke Trial (DIAS): a phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. *Stroke*. 2005;36:66–73.
2. Grandin CB. Assessment of brain perfusion with MRI: methodology and application to acute stroke. *Neuroradiology*. 2003;45:755–766.
3. Hjort N, Butcher K, Davis SM, Kidwell CS, Koroshetz WJ, Rother J, Schellinger PD, Warach S, Ostergaard L. Magnetic resonance imaging criteria for thrombolysis in acute cerebral infarct. *Stroke*. 2005;36:388–397.
4. Ostergaard L, Weisskoff RM, Chesler D, Gyldensted C, Rosen BR. High resolution measurement of cerebral blood flow using intravascular tracer bolus passages, part I: mathematical approach and statistical analysis. *Magn Reson Med*. 1996;36:715–725.
5. Calamante F, Gadian DG, Connelly A. Quantification of perfusion using bolus tracking magnetic resonance imaging in stroke: assumptions, limitations, and potential implications for clinical use. *Stroke*. 2002;33:1146–1151.
6. Wintermark M, Sesay M, Barbier E, Borbely K, Dillon WP, Eastwood JD, Glenn TC, Grandin CB, Pedraza S, Soustiel JF, Nariai T, Zaharchuk G, Caille JM, Dousset V, Yonas H. Comparative overview of brain perfusion imaging techniques. *Stroke*. 2005;36:e83–e99.
7. Perthen JE, Calamante F, Gadian DG, Connelly A. Is quantification of bolus tracking MRI reliable without deconvolution? *Magn Reson Med*. 2002;47:61–67.
8. Thijs VN, Somford DM, Bammer R, Robberecht W, Moseley ME, Alberts GW. Influence of arterial input function on hypoperfusion volumes measured with perfusion-weighted imaging. *Stroke*. 2004;35:94–98.
9. Rose SE, Janke AL, Griffin M, Finnigan S, Chalk JB. Improved prediction of final infarct volume using bolus delay-corrected perfusion-weighted MRI: implications for the ischemic penumbra. *Stroke*. 2004;35:2466–2471.
10. Latchaw RE, Yonas H, Hunter GJ, Yuh WT, Ueda T, Sorensen AG, Sunshine JL, Biller J, Wechsler L, Higashida R, Hademenos G. Guidelines and recommendations for perfusion imaging in cerebral ischemia: a scientific statement for healthcare professionals by the writing group on perfusion imaging, from the Council on Cardiovascular Radiology of the American Heart Association. *Stroke*. 2003;34:1084–1104.
11. Carpenter T, Armitage PA, Bastin ME, Wardlaw JM. DSC perfusion MRI: quantification and reduction of systematic errors arising in areas of reduced cerebral blood flow. *Magn Reson Med*. 2006;55:1342–1349.
12. Yamada K, Wu O, Gonzalez RG, Bakker D, Ostergaard L, Copen WA, Weisskoff RM, Rosen BR, Yagi K, Nishimura T, Sorensen AG. Magnetic resonance perfusion-weighted imaging of acute cerebral infarction: effect of the calculation methods and underlying vasculopathy. *Stroke*. 2002;33:87–94.
13. Rose SE, Chalk JB, Griffin MP, Janke AL, Chen F, McLachan GJ, Peel D, Zelaya FO, Markus HS, Jones DK, Simmons A, O'Sullivan M, Jarosz JM, Strugnell W, Doddrell DM, Semple J. MRI based diffusion and

perfusion predictive model to estimate stroke evolution. *Magn Reson Imaging*. 2001;19:1043–1053.
14. Rivers CS, Wardlaw JM, Armitage P, Bastin ME, Carpenter TK, Cvoro V, Hand PJ, Dennis MS. Do acute diffusion- and perfusion-weighted MRI lesions identify final infarct volume in ischemic stroke? *Stroke*. 2006;37:98–104.
15. Parsons MW, Barber PA, Chalk J, Darby DG, Rose S, Desmond PM, Gerraty RP, Tress BM, Wright PM, Donnan GA, Davis SM. Diffusion- and perfusion-weighted MRI response to thrombolysis in stroke. *Ann Neurol*. 2002;51:28–37.
16. Sorensen AG, Copen WA, Ostergaard L, Buonanno FS, Gonzalez RG, Rordorf G, Rosen BR, Schwamm LH, Weisskoff RM, Koroshetz WJ. Hyperacute stroke: simultaneous measurement of relative cerebral blood volume, relative cerebral blood flow, and mean tissue transit time. *Radiology*. 1999;210:519–527.
17. Butcher KS, Parsons M, MacGregor L, Barber PA, Chalk J, Bladin C, Levi C, Kimber T, Schultz D, Fink J, Tress B, Donnan G, Davis S, for the EPITHET Investigators. Refining the perfusion-diffusion mismatch hypothesis. *Stroke*. 2005;36:1153–1159.
18. Grandin CB, Duprez TP, Smith AM, Oppenheim C, Peeters A, Robert AR, Cosnard G. Which MR-derived perfusion parameters are the best predictors of infarct growth in hyperacute stroke? comparative study between relative and quantitative measurements. *Radiology*. 2002;223:361–370.
19. Schellinger PD, Latour LL, Wu CS, Chalela JA, Warach S. The association between neurological deficit in acute ischemic stroke and mean transit time: comparison of four different perfusion MRI algorithms. *Neuroradiology* 2006;48:69–77.
20. Beaulieu C, de Crespigny A, Tong DC, Moseley ME, Albers GW, Marks MP. Longitudinal magnetic resonance imaging study of perfusion and diffusion in stroke: evolution of lesion volume and correlation with clinical outcome. *Ann Neurol*. 1999;46:568–578.
21. Derex L, Nighoghossian N, Hermier M, Adeleine P, Berthezene Y, Philippeau F, Honnorat J, Froment JC, Trouillas P. Influence of pre-treatment MRI parameters on clinical outcome, recanalization and infarct size in 49 stroke patients treated by intravenous tissue plasminogen activator. *J Neurol Sci*. 2004;225:3–9.
22. Barber PA, Parsons MW, Desmond PM, Bennett DA, Donnan GA, Tress BM, Davis SM. The use of PWI and DWI measures in the design of 'proof-of-concept' stroke trials. *J Neuroimaging*. 2004;14:123–132.
23. Rohl L, Geday J, Ostergaard L, Simonsen CZ, Vestergaard-Poulsen P, Andersen G, Le Bihan D, Gyldensted C. Correlation between diffusion- and perfusion-weighted MRI and neurological deficit measured by the Scandinavian Stroke Scale and Barthel Index in hyperacute subcortical stroke (< or = 6 hours). *Cerebrovasc Dis*. 2001;12:203–213.
24. Shih LC, Saver JL, Alger JR, Starkman S, Leary MC, Vinuela F, Duckwiler G, Gobin YP, Jahan R, Villablanca JP, Vespa PM, Kidwell CS. Perfusion-weighted magnetic resonance imaging thresholds identifying core, irreversibly infarcted tissue. *Stroke*. 2003;34:1425–1430.
25. Butcher K, Parsons M, Baird T, Barber A, Donnan G, Desmond P, Tress B, Davis S. Perfusion thresholds in acute stroke thrombolysis. *Stroke*. 2003;34:2159–2164.
26. Chalela JA, Kang D-W, Luby M, Ezzeddine M, Latour LL, Todd JW, Dunn B, Warach S. Early MRI findings in patients receiving tissue plasminogen activator predict outcome: insights into the pathophysiology of acute stroke in the thrombolysis era. *Ann Neurol*. 2004;55:105–112.
27. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet*. 1991;337:1521–1526.
28. Ostergaard L, Sorensen AG, Kwong KK, Weisskoff RM, Gyldensted C, Rosen BR. High resolution measurement of cerebral blood flow using intravascular tracer bolus passages, part II: experimental comparison and preliminary results. *Magn Reson Med*. 1996;36:726–736.
29. Wu O, Ostergaard L, Weisskoff RM, Benner T, Rosen BR, Sorensen AG. Tracer arrival timing-insensitive technique for estimating flow in MR perfusion-weighted imaging using singular value decomposition with a block-circulant deconvolution matrix. *Magn Reson Med*. 2003;50:164–174.
30. Baron JC. How healthy is the acutely reperfused ischemic penumbra? *Cerebrovasc Dis* 2005;20(suppl 2):25–31.
31. Price CJ, Wang D, Menon DK, Guadagno JV, Cleij M, Fryer T, Aigbirhio F, Baron JC, Warburton EA. Intrinsic activated microglia map to the peri-infarct zone in the subacute phase of ischemic stroke. *Stroke*. 2006;37:1749–1753.
32. Kane I, Sandercock P, Wardlaw J. Magnetic resonance perfusion diffusion mismatch and thrombolysis in acute ischaemic stroke: a systematic review of the evidence to date. *J Neurol Neurosurg Psychiatry*. 2007;78:485–491.
33. Bandera E, Botteri M, Minelli C, Sutton A, Abrams KR, Latronico N. Cerebral blood flow threshold of ischemic penumbra and infarct core in acute ischemic stroke: a systematic review. *Stroke*. 2006;37:1334–1339.

Magnetic resonance perfusion diffusion mismatch and thrombolysis in acute ischaemic stroke: a systematic review of the evidence to date

I Kane, P Sandercock and J Wardlaw

J. Neurol. Neurosurg. Psychiatry 2007;78;485-491; originally published online 20 Oct 2006;
doi:10.1136/jnnp.2006.100347

PAPER

Magnetic resonance perfusion diffusion mismatch and thrombolysis in acute ischaemic stroke: a systematic review of the evidence to date

I Kane, P Sandercock, J Wardlaw

See Editorial Commentary, p 443

J Neurol Neurosurg Psychiatry 2007;**78**:485–490. doi: 10.1136/jnnp.2006.100347

See end of article for authors' affiliations

Correspondence to: Professor J Wardlaw, Division of Clinical Neurosciences, Western General Hospital, Edinburgh EH4 2XU, UK; jwardlaw@staffmail.ed.ac.uk

Received 18 June 2006
Revised 11 October 2006
Accepted 12 October 2006
Published Online First 20 October 2006

Background: The mismatch between perfusion and diffusion lesions on magnetic resonance perfusion-weighted imaging (PWI)/diffusion-weighted imaging (DWI) may help identify patients for thrombolysis. Evidence underlying this hypothesis was assessed.

Methods: All papers describing magnetic resonance PWI/DWI findings in patients with acute ischaemic stroke, and their functional and/or radiological outcome at 1 month, with or without thrombolysis were systematically reviewed.

Results: 11 papers fulfilled the inclusion criteria. Among these, there were 5 different mismatch definitions and at least 7 different PWI methods. Only 3 papers including 61 patients with and 18 without mismatch provided data on mismatch, outcome and influence of thrombolysis. Mismatch (*v* no mismatch) without thrombolysis was associated with a non-significant twofold increase in the odds of infarct expansion (odds ratio (OR) 2.2, 95% confidence interval (CI) 0.34 to 14.1), which did not change with thrombolysis (OR 2.0, 95% CI 0.37 to 10.9). Half of the patients without mismatch also had infarct growth (with or without thrombolysis). No data were available on functional outcome.

Conclusions: Standardised definitions of mismatch and perfusion are needed. Infarct growth may occur even in the absence of mismatch. Currently, data available on mismatch are too limited to guide thrombolysis in routine practice. More data are needed from studies including patients with and without mismatch, and randomised treatment allocation, to determine the role of mismatch.

Ischaemic stroke is a global problem, for which few acute treatments are available. Thrombolysis has to be given rapidly and, when guided by plain computed tomography scan of the brain, carries a risk of intracranial haemorrhage. Imaging the mismatch between diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) on magnetic resonance imaging (MRI) (or presumed reversible ischaemia on computed tomography perfusion[1]) might help identify patients with tissue at risk of infarction (even beyond the current 3 h time window), thereby avoiding thrombolysis in those with little chance of benefit.[2 3] These techniques are used increasingly where technology is available, and in acute-stroke trials (http://www.strokecenter.org/trials).[4]

The increasing use of this approach in trials and routine practice suggests that there are clear definitions of what constitutes mismatch and substantial evidence to justify its use. However, it is now known that the DWI lesion is not irreversible (initial DWI lesions may disappear spontaneously or after thrombolysis[5]), and that the appearance of PWI lesion depends on which of the many methods were used to calculate it. Different perfusion parameters (eg, mean transit time (MTT), regional cerebral blood flow[6] and arterial input function[7]) give different perfusion lesion volumes in the same patient. Thus, it is unclear whether the presence (*v* absence) of mismatch affects prognosis. If mismatch is to be used to select patients for treatment, then the key point is to determine whether thrombolysis has a greater effect in the presence than in the absence of mismatch. This requires a randomised controlled trial in which patients with and without mismatch are randomly selected to receive thrombolysis or control treatment, an expensive and difficult undertaking given the large sample size needed.[8]

As there is already a considerable body of literature available on the magnetic resonance mismatch concept, we undertook this systematic review to assess all current evidence on the effect of magnetic resonance PWI/DWI mismatch in patients with acute ischaemic stroke on outcome (clinical and radiological) and whether this is modified by thrombolysis. We set rigorous prespecified inclusion and exclusion criteria based on scientific principles for observational studies and randomised trials to minimise bias.

METHODS

Design

We sought papers describing PWI/DWI mismatch and outcome in the presence or absence of thrombolysis. We included papers published in full to obtain detailed methodological data and results.

Search strategy

We developed a search strategy with the Cochrane Stroke Group for articles published between January 1996 and May 2005. We searched Medline and EMBASE (using the terms "diffusion weighted", "perfusion weighted", "thrombolysis" and "magnetic resonance imaging", exploded to maximise findings) and reference lists in the identified articles for further relevant papers.

Inclusion criteria

We included prospective studies of human acute stroke, of at least 20 patients, imaged at presentation with acute stroke using magnetic resonance, DWI and PWI, with clinical

Abbreviations: DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging; mRS, modified Rankin Score; MTT, mean transit time; NIHSS, National Institutes of Health Score; PWI, perfusion-weighted imaging; rt-PA, recombinant tissue-type plasminogen activator

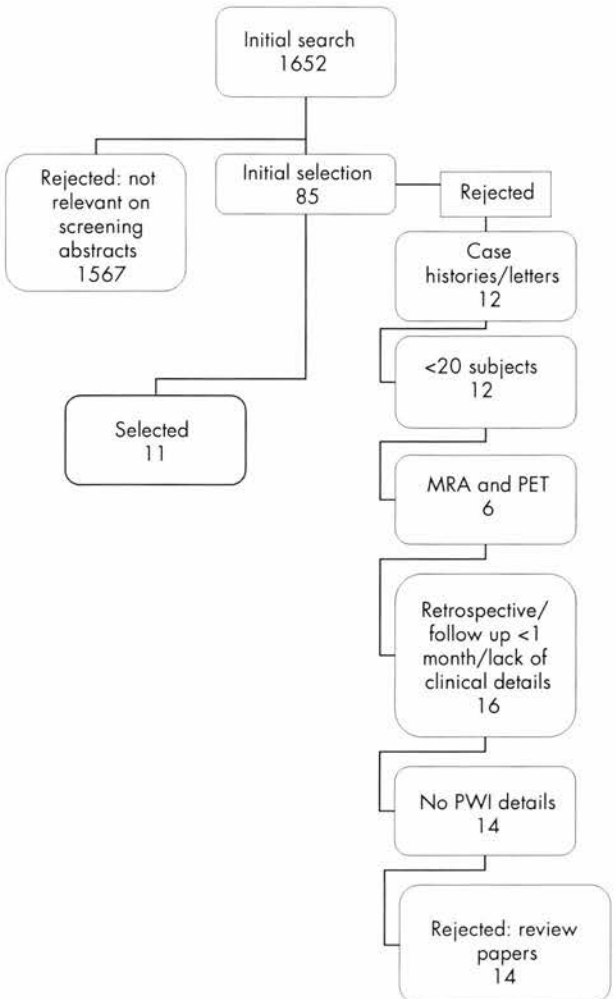


Figure 1 Selection of papers for systematic review. MRA, magnetic resonance angiography; PET, positron emission tomography; PWI, perfusion-weighted imaging.

assessment at baseline and follow-up at least 1 month after stroke using a recognised assessment scale, and where possible radiological follow-up, in which patients did or did not receive thrombolysis.

Exclusion criteria

We excluded articles published before 1996 (before that neither magnetic resonance PWI/DWI nor thrombolysis was widely used in acute stroke), retrospective studies (because of the potential for bias), with <20 patients (very small sample sizes are prone to bias and provide little robust data to inform clinical practice), and with functional and/or radiological outcome assessed at less than a month after stroke (before that would be too early to assess functional outcome; radiologically, ischaemic lesions may still be evolving,[9] "fogging" may cause underestimation,[10] and oedema may cause overestimation of the final lesion volume[11]).

Data extraction

Data were collected on a standardised assessment form by one reviewer. Queries were independently checked by another reviewer. We collected the sample size, patients' clinical characteristics, clinical scores (eg, National Institutes of Health Score (NIHSS)), time from onset of symptom to imaging, details of the magnetic resonance sequences performed and post-processing techniques, definition of PWI/DWI mismatch, evidence of infarct expansion (increase in the lesion volume from the acute baseline DWI to final T_2), whether interpretation of the magnetic resonance images was blinded to clinical details or imaging, details of patients excluded from analysis, whether administration of thrombolysis was randomised or not, and any information on functional or radiological outcome in those who received or did not receive thrombolysis with or without PWI/DWI mismatch. We compared imaging at presentation with final follow-up performed at 1 month or more. We did not examine scan data from intermediary time points (if available) because they are unreliable for estimation of functional outcome or final infarct extent (see above). We were careful to avoid including duplicate publications of the same patients. We defined poor functional outcome as modified Rankin Score (mRS) ≥ 1 or Barthel Index<90.

Analysis

We summarised study population demographics, proportions with or without mismatch, number treated with thrombolysis, with poor functional outcome or infarct expansion. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to determine associations between mismatch, infarct expansion, functional outcome and any influence of thrombolysis. We aimed at comparing functional and radiological outcomes in patients with mismatch with those without mismatch, and to determine whether thrombolysis changed the relationship between mismatch and functional or radiological outcome.

RESULTS

The search identified 1652 papers on any aspect of DWI and PWI, of which 85 were potentially relevant to DWI/PWI mismatch and outcome with or without thrombolysis. Eleven papers (641 patients) fulfilled all prespecified inclusion criteria (for reasons for rejection, often more than one reason, see fig 1).

Ten included reports[11–20] were prospective observational studies, and one[4] was a placebo-controlled, double-blind, randomised, dose-finding phase II trial of desmoteplase. These papers derive from six research groups. Median time to baseline magnetic resonance imaging ranged from 1.5 to 6 h after stroke. Seven papers had radiological follow-up at 1 month or more[11–16] in most patients (table 1).

The most common baseline clinical score was the NIHSS, used in all but two papers,[19 20] by an individual explicitly stated to be trained in its use. In all but one paper,[11] other scores (eg, Barthel Index and mRS) were recorded at follow-up. Eight papers gave incomplete details of blinding of clinical and radiological assessors. Three papers (27%)[17 18 20] did not mention blinding at all.

Measurement of perfusion lesion

All groups used gadolinium-based dynamic susceptibility contrast imaging to assess perfusion, the dose varying from 0.1 to 0.2 mmol/kg. The method for perfusion lesion assessment varied: four papers calculated time to peak[11 16 18 20]; the others used some form of MTT measurement, quantitative in three cases (table 2).[12 14 15]

Assessment of perfusion/diffusion mismatch

There was no consistent definition of mismatch. Among the 11 papers from 6 research groups, there were 5 different definitions of mismatch. Mismatch was determined by "visual inspection" in two studies,[4 20] and by measuring lesion volumes on a workstation in the rest, using various lesion boundary definitions (eg, MTT >4 s compared with the contralateral side) (table 2).

Table 1 Methodological details of included studies

Author	Publication date	Sample size	Incomplete imaging*/died	Clinical score	Other outcome scores at ⩾ 1 month	Time to acute MRI	Time to final MRI (days)
Beaulieu C[11]	1999	21	6	NIHSS	None	Mean (SD) 5.2 (1.2) h	Mean (SD) 42 (22)
Barber P[12]	2004	49	4	NIHSS	BI and mRS	Median 4 h (IQR 3.3–5)	Median 84 (IQR 70–89)
Rohl L[14]	2001	22	1	SSS	BI	Mean 5 h	Range 22–42 (1@102)
Parsons M[15]	2002	40	4	NIHSS	mRS	Treatment group mean (SD) 3.8 (1.2) h Controls 3.7 (1.2)	Treatment group mean (SD) 77.9 (17.1) Controls 81.4 (12)
Barber P[13]	1999	26	5	CNS	BI and mRS	Mean (SD) 12.1 (7.6) h	Mean (SD) 90.1 (30.3)
Hacke W[4†]	2005	104	18	NIHSS	BI and mRS	Median 325 min	Due at 30
Derex L[16]	2004	49	5	NIHSS	mRS	Mean (SD) 3 h 37 (52) mins	Due at 60
Schellinger P[17]	2001	51	1	NIHSS and SSS	BI and mRS	Mean (SD) 3.33 (1.29) h	Due at 5
Chalela J[19]	2004	42	5	NIHSS	mRS	Median to: DWI 84 min, PWI 92 min	Median to: DWI 253 mins, PWI 269 mins
Rother J[18]	2002	139	10	NIHSS	mRS	Median 180 min (75–360)	Due at 7
Ribo M[20]	2005	122	Not specified	NIHSS	mRS	Median group A: 136 min (60–180); group B: 223 min (185–360)	CT 24–48 h

BI, Barthel Index; CNS, central nervous system; mRS, modified Rankin Score; NIHSS, National Institutes of Health Score; SSS, Scandinavian Stroke Scale.

Overall assessment of PWI/DWI mismatch on outcome and effect of thrombolysis

Among the 11 studies initially included in the review, we were able to extract data regarding mismatch and outcome (without or with thrombolysis) only from three.[11 14 15] Although all of these studies recruited at least 20 patients, not all of the original sample contributed to the data, mainly due to incomplete imaging (table 1). In the rest, it was not possible to separate the results for thrombolysis for patients with and those without thrombolysis from those of patients without mismatch,[12 16 18] although some did have outcome data. Some papers only reported recanalisation and outcome, not mismatch.[13 17] All three papers with usable data included patients with and without mismatch, and two[11 15] examined the effects of thrombolysis. In total, there were 61 patients with, and 18 without mismatch. Final follow-up scans were not available (patient died or scan was not performed) for 7 of 61 patients, some with mismatch at baseline and some without. Only two papers reported functional outcome.[14 15]

PWI/DWI mismatch and outcome: no thrombolysis

Two papers[14 15] provided data on mismatch and functional outcome, and three[11 14 15] on infarct expansion at 1 month or more (total n = 50 patients) in patients who did not receive thrombolysis: 41 of 50 patients had mismatch (by any definition), of whom 33 (80%) had any infarct expansion and 6 (20%) did not (follow-up scans were missing for two patients); 9 of 50 patients had no mismatch, of whom 5 (56%) developed infarct expansion. Therefore, mismatch was associated with a non-significant twofold increase in the odds of infarct expansion (OR 2.2, 95% CI 0.34 to 14.1). Note that the wide CIs include the possibility of both a reduction and an increase in the risk. Data on functional outcome were not presented in a way that allowed calculation of ORs. However, the mean Barthel Index or mRS at final follow-up was non-significantly worse in those with mismatch at baseline than in those without mismatch (table 3, fig 2).

PWI/DWI mismatch and outcome: with thrombolysis

Two studies provided data on mismatch, radiological outcome (but only one on functional outcome[15]) and thrombolysis (total n = 29).[11 15] Note that in one,[11] thrombolysis was actually given immediately before the first MRI, meaning that the baseline scans may have already been affected by thrombolysis, thus making interpretations about the effects of recombinant tissue-type plasminogen activator (rt-PA) in these patients difficult.

Table 2 Definition and frequency of PWI/DWI mismatch in studies meeting methodological inclusion criteria

Author	Definition of PWI/DWI mismatch	Workstation/ visual measurement	Number with mismatch	Dose of gadolinium (mmol/kg)*	Perfusion measure	Number treated with thrombolysis
Beaulieu C[11]	Differences of at least ±10%	Workstation	11 (52%) PWI>DWI 7 (33%) PWI ⩽ DWI	0.2	TTP*	11 (52%)
Barber P[12]	PWI >acute DWI	Workstation	77%	0.1	MTT†	12 (24%)
Rohl L[14]	>10% difference between acute DWI lesion and MTT map lesion	Workstation	18 (82%)	0.1	MTT†	None
Parsons M[15]	Acute MTT (delay >4 s) lesion volume 20%>DWI lesion	Workstation	16 (84%) treatment group 16 (76%) control group	0.2	MTT†	19 (48%)
Barber P[13]	PWI >acute DWI	Workstation	14 (56%)	0.1	rMTT*	None
Hacke W[4]	⩾20% PWI/DWI mismatch	Visual initially then workstation	104 (100%)	0.1	MTT*	75 (72%)
Derex L[16]	PWI/DWI volume ratio of ⩾1.2	Workstation	42 (85%)	0.1	TTP*	All (100%)
Schellinger P[17]	PWI/DWI volume ratio of >1.2	Workstation	40/51 (78%)	25 ml	MTT*	24 (47%)
Chalela J[19]	MTT lesion minus DWI lesion at each time point.	Workstation	Not specified	0.1	MTT*	All (100%)
Rother J[18]	PWI/DWI volume ratio of >1.2	Workstation	120/139 (86.3%)	25 ml	TTP*	76 (55%)
Ribo M[20]	Group B: DWI/PWI mismatch >50%	Visual	Group B:43/122 (35%)	Bolus	TTP*	All (100%)

DWI, diffusion-weighted imaging; MTT, mean transit time; PWI, perfusion-weighted imaging; TTP, time to peak.
*Semi-quantitative measure.

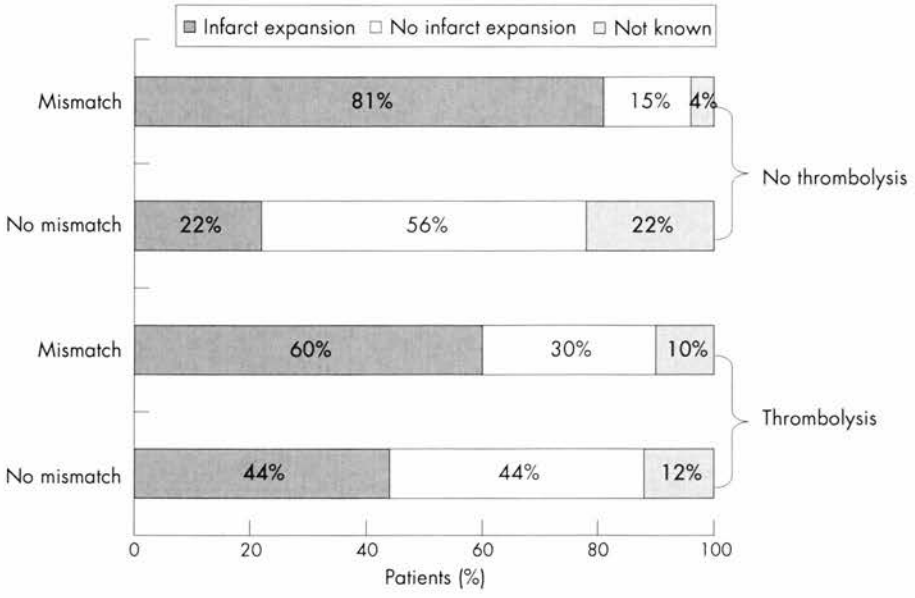


Figure 2 Fate of the acute magnetic resonance diffusion-weighted imaging lesion in patients with or without mismatch and/or thrombolysis.

However, we included these data on the basis that the effects of rt-PA are not instantaneous. With this in mind, we can conclude that 12 of 20 (60%) patients with mismatch had infarct growth (data missing for two patients) after thrombolysis, whereas 8 of 20 (40%) did not; 4 of 9 (44%) patients without mismatch had infarct expansion (data missing for one patient) with thrombolysis, 5 of 9 (50%) did not. Thus, there was a similar OR for the risk of infarct expansion in the presence of mismatch with thrombolysis (OR 2, 95% CI 0.37 to 10.9) as that without thrombolysis. The wide CIs include the possibility of either reduction or increase in the risk. The one paper with clinical outcome data[15] compared patients with mismatch who received thrombolysis with 16 historical controls with mismatch who did not receive thrombolysis (table 2), but such historical comparisons are prone to bias and are unreliable. Hence, there are no meaningful data on clinical outcomes in patients with or without mismatch in the presence of thrombolysis (table 4, fig 2).

To account for missing follow-up scans, we calculated "best" (assuming that all the patients with missing data did not have infarct expansion) and "worst" (assuming that all the patients with missing data did have infarct expansion) case scenarios (tables 3 and 4). In the best case scenario, mismatch without thrombolysis was associated with a 14-fold increase in the risk of infarct expansion (OR 14.4, 95% CI 2.5 to 83.2), and mismatch with thrombolysis was associated with a twofold increase in the risk of infarct expansion (OR 2.5, 95% CI 0.48 to 12.9). In the worst case scenario, mismatch without thrombolysis was associated with a sevenfold increase in the risk of infarct expansion (OR 7.3, 95% CI 1.5 to 35.2) and mismatch with thrombolysis was associated with a twofold increase in the risk of infarct expansion (OR 1.86, 95% CI 0.37 to 9.49). However, note that the marked change in OR when outcome changed for only a few patients, combined with the wide CIs, indicates that these data, although promising, are unreliable and highly unstable, and require confirmation in large, methodologically sound studies.

DISCUSSION

This review highlights the urgent need for more data to confirm and refine or refute the mismatch concept, and for standardisation of methods to assess mismatch and PWI lesions. Despite more than 1500 papers reporting some aspect of PWI/DWI mismatch, many advocating its use to identify "tissue at risk", there is very limited evidence even to say whether patients with mismatch have a different outcome from those without mismatch, or crucially, what the effect of rt-PA might be. These data were very fragmented and difficult to manage systematically, and there was little that was ultimately usable. Indeed, some might argue that we should have excluded even more, such as the study that performed magnetic resonance DWI/PWI just after rt-PA. However, we reasoned that others may have adopted the same approach without explicitly mentioning it, and that this was a relatively minor flaw among many more fundamental ones. We did not seek additional unpublished information from authors because personal communications are not peer-reviewed and may be misleading, and the published literature is the accessible knowledge base. Therefore, current opinion should not be based on information that is absent from the published literature, because unpublished information is not accessible to all to evaluate and form their own opinion.

The inclusion criteria for the review included studies with >20 patients because of the well-known problem of bias in smaller studies. Other criteria such as type and site of arterial occlusion were outside the scope of this systematic review and were therefore not included.

The lack of standardisation of the DWI and PWI imaging is a major problem. Perfusion imaging used different doses of contrast and different processing techniques, and measured different parameters in different ways. It is unclear whether one should use complex and time-consuming methods of analysis of PWI data incorporating the arterial input function (and if so which[7]) or, as suggested recently, use simpler semiquantitative methods such as T_{max}, which may be just as good.[21] There was no consistency in the definition or measurement of mismatch either. The 5 definitions from the 6 research groups ranged from a PWI lesion >acute DWI lesion[12 13 19] to a PWI lesion 50% >acute DWI lesion.[20] Two papers specified visual inspection, but the others measured lesion volume on a workstation. Few studies[12 13 16] commented on the observer reliability of any of these PWI/DWI assessments.

Nonetheless, the pattern suggested by fig 2 does indeed, rather tantalisingly, suggest that patients with mismatch are

Table 3 Details of patients with and without mismatch not treated with thrombolysis

Author	Number with mismatch	Number without mismatch	Baseline NIHSS: mismatch Mean (range)	Baseline NIHSS: no mismatch Mean (range)	Outcome score: mismatch Mean (range)	Outcome score: no mismatch Mean (range)	Mismatch and no infarct expansion	Mismatch and infarct expansion	No mismatch and no infarct expansion	No mismatch and infarct expansion	No final follow-up scan
Beaulieu C[11]	7	1	14 (6–24)	7	No data	No data	2	3	1	0	2 (both mismatch)
Rohl L[14]	18	3	SSS 38 (11–56)	SSS 41(31–56)	BI 86 (25–100)	BI 98 (94–100)	3	15	1	2	0
Parsons M[15]	16	5	15 (7–20)	16(10–20)	mRS 3 (0–6)	mRS 2 (1–4)	1	15	3	0	2 (both no mismatch)
Total	41	9					6 (15%)	33 (81%)	5 (56%)	2 (22%)	4
Best case* scenario							8 (20%)	33 (81%)	7 (78%)	2 (22%)	0
Worst case scenario†							6 (15%)	35 (85%)	5 (56%)	4 (44%)	0

BI, Barthel Index; mRS, modified Rankin Score; NIHSS, National Institutes of Health Score; SSS, Scandinavian Stroke Scale.
*Assumes no infarct growth occurred in patients with missing scans.
†Assumes infarct growth occurred in patients with missing scans.

Table 4 Details of patients with and without mismatch treated with thrombolysis

Author	Number with mismatch	Number without mismatch	Baseline NIHSS: mismatch Mean (range)	Baseline NIHSS: no mismatch Mean (range)	Outcome score: mismatch	Outcome score: no mismatch	Mismatch and no infarct expansion	Mismatch and infarct expansion	No mismatch and no infarct expansion	No mismatch and infarct expansion	No final follow-up scan
Beaulieu C[11]	4	6	14 (8–24)	7 (2–14)	No data	No data	0	3	3	3	1 (mismatch patient)
Parsons M[15]	16	3	15 (9–220	15 (12–19)	mRS 2 (1–6)	mRS 4 (2–6)	6	9	1	1	2 (1 mismatch, 1 without)
Total	20	9					6 (30%)	12 (60%)	4 (44%)	4 (44%)	3
Best case scenario*							8 (40%)	12 (60%)	5 (56%)	4 (44%)	0
Worst case scenario†							6 (30%)	14 (70%)	4 (44%)	5 (56%)	0

mRS, modified Rankin Score; NIHSS, National Institutes of Health Score.
*Assumes no infarct growth occurred in patients with missing scans.
†Assumes infarct growth occurred in patients with missing scans.

more likely than patients without mismatch to have infarct growth, and that the proportion of patients with mismatch who had infarct growth may be reduced by thrombolysis. However, there are no data on functional outcome (more relevant than radiological outcomes), and these data are not from randomised comparisons, but from rather small observational studies of different patients with widely differing definitions, sometimes with historical controls. Clearly, some patients without mismatch definitely get infarct growth, so the absence of mismatch does not mean that there is no "tissue at risk" of infarct growth. This suggests little justification for excluding patients without mismatch either from routine acute stroke treatments or possibly from trials. If the mismatch theory is correct, then there is an urgent need to gather more robust evidence to support its use.

To move forward, common standards and definitions for mismatch are needed. A large randomised trial of thrombolysis against control in patients with and without mismatch is needed to reliably determine whether the degree of mismatch really does influence response to thrombolytic treatment. The EPITHET (http://www.strokecenter.org/trials) study has this design, although patients are recruited on the basis of their computed tomography results and not on the basis of magnetic resonance mismatch, which may lead to an imbalance of patients with and without mismatch in the treatment and control groups. Certainly, until there is better evidence, patients without mismatch should probably not be denied any routine acute treatments, because about 50% will get infarct expansion that might be prevented by acute treatments such as thrombolysis. The lack of data underpinning the mismatch theory should also be acknowledged in the design of any future trials of novel therapeutic agents (eg, new thrombolytic or neuroprotective agents) planning to use mismatch as an inclusion criterion. These problems also apply to computed tomography perfusion. It certainly should not be assumed that presumed reversible ischaemia on computed tomography perfusion identifies "tissue at risk" without adequate data, and standards should be agreed urgently.

ACKNOWLEDGEMENTS

We thank Brenda Thomas of the Cochrane Stroke Review Group for her help with the search strategy and the Health Foundation who funded Dr Ingrid Kane.

Authors' affiliations
I Kane, Department of General Medicine, St Richard's Hospital, Chichester, UK
P Sandercock, J Wardlaw, Division of Clinical Neurosciences, University of Edinburgh, Edinburgh, UK

Competing interests: None.

REFERENCES

1 **Parsons MW**, Pepper EM, Chan V, *et al.* Perfusion computed tomography: prediction of final infarct extent and stroke outcome. *Ann Neurol* 2005;**58**:672–9.
2 **Schlaug G**, Benfield A, Baird AE, *et al.* The ischemic penumbra. Operationally defined by diffusion and perfusion MRI. *Neurology* 1999;**53**:1528–37.
3 **Shih LC**, Saver JL, Alger JR, *et al.* Perfusion-weighted magnetic resonance imaging thresholds identifying core, irreversibly infarcted tissue. *Stroke* 2003;**34**:1425–30.
4 **Hacke W**, Albers G, Al Rawi Y, *et al.* The Desmoteplase in Acute Ischemic Stroke Trial (DIAS): a phase II MRI-based 9-h window acute stroke thrombolysis trial with intravenous desmoteplase. *Stroke* 2005;**36**:66–73.
5 **Fiehler J**, Foth M, Kucinski T, *et al.* Severe ADC decreases do not predict irreversible tissue damage in humans. *Stroke* 2002;**33**:79–86.
6 **Butcher K**, Parsons M, Baird T, *et al.* Perfusion thresholds in acute stroke thrombolysis. *Stroke* 2003;**34**:2159–64.
7 **Thijs VN**, Somford DM, Bammer R, *et al.* Influence of arterial input function on hypoperfusion volumes measured with perfusion-weighted imaging. *Stroke* 2004;**35**:94–8.
8 **Schulz K**, Grimes DA. Multiplicity in randomised trials II: subgroup and interim analyses. *Lancet* 2005;**365**:1657–61.
9 **Warach S**, Gaa J, Siewert B, *et al.* Acute human stroke studied by whole brain echo planar diffusion-weighted magnetic resonance imaging. *Ann Neurol* 1995;**37**:231–41.
10 **O'Brien P**, Sellar RJ, Wardlaw JM. Fogging on T2-weighted MR after acute ischaemic stroke: how might this occur and what are the implications? *Neuroradiology* 2004;**46**:635–41.
11 **Beaulieu C**, de Crespigny A, Tong DC, *et al.* Longitudinal magnetic resonance imaging study of perfusion and diffusion in stroke: evolution of lesion volume and correlation with clinical outcome. *Ann Neurol* 1999;**46**:568–78.
12 **Barber PA**, Parsons MW, Desmond PM, *et al.* The use of PWI and DWI measures in "proof-of-concept" stroke trials. *J Neuroimaging* 2004;**14**:123–32.
13 **Barber PA**, Davis SM, Darby DG, *et al.* Absent middle cerebral artery flow predicts the presence and evolution of the ischemic penumbra. *Neurology* 1999;**52**:1125–32.
14 **Rohl L**, Geday J, Ostergaard L, *et al.* Correlation between diffusion- and perfusion-weighted MRI and neurological deficit measured by the Scandinavian Stroke Scale and Barthel Index in hyperacute subcortical stroke (< or = 6 hours). *Cerebrovasc Dis* 2001;**12**:203–13.
15 **Parsons MW**, Barber PA, Chalk J, *et al.* Diffusion- and perfusion-weighted MRI response to thrombolysis in stroke. *Ann Neurol* 2002;**51**:28–37.
16 **Derex L**, Nighoghossian N, Hermier M, *et al.* Influence of pretreatment MRI parameters on clinical outcome, recanalization and infarct size in 49 stroke patients treated by intravenous tissue plasminogen activator. *J Neurol Sci* 2004;**225**:3–9.
17 **Schellinger PD**, Fiebach JB, Jansen O, *et al.* Stroke magnetic resonance imaging within 6 hours after onset of hyperacute cerebral ischemia. *Ann Neurol* 2001;**49**:468–9.
18 **Rother J**, Schellinger PD, Gass A, *et al.* Effect of intravenous thrombolysis on MRI parameters and functional outcome in acute stroke <6 hours. *Stroke* 2002;**33**:2438–45.
19 **Chalela JA**, Kang DW, Luby M, *et al.* Early magnetic resonance imaging findings in patients receiving tissue plasminogen activator predict outcome: insights into the pathophysiology of acute stroke in the thrombolysis era. *Ann Neurol* 2004;**55**:105–12.
20 **Ribo M**, Molina CA, Rovira A, *et al.* Safety and efficacy of intravenous tissue plasminogen activator stroke treatment in the 3- to 6-hour window using multimodal transcranial Doppler/MRI selection protocol. *Stroke* 2005;**36**:602–6.
21 **Butcher K**, Parsons M, MacGregor L, *et al.* Refining the perfusion-diffusion mismatch hypothesis. *Stroke* 2005;**36**:1153–9.

Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2006;21:348–352
DOI: 10.1159/000091541

Received: August 10, 2005
Accepted: November 12, 2005
Published online: February 15, 2006

Impact of Stroke Syndrome and Stroke Severity on the Process of Consent in the Third International Stroke Trial

Ingrid Kane[a] Richard Lindley[b] Steff Lewis[a] Peter Sandercock[a]
on behalf of the IST-3 Collaborative Group

[a]Division of Clinical Neurosciences, Western General Hospital, Edinburgh, UK; [b]Western Clinical School, University of Sydney, Sydney, Australia

Key Words
Consent procedures · Ischaemic stroke · Thrombolysis

Abstract
Background: Obtaining informed consent for a patient's participation in a randomized trial of treatment for use in a medical emergency may be achieved in a variety of ways. We sought to assess the process of consent and to evaluate the influence of the patient's neurological deficit on the method used to obtain consent in the first 300 patients recruited into the Third International Stroke Trial (IST-3). ***Methods:*** IST-3 is the first large-scale randomized controlled trial of intravenous thrombolysis in acute ischaemic stroke. The clinician could use one of four procedures to recruit the patient: written consent, witnessed consent, assent, or a waiver of consent. The patient's neurological deficits were recorded at baseline. We analysed the relationship between the neurological deficits at baseline and the consent procedure. ***Results:*** The method of consent used was written consent in 71 subjects (24%), witnessed verbal consent in 30 subjects (10%), assent by a relative in 197 subjects (66%), and waiver of consent in 2 subjects (1%). Patients with severe neurological deficits (as measured either by their stroke syndrome or their lower predicted probability of being alive and independent at 6 months) were more likely to be recruited by assent. Patients able to give written consent had less severe strokes. ***Conclusions:*** Patients with non-lacunar hemispheric stroke syndromes or with a more severe neurological deficit were less likely to give written consent. Excluding such patients from acute stroke treatment trials would eliminate many otherwise eligible subjects, who have a poor predicted outcome without treatment and yet might benefit from acute treatments such as thrombolysis. Flexible consent procedures developed for IST-3 have made it feasible to recruit the target population.

Introduction

It is important to evaluate new interventions for the treatment of medical emergencies (such as acute stroke) by means of randomized controlled trials. The standard approach to recruitment in a randomized trial of a non-emergency treatment is to require fully informed written consent after giving the patient sufficient time to consider the matter. This is clearly not practicable in the emergency treatment of acute stroke, where patients may have a variety of neurological deficits which either impair ef-

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1015–9770/06/0216–0348$23.50/0

Accessible online at:
www.karger.com/ced

Dr. Ingrid Kane
Division of Clinical Neurosciences
Western General Hospital
Edinburgh, EH4 2XU (UK)
Tel. +44 131 537 3228, Fax +44 131 332 5150, E-Mail Ingrid.Kane@ed.ac.uk

fective spoken or written communication and/or writing (e.g., coma, confusion, paralysis, aphasia) [1, 2]. There is substantial variation between countries in the legal and regulatory requirements for consent procedures for trials being conducted in such patients. In Europe and the USA, such research can only be conducted if several stringent conditions are met, which may render some types of research impractical.

Although stroke is a significant cause of death and disability, and the care of stroke patients places a huge burden on health services and families throughout the world, there are few effective emergency medical treatments for use in the acute phase of the illness. For patients with acute ischaemic stroke, thrombolysis with recombinant tissue plasminogen activator (rt-PA) can reduce disability in survivors and is of net benefit, despite a 3% risk of fatal intracranial bleeding [3]. In the USA and Europe, rt-PA is approved for use in acute ischaemic stroke in highly selected patients who present very early and can be assessed and treated within 3 h of symptom onset. The American Heart Association guidelines state that, when considering treatment in routine clinical practice with intravenous rt-PA, written consent is not a necessity, but patients and their relatives should be informed about the potential risks and benefits [4]. Ciccone [5] has proposed a practical approach to consent in this setting. A recent study by Rosenbaum et al. [6] highlighted that while such consent was often not documented, patients with diminished capacity seemed to have given consent. A systematic review also highlighted difficulties in obtaining informed consent as a barrier to effective delivery of thrombolytic treatment [7].

The Third International Stroke Trial (IST-3) is a large-scale trial (6,000 patients) which seeks to determine whether a wider variety of patients might benefit from thrombolytic therapy, beyond the very restricted group defined by the current approval. In order to achieve this sample size, the trial methods had to be simple, flexible, yet ethically acceptable. Therefore, the trial team developed [8] and obtained ethical approval for a set of flexible consent procedures that allow patients with different types of stroke and different degrees of neurological impairment to be included. In this analysis, we aimed to examine which method of consent was employed and to explore the impact of the patient's initial neurological deficit on the method of consent that was employed in the first 300 patients recruited. This would, in turn, help assess the feasibility of recruiting patients into the trial, and also to inform future research and clinical practice in acute stroke care.

Methods

IST-3 is a multicentre randomized controlled trial of intravenous rt-PA in patients with acute ischaemic stroke. Patients, aged over 18, who can be assessed and have treatment started within 6 h of symptom onset, are eligible for the trial. Consent or assent must be obtained before randomization. The full trial protocol can be found at www.ist3.com.

We developed draft patient information leaflets and consent forms. To improve the quality of the informed consent process, we then subjected the draft forms to an iterative process of testing and further development that closely involved patients and potential patients [8]. The trial information leaflets include approximate percentage benefits and risks derived from the latest Cochrane review [3]. There are three methods of consent/assent which may be employed to recruit patients into the trial. The UK multicentre research ethics committee has approved these. The first, and the ideal, is written consent from the patients themselves. However, if patients are unable to write, for example if the dominant hand is affected, they are able to give witnessed consent if they have no problems with communication. If the patients are unable to give informed consent as a consequence of their stroke (e.g., due to aphasia), assent can be sought from patients' relatives (in North America, this is known as surrogate consent). In some countries, under exceptional circumstances, a fourth method, i.e. waiver of consent, is also permitted, usually on condition that an independent physician agrees that recruitment of that individual into the trial is appropriate and that if the patient recovers, the option to withdraw consent may be offered (this is not exactly comparable with what is referred to as 'deferred consent'). When obtaining consent to enter a patient into the trial, the randomizing clinician has a discussion with the patient and the family and the trial information leaflets are used as a guide to the conversation, employing simple language that is easy to understand. The method of consent is recorded in the hospital records and on the trial 7-day follow-up form. The presence or absence of the key neurological deficits is recorded at randomization. A computer algorithm uses these data to assign a stroke syndrome to each patient: total anterior circulation, partial anterior circulation, lacunar or posterior stroke syndrome. A separate algorithm, based on a validated prognostic model [9], uses the baseline clinical data to calculate a predicted probability that the patient will be alive and independent at 6 months after the stroke.

Results

We analysed data for the first 300 patients randomized into the trial. The method of consent employed was written consent in 71 patients (24%), witnessed verbal consent in 30 patients (10%), assent by a relative in 197 patients (66%), and waiver of consent in 2 patients (1%).

Table 1 shows the impact of individual neurological deficits on the method of consent. In patients with dysphasia, 92% were randomized into the trial with assent of a relative or by witnessed verbal consent. In patients

Table 1. Method of consent and neurological deficit

Neurological deficit at baseline	Method of consent			
	written consent[1]	witnessed verbal consent	assent by a relative	waiver of consent
Motor deficit only	18 (69)	2 (8)	6 (23)	0 (0)
Dysphasia	13 (7)	14 (8)	145 (83)	2 (1)
Visuospatial disorder	26 (14)	20 (10)	145 (76)	1 (1)
Lesion location (final diagnosis)[2]				
Right hemisphere	45 (36)	13 (10)	66 (54)	0 (0)
Left hemisphere	23 (14)	15 (9)	128 (76)	2 (1)
Cerebellar or brainstem	2 (67)	1 (33)	0 (0)	0 (0)
Not localizable[3]	1 (20)	1 (20)	3 (60)	0 (0)
Total	71 (24)	30 (10)	197 (66)	2 (1)

Figures indicate number of patients, with percentages in parentheses.

[1] Percentages are of row totals.

[2] Final diagnosis is determined at 7 days on the basis of all the neuroimaging data, ancillary investigations and the patient's clinical course.

[3] Some patients had a clinical syndrome consistent with localization in either hemisphere or the posterior fossa, but had no relevant visible lesion on brain imaging.

with visuospatial disorders, most commonly due to a non-dominant hemisphere stroke, the majority were recruited by assent of a relative (76%) or by witnessed verbal consent (10%). Those without such a deficit were more likely to be able to give written consent. As expected, the hemisphere affected by the stroke has a clear influence: patients with left hemisphere lesions were less likely to be able to give written consent than patients with right hemisphere lesions, i.e. 14 versus 36%, respectively (difference 22%; 95% confidence interval 13–32).

As demonstrated in figure 1, consent of those patients with most severe strokes (i.e. total anterior circulation stroke) was given by either assent of a relative or by witnessed verbal consent in the majority of cases. In patients with the milder partial anterior circulation stroke syndrome, about a third of patients were able to give written consent. The numbers in the lacunar stroke and posterior circulation stroke subtypes were small, but written consent in these groups was common.

Figure 2 confirms the observations from figure 1, demonstrating a trend that patients randomized into the trial with written consent have less severe strokes, and those consented with assent or waiver of consent had, on average, more severe strokes.

Discussion

These analyses confirm that the consent procedures we have developed were feasible and permitted patients with a range of neurological deficits to be recruited. In general, the severer the stroke (either determined by clinical stroke syndrome or predicted outcome), the less likely was written informed consent to be employed, as one would expect. The proportion of patients with total anterior circulation stroke syndrome was greater in the assent group compared with the written consent group (fig. 1). When stroke severity was assessed by the predicted probability of outcome, patients giving written consent were judged to have milder strokes (fig. 2).

The data also suggest that the severer the stroke deficit, the more likely that assent will be needed as the method of consent (table 1). In particular, the data show that those with any type of higher cerebral dysfunction, e.g., dysphasia or a visuospatial disorder, could not take part in a trial such as IST-3 without the option of a flexible consent procedure. If the left hemisphere is affected by the stroke, then assent is more likely since patients are more likely to be dysphasic or – even if they do not have such a higher cerebral dysfunction – their dominant (writing) arm is likely to be affected making writing difficult or impossible.

If only the patients who are able to provide written informed consent were included in acute stroke trials,

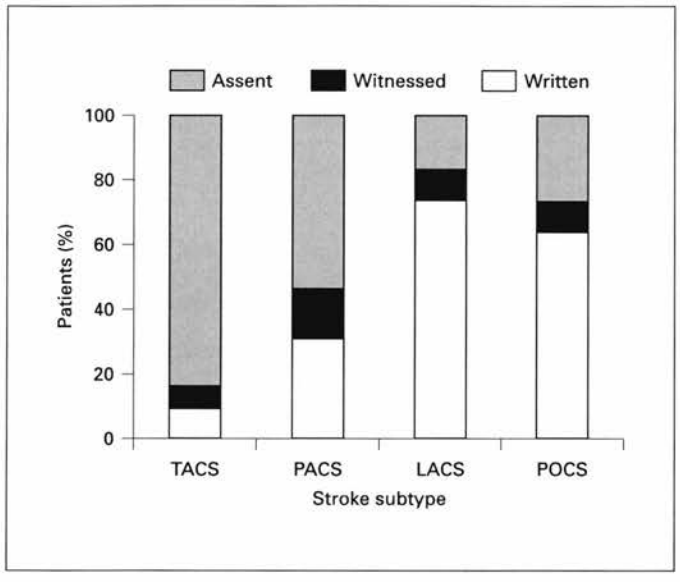


Fig. 1. Effect of stroke syndrome on method of consent. The percentage of patients within each stroke subtype and the type of consent used to recruit them into the trial depending on their stroke subtype: total anterior circulation stroke (TACS), partial anterior circulation stroke (PACS), lacunar stroke (LACS) and posterior circulation stroke (PACS). Note: only 2 cases had waiver of consent, both of which have been omitted from this figure. Both had TACS-type strokes.

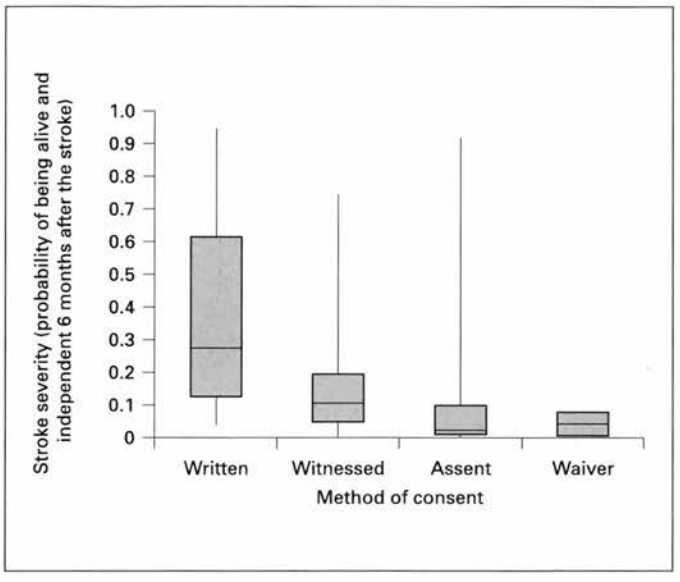


Fig. 2. Effect of stroke severity on the method of consent. Stroke severity is assessed by the predicted probability of the patient being alive and independent 6 months after their stroke. The predicted probability is calculated from their pre-treatment neurological deficit with a validated prognostic model. Hence, a probability of zero represents a very severe stroke with a low probability of good outcome and 1.0 a very mild stroke with a very high probability of a good outcome. The patients have been grouped according to the method of consent used to recruit them into IST-3. It does not take into account the effect of post-randomization treatment. In this plot, the box represents the interquartile range. The whiskers extend from the box to the highest and lowest values. The line across each box indicates the median. If it is assumed that the method of consent is an ordered categorical variable and a Jonckheere test is performed, then the trend is significant ($p < 0.001$), with those giving written consent having a less severe stroke, as assessed by this measure.

they would generate estimates of treatment effect applicable to a group with a good prognosis (irrespective of treatment allocation). The IST-3 consent procedures conform to legal requirements and allow a wider variety of patients to be included in the trial. These patients may have as much benefit from thrombolysis treatment as patients with milder strokes. Indeed, previously fit and active elderly people who are affected by a severe stroke should surely have the opportunity to participate in research. According to the World Medical Association Declaration of Helsinki policy on the ethics of medical research involving human subjects, it is stated 'for a research subject who is legally incompetent, physically or mentally incapable of giving consent, or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons' [10]. Research on emergency medical treatments is necessary in stroke patients who are unable to give consent due to the nature of their stroke. Without studying them, we would be unable to move forward and provide an evidence base for giving these groups of people such acute treatments in emergency settings when time is limited and decisions have to be made very quickly.

When considering treatments whose benefits decline with increasing time from onset of symptoms, the need to avoid delay reduces the time available to the patient, the family and the doctor for discussion and weighing up risks and benefits. Data from the recent MRC CRASH trial showed there were significant reductions in time to randomization when waiver of consent was used compared with assent by relatives [11]. This reduction in time delay may be crucial to maximizing the benefit from treatment and hence the likelihood of the trial producing a

clear and positive result, if treatment is clearly effective. One way to do this may be to increase public understanding and awareness of conditions like acute stroke by improving public education in groups at risk of stroke. At least, in this case, people have a chance to think about potential situations that may arise in the future and what sort of risks of treatment they may find acceptable.

The EU directive on clinical trials makes waiver of consent for trials in emergency situations difficult, if not impossible. This will be a major obstacle to evaluating interventions that could have substantial impact on mortality and disability.

These data confirm that the consent procedures developed for IST-3 have proved feasible and have enabled the balance of risk and benefit of thrombolytic therapy to be assessed in a randomized trial in a wider variety of patients than previously. This is an area where there is scope to develop still better tools to improve the process of informed consent in acutely ill people.

Acknowledgements

IST-3 is sponsored by the University of Edinburgh and the Lothian Health Board. It is supported by grants from the Stroke Association, the Health Foundation and the Medical Research Council. There is also support from the Norwegian Research Council, AFA Insurances, the Swedish Heart Lung Foundation, the Polish Government and the Heart Foundation of Australia. Boehringer Ingelheim supplied the drug and placebo for the first 300 patients in the initial phase of the study. Professor Richard Lindley is supported by an infrastructure grant from NSW Health and the Commonwealth and is funded by the Moran Foundation for Older Australians.

References

1 Bateman BT, Meyers PM, Schumacher HC, Mangla S, Pile-Spellman J: Conducting stroke research with an exception from the requirement for informed consent. Stroke 2003;34:1317–1323.

2 Demarquay G, Derex L, Nighoghossian N, Adeleine P, Philippeau F, Honnorat J, Trouillais P: Ethical issues of informed consent in acute stroke. Analysis of the modalities of consent in 56 patients enrolled in urgent therapeutic trials. Cerebrovasc Dis 2005;19:65–68.

3 Wardlaw JM, del Zoppo G, Yamaguchi T, Berge E: Thrombolysis for acute ischaemic stroke (Cochrane review); in The Cochrane Library. Oxford, Update Software©, Cochrane Library, John Wiley & Sons Ltd., 2003, issue 4.

4 Adams HP Jr, Adams RJ, Brott T, del Zoppo GJ, Furlan A, Goldstein LB, Grubb RL, Higashida R, Kidwell C, Kwiatkowski TG, Marler JR, Hademenos GJ, Stroke Council of the American Stroke Association: Guidelines for the early management of patients with ischemic stroke: a scientific statement from the Stroke Council of the American Stroke Association. Stroke 2003;34:1056–1083.

5 Ciccone A: Consent to thrombolysis in acute ischaemic stroke: from trial to practice. Lancet Neurol 2003;2:375–378.

6 Rosenbaum JR, Bravata DM, Concato J, Brass LM, Kim N, Fried TR: Informed consent for thrombolytic therapy for patients with acute ischemic stroke treated in routine clinical practice. Stroke 2004;35:e353–e355.

7 Kwan J, Hand P, Sandercock P: A systematic review of barriers to delivery of thrombolysis for acute stroke. Age Ageing 2004;33:116–121.

8 Koops L, Lindley RI: Thrombolysis for acute ischaemic stroke: consumer involvement in design of new randomised controlled trial. BMJ 2002;325:415–417.

9 Counsell C, Dennis M, McDowall M, Warlow C: Predicting outcome after acute and subacute stroke. Development and validation of new prognostic models. Stroke 2002;33:1041–1047.

10 World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. Accessed at http//www.wma.net/e/policy/b3.htm.

11 The CRASH Trial Management Group: Research in emergency situations: with or without relatives consent. Emerg Med J 2004;21:703.