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Imaging Stroke Patients with Unclear Onset Times

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Abstract

Despite significant progress in stroke prevention and acute treatment, stroke remains a leading cause of death and adult morbidity worldwide. By defining “stroke symptom onset” in the most conservative manner, namely the time the patient was last known to be well, many patients whose onsets are unwitnessed are automatically ineligible for thrombolytic therapy even if their true time of onset would make them eligible. Many groups are trying to determine if advanced brain imaging can serve as a substitute “witness” to estimate stroke onset and duration in those patients who do not have a human witness. We review and compare some of these imaging-based approaches to thrombolysis eligibility, which if successful, can potentially expand the use of thrombolytic therapy to a broader stroke patient population.

Keywords

stroke; brain ischemia; thrombolytic therapy; diffusion magnetic resonance imaging; perfusion magnetic resonance imaging; time

Introduction

Stroke is the fourth leading cause of death¹, and the leading cause of serious long-term disability in the United States. Each year, approximately 795,000 people experience new or recurrent strokes; of these, 87% are ischemic². The economic cost of this devastating disease for 2009 was estimated to be \$68.9 billion². The only current approved therapy for the treatment of acute ischemic stroke is intravenous (IV) alteplase or recombinant tissue plasminogen activator (rt-PA) administered within three hours from when the patient was

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last known to be well. More than a decade has passed since the United States Food and Drug Administration (FDA) approved the use of IV rt-PA for the treatment of acute ischemic stroke. Yet, rt-PA is still underused worldwide and estimated to be given to less than 5% of patients^{3, 4}. The main reasons for this low rate are attributed to the delay in patient arrival, and the conservative definition of time of stroke onset in cases of unwitnessed onset, which is the time the patient was last known to be well. In 2008, the results from the third study of the European Cooperative Acute Stroke Study (ECASS 3), a randomized, double-blind, placebo controlled, clinical trial, demonstrated that in a carefully selected population, rt-PA could be safely given to patients treated within 4.5 hours from symptom onset⁵. Although this is a promising step towards expanding the use of rt-PA, according to the Paul Coverdell National Acute Stroke Registry Surveillance Report from four states (Georgia, Illinois, Massachusetts and North Carolina), during the period of 2005 through 2007, 57% of acute stroke patients arrived at the hospital with unknown time of symptom onset⁴. Since thrombolytic therapy is based on the patient's last known well time, these patients would be considered outside the treatment window. The key to offering thrombolytic therapy to patients with unwitnessed strokes is to clearly differentiate between the time when the patient was "last known well" and the time when the patient was discovered with symptoms. For witnessed strokes, these are one and the same. For strokes whose onsets are unwitnessed, the difference in times is unknown (by definition) and could be the difference between being eligible or ineligible for therapeutic intervention. Special cases of strokes with unknown onset are "wakeup strokes", where there is no definite evidence that proves the strokes started *before* the patient woke up, and the stroke may have caused the patient to awaken. These patients are found in bed as opposed to on the floor or in the bathroom or kitchen. There are presumably no delays in bringing these patients directly to the hospital, whereas the patients with unknown onset time may have been left unattended at home for minutes to hours. If a technique existed that could reliably substitute for the human "witness" and provide evidence that the duration of the stroke was in fact within the therapeutic time window (e.g. less than 4.5 hours), then these patients could be considered for IV rt-PA therapy. A number of stroke researchers have suggested that imaging, in particular specific MRI findings, could provide such information, and, therefore could help "bracket" the time of onset based on tissue changes. This article will discuss the data supporting the use of imaging for selecting patients for thrombolytic therapy when precise stroke onset times are unavailable. Figure 1 shows how imaging could potentially be used for triaging these patients for thrombolytic therapy. We will first provide background information on this stroke population, including discussing previous studies that investigated the feasibility of extending thrombolytic therapy. We will then investigate imaging options that can potentially make giving rt-PA to this group safer. The first option is to use imaging as a surrogate for stroke duration and find techniques that can determine whether the patient is within the therapeutic time window or not. The second option is to use imaging as a surrogate for tissue viability. It is important to keep in mind that the idea of an MRI-based estimate of time of stroke onset is a separate, but closely linked idea to that of using imaging or other biomarkers to identify a "tissue clock" instead of a "wall clock" to identify candidates for intervention. We therefore discuss the two distinct approaches separately. Finally, we also briefly describe some of the proposed and on-going clinical trials involving these patients.

Patients with unclear stroke onsets: Background

The precise time from onset of symptoms to hospital arrival is not recorded or known for the majority of stroke patients⁴. Further, an estimated 16 to 28% of stroke patients awaken with symptoms⁶⁻¹⁰. It was suggested early on by Marshall that for a majority of these patients, the strokes may have occurred between 12:00 AM and 6:00 AM¹¹, making many of these patients clearly outside the therapeutic time window if hospital arrival is delayed until

discovery in the morning. Marshall posited that night-time decreases in blood pressure in patients with dysfunctional autoregulation may result in reduced cerebral blood flow (CBF). His suppositions were based on findings from 554 non-embolic ischemic stroke patients. Other studies, performed across all stroke subtypes, however, found that most strokes occur in the early morning, between 6:01 AM and 12:00 PM 7–10, 12. A retrospective study of 1272 patient datasets collected for the TOAST trial¹³, where patients who awakened with symptoms (N=323, 25% of the datasets) were analyzed separately, found only 7% of the 1272 patient dataset (N=87), had onsets between 12:01 AM and 6:00 AM. A meta-analysis of 31 publications, involving 11,816 patients, reported similar results, with a 49% increased risk of stroke between 6 AM and noon, and 35% decreased risk between midnight and 6 AM compared to the other 18 hours¹⁴. These observations have led many to conclude that there exists a circadian pattern in the frequency of stroke similar to that reported for myocardial infarction. This pattern may be partially explained by the circadian rhythm of blood pressure, cortisol secretion, blood viscosity, hematocrit, activated partial thromboplastin time, prothrombin time, and platelet aggregation^{10, 12}. Implications of these findings are that many wake-up stroke patients, whose last known well time is the night before, may with high likelihood have had their onsets around awakening and could therefore be treated safely with rt-PA, assuming they meet all clinical and imaging criteria for the on-label use of IV rt-PA.

There have been several studies investigating radiological differences between wake-up stroke patients and non-wake-up stroke patients to determine whether MRI could play a role in triaging these patients. Fink et al. investigated ADC differences between patients with well known onset times and those who woke-up with symptoms¹⁵. In Fink's study, 364 patients were retrospectively examined from a prospective dataset consisting of 100 wake-up stroke patients. There was no statistical difference between times seen from symptom discovery for the two groups (6.0 vs 5.9 h, $P=0.83$), but fewer wake-up stroke patients were imaged within 3 h of symptom discovery (29% vs 45%, $P=0.006$). The rates of mismatch on diffusion-weighted MRI (DWI) and perfusion-weighted MRI (PWI) in both groups (82% vs. 73%, $P=0.4$) were similar. Clinical features (e.g. NIHSS, age, gender) were not significantly different between the two groups ($P>0.05$). Using linear regression analysis, ADC values were found to be negatively associated with stroke onset time ($\beta=-0.184$ $P=0.10$). ADC was lower in the wake-up stroke group compared to the non-wakeup group seen within 3 h of onset (566 vs 665 $\mu\text{m}^2/\text{s}$, $P<0.01$).

There have also been several studies investigating CT's possible role in triaging patients with unknown onset times. Todo et al. researched differences on CT between cardioembolic stroke patients imaged within 3 h of symptom discovery¹⁶. Patients were divided into three groups: patients with known-onset times (N=46), wake-up stroke patients (N=17), and patients with unclear onset times who were not found on awakening (N=18). The patients in the unclear onset time group presented with hypodense regions on CT more often than the wake-up stroke (56% vs 11%, $P=0.012$) and known-onset (56% vs 0%, $P<0.001$) groups. Silva et al. examined group differences in CT angiography (CTA) and CT perfusion (CTP) between patients with known-onset times (N=420), wake-up strokes (N=131), and unclear onset times, not including those with strokes upon awakening (N=125)¹⁷. The unclear onset time group had more severe strokes as measured by NIH Stroke Scale (NIHSS 8 [3–16], $P<0.01$) compared to the known onset (NIHSS 5 [2–11]) and wake-up stroke (NIHSS 5 [2–11]) groups. The unclear onset group also presented with larger CTA source image (CTA-SI) lesion volumes (46.6 [0–220.8] cm^3 , $P=0.04$) compared to the known onset (14.3 [0–137.4] cm^3) and wake-up stroke (14.4 [0–217.3] cm^3) groups. Presence of large vessel intracranial occlusions was similar in the three groups (wake-up: 35%, known onset: 46%, unclear onset: 39%; $P=0.2$). Frequency of CTP mismatch, defined as at least a 25% larger perfusion lesion on CBF maps compared to cerebral blood volume (CBV) maps, was not

significantly different across the three groups (wake-up: 37%, known onset: 41%, unclear onset: 37%; $P=0.9$) for the subset of patients who received admission CTP scans ($N=393$).

Treating wake-up and unclear onset stroke patients

There have been attempts to treat wake-up stroke patients prospectively, and these have shown some encouraging signs of efficacy in highly selected patients. Iosif et al. presented case reports in two wake-up stroke patients.¹⁸ Both patients exhibited mismatches in lesion volumes between DWI and CBF maps and little or no signal intensity changes on fluid attenuated inversion recovery (FLAIR) images, which have are thought to be indicative of early stage stroke. Based on these findings, both patients were given a combination of intra-arterial mechanical and IV chemical thrombolytic therapy (rt-PA) and both had a good outcome as measured by modified Rankin Scale ($mRS < 2$). Furthermore Hellier et al. used perfusion CT for deciding to treat two patients with unclear stroke onset times with thrombolytic therapy.¹⁹ In this study, decision to treat with mechanical thrombectomy or intravenous rt-PA was based on subtle non-contrast CT hypodensity, and mismatches between CBV and time-to-peak (TTP) maps, for which the TTP map indicated the entire ipsilateral MCA territory was at risk. As in the previous case study, both patients had good outcomes.

In addition to case studies, prospective studies involving larger patient cohorts have also been performed, and these have been much less encouraging. A phase III trial of abciximab (AbESTT-II), a platelet glycoprotein IIb/IIIa inhibitor, which was stopped prematurely due to a significant increase in rate of symptomatic intracranial hemorrhage (sICH) and fatal intracranial hemorrhage (ICH) detected within 3 months, included a pre-specified subgroup of stroke patients who awakened with symptoms^{20, 21}. The study involved 43 wake-up stroke patients - 22 treated with abciximab, 21 with placebo - and 758 non-wake-up stroke patients. Increased sICH was found in the treated wake-up arm versus the treated non-wake-up group at 3 months (18.2% vs. 4.8%, $P=0.03$). Comparison of 3-month mRS outcomes between all 43 wake-up and 758 non-wake-up stroke subjects showed that wake-up stroke subjects had significantly worse outcomes (wake-up: 9.3% good outcome non-wake-up: 29.2% good outcome; $P=0.005$) with even the placebo arm having poorer 3 month outcome (14% good outcome) compared to the non-wake-up group. Notably, the general baseline characteristics were similar between wakeup and non-wakeup groups treated with abciximab (e.g. age, gender, NIHSS) with the exception of prior history of stroke (wake-up: 36%, non-wake-up 14%; $P=0.04$) and imaging. More abnormalities were observed on baseline CT (86% vs 59%) in the abciximab-treated wake-up stroke group than in the non-wake-up group despite criteria excluding patients with CT findings involving more than 50% of the middle cerebral artery (MCA) territory. Potentially, more restrictive imaging criteria may have improved patient selection in terms of safety and likely to benefit profile.

A retrospective single-center study by Barreto, et al. of wake-up stroke patients who were treated with rt-PA on a compassionate basis suggest that rt-PA may be safely administered to a select population of wake-up stroke patients⁶. Patients were excluded if they presented with a hypodensity larger than one-third of the MCA territory on baseline non-contrast cranial CT scan, an imaging criteria more restrictive than that of AbESTT-II. Barreto, et al. examined 46 rt-PA-treated and 34 non-rt-PA-treated wake-up-stroke patients as well as 174 on-label rt-PA treated patients (treated within 3 hours from last known well). Of the 46 wake-up stroke patients, 28 received IV rt-PA alone, 14 intra-arterial (IA) therapy alone and 4 combined full-dose IV rt-PA and IA treatment. The authors found that the wake-up stroke patients treated with thrombolytic therapy had a significantly higher rate of favorable outcome (discharge mRS score 0–2: 28% vs 13%, $P=0.006$), but significantly higher mortality (15% vs 0 %, $P=0.02$) than non-treated wakeup stroke patients. There was a 4.3% rate of sICH in the rt-PA-treated wake-up stroke patients, compared to 0% in the non-rt-PA-

treated group and 2.9% rate in the on-label-treated group. These differences were not statistically significant, likely due to the low incidence of sICH and small sample sizes involved. There was a higher rate of early changes on baseline CT (28% vs 12%; $P=0.009$) and higher baseline NIHSS (16 vs 11; $P=0.001$) in the rt-PA treated wake-up stroke group compared to the on-label-treated group. There were also more cases of cardioembolic strokes (44% vs 27%) in the treated wake-up stroke group, with fewer small vessel (2% vs 14%) and unknown etiology (11% vs 23%) stroke subtypes compared to the on-label rt-PA-treated group. Imbalances in stroke subtypes, and stroke severity may explain the slightly higher, but not statistically significant increased rates of sICH (4.3% vs 2.9%, $P=0.64$) and mortality (15% vs 10%, $P=0.29$) in the treated wake-up stroke group compared to the on-label treated group. Rates of favorable outcome were statistically comparable (28% vs 48%, $P=0.64$) between the two groups. The difference between mortality rates in the treated and non-treated wake-up stroke groups was attributed to greater stroke severity in the treated wake-up stroke group, since the more critically ill patients were more likely to receive rt-PA on a compassionate basis due to their expected poorer outcome. Because treatment was not randomized it is difficult to make definitive conclusions of safety and efficacy of rt-PA in wake-up-stroke patients from this study.

A retrospective study of patients with unclear onset time by Cho, et al. involved three medical centers in Korea [22]. Cho, et al. examined the outcome in patients who arrived more than 3 hours from last known well time, and therefore were ineligible for on-label rt-PA therapy, but who exhibited MRI favorable characteristics and were therefore treated with either IV rt-PA if the patient arrived within 3 hours of symptom discovery or IA urokinase if the arrival time was within 6 hours of symptom discovery. An MR-favorable profile was defined as patients exhibiting a mismatch in DWI and PWI lesion volumes and absence of pronounced FLAIR hyperintensities in tissue spatially co-incident with the acute DWI lesions. Based on this definition, 32 patients with unclear onset times (including wake-up strokes), and 223 with known onset times were examined. No significant differences were found in rates of recanalization, early neurological improvement (4-point or greater improvement in NIHSS on Day 1 or Day 7), 24 to 48 h sICH (6.3% vs 5.8%) and rates of 3 month favorable outcome (mRS 0–1: 37.5% vs 35%; mRS 0–2: 50% vs 49.3%) between the two groups suggesting that thrombolysis can be safely administered to patients exhibiting favorable MRI profiles. Furthermore, these MRI-selected unclear onset time patients exhibited rates of favorable outcome comparable to known-onset time patients who received on label IV rt-PA.

These preliminary results where rt-PA was administered to patients with unknown onset times are promising and suggest rt-PA can potentially be safely administered as long as careful patient-selection using neuroimaging criteria is performed.

Imaging-based triage for therapeutic intervention

The next steps for extending thrombolytic therapy to patients with unclear onset times are large-scale clinical trials where treatment is decided based on admission neuroimaging profiles. In the studies discussed above, a variety of inclusion and exclusion criteria have been used (from simple non-contrast CT to multiparametric CT and MRI favorable profiles) with varying degrees of success and failure. Therefore, which imaging criteria are used will be critical for treating unclear onset or wake-up stroke patients safely. There are two approaches one can use in deciding this criteria – one is to determine which imaging parameter or combination of parameters best correlate with stroke onset time, and hence serve as a surrogate for time from stroke onset, and the other is to determine which parameters best correlate with severity of tissue injury. There are arguments supporting either approach, although both approaches will likely produce similar results since time from

symptom discovery is itself a surrogate for ischemic injury. Instead of identifying a surrogate (i.e. stroke duration) for a surrogate of tissue pathology, one may argue that one should instead concentrate on measuring tissue viability, regardless of time of imaging from stroke onset. While this argument has merits, thrombolysis is currently only approved for treatment based on a time window of 3 hours 23, and 4.5 hours from last known well for a selected population 24. This time limitation supports research efforts for imaging surrogates of stroke duration. We discuss both approaches, first describing attempts at correlating imaging findings with onset time, and then attempts towards identifying salvageable tissue. We focus on MRI patterns of early imaging changes although there have been correlative studies involving CT patterns in the hyperacute stage, but that is beyond the scope of this manuscript.

Image-based markers of stroke duration

Experimental studies correlating imaging and stroke duration—In one of the first studies demonstrating DWI sensitivity to early stroke changes, Moseley et al. demonstrated in an MCA stroke model in cats (N=8) that the signal intensity ratio (SIR) of tissue in the ipsilateral MCA territory significantly increased on DWI within 1 h post-MCA occlusion (MCAO), while staying relatively unchanged on T2-weighted MRI (T2WI) until 6–8 h post-MCAO 25. The hyperintense regions on DWI and T2WI corresponded with regions of infarction identified by post-mortem histology. In a transient MCAO model in rats (N=18), Mintorovitch et al. showed that DWI became abnormal within 15 minutes, while T2-WI became abnormal at approximately 2 hours post-occlusion 26. No significant change in T2-WI was observed until immediately after reperfusion, likely due to vasogenic edema from reperfusion injury. With reperfusion, DWI and T2-WI hyperintensities resolved by 4 hours post-reperfusion. Jiang et al. compared temporal ADC changes with histology after transient-MCAO in rats (N=14) using a neuronal grading score 27. Measuring MRI changes 0 to 2 hours during ischemia and 0 to 4 hours post-reperfusion, Jiang et al. showed that while ADC correlated well with neuronal grading score at 2 hours post-MCAO prior to reperfusion, it correlated poorly at early time points and chronic time-points (24, 48, 72, 96, and 168 h) after reperfusion. Knight et al. examined temporal changes on DWI, proton spin density (PD), T1- and T2-weighted imaging with regional neuronal grading, neuronal counts and hemispheric neutrophil counts in an MCA stroke model in rats (N=34) at 2, 4, 6, 8, 24, 48, 96 and 168 h post-MCAO 28. The authors found that DWI was the only parameter to correctly identify tissue injured by ischemia within 4 hours, while T1- and T2-WI abnormalities were not visually apparent until after 8 hours post-MCAO due to poor contrast-to-noise. ADC values were observed to first sharply decrease within 2 hours-post-MCAO in the most severely injured regions of the brain before pseudo-normalizing at approximately 24 to 48 hours, while T1- and T2-WI signal intensity steadily decreased and increased, respectively, peaking at 24 hours, and PD signal intensity steadily increased, peaking at 48 hours.

Diffusion-positive, FLAIR-negative Mismatch—Findings from animal experiments support the hypothesis that mismatches between changes observed in DWI and T2-WI can be used to stage extent of ischemic injury. Based on previous experiments, it is reasonable to expect that tissue presenting with abnormal ADC and normal FLAIR or T2-WI, represents tissue at an early stage of ischemia, likely within 3 to 4 hours of onset, and therefore has a high likelihood of recovering with restoration of blood flow. An example of such a DWI-positive FLAIR-negative mismatch is shown in Figure 2a, from a patient imaged within 1.5 hours of symptom onset along with a patient considered DWI-positive and FLAIR-positive imaged at 6.2 hours from when he was last known to be well. Recent studies have shown that patients seen within 3 to 4.5 hours from stroke onset present with minimal abnormalities on FLAIR imaging 29–32. Tables 1 and 2 summarize the results from these studies for

identifying patients imaged within 3 hours and 4.5 hours, respectively. Thomalla et al. showed that in a consecutive series of patients with territorial infarction seen within 6 hours of stroke onset, negative FLAIR and positive DWI was 93% specific and 48% sensitive for classifying which patients were imaged within 3 hours of symptom onset 29. They also found that patients who were FLAIR-positive (N=65) were imaged significantly later (180 [120–240] min vs. 120 [100–150] min; $P<0.001$) and had more severe DWI ASPECTS scores 33 (6 [5–7] vs. 8 [6–9]; $P<0.001$) compared to FLAIR-negative patients (N=39). The frequency of FLAIR-positive scans increased from 50% in patients imaged within 3 hours to 93.3% for patients imaged at 3 to 6 hours. Ebinger, et al. reported that for patients with DWI positive lesions greater than 0.5 cm³, FLAIR-negative scans were 80% specific and 51% sensitive for patients imaged within 3 hours 30. Aoki et al. showed in MRI studies acquired within 24 hours from stroke onset that DWI-positive and FLAIR-negative scans were 83% sensitive and 71% specific for identifying stroke onsets within 3 hours 31. Petkova et al. showed that for patients imaged within 12 hours of stroke onset, FLAIR-negative scans were 82% sensitive and 97% specific for identifying patients imaged within 3 hours of stroke onset (N=63) 32. When taking into consideration large DWI abnormalities with subtle FLAIR abnormalities limited to the cortex (for example, see Figure 2c) and classifying those to be FLAIR negative, results improved to 94% sensitivity with the same 97% specificity. The reduced specificity in Ebinger's study compared to the other three studies may be due to the milder strokes investigated, involving small lesion volumes (1.47 [0.49–4.33] cm³), although some differences could be due to the use of a 3T magnet 32 for Ebinger's study while the others used 1.5 T systems. All four studies are limited by being a retrospective single center study; hence, the generalizability of the results have been questioned, despite consistency. This stems in part from poor inter-rater agreement ($\kappa=0.29$) reported by Thomalla compared to good ($\kappa=0.65$) to excellent agreement ($\kappa=0.97$) reported by Aoki and Petkova, respectively. The differences in these studies may be due to the use of four raters in Thomalla's study (for which two of the raters were neurologists and two were neuroradiologists) and only two raters with similar training in the Aoki (neurologists) and Petkova studies (neuroradiologists). There may also have been differences in the level of training and instruction provided to the readers prior to evaluation of images. The observational PRE-FLAIR study 34 tests the generalizability of the preliminary results of Thomalla, et al 29 by investigating on a multi-center basis the performance of combining FLAIR with DWI as a surrogate marker for lesion age. The results of this study should address concerns of reproducibility of these results across different scanners using diverse imaging protocols.

Whether a FLAIR lesion is considered negative or positive, and hence an early or late stage stroke, likely depends on the degree of contrast that is used to display the image (Figure 3) and may explain the varying degrees of consensus reported across studies. This has led to the investigation of relative signal intensities (rSI) or signal intensity ratios (SIR) of FLAIR voxels coincident with abnormal DWI with respect to normal contralateral voxels as a predictor of stroke age. Using a FLAIR SIR of tissue in abnormal DWI to mirrored "normal" tissue in the contralateral hemisphere, Petkova et al found that classifying patients with less than or equal to 7% increase in SIR as early resulted in 90% sensitivity and 92% specificity in identifying patients imaged within 3 hours from symptom onset 32. Ebinger et al. found that FLAIR SIR poorly correlated with time from stroke onset with a Spearman correlation coefficient of -0.152 ($P=0.128$) 30. In contrast, Petkova et al. found a significant correlation between FLAIR SIR and time from stroke onset with a Pearson's coefficient $R=0.63$ ($P<0.001$). The discrepancies in the results of the two studies may be partly explained by differences in the methodology. Ebinger et al. only correlated rSI based on FLAIR lesions, while Petkova et al. measured SIR based on back-projected DWI lesions, which resulted in the inclusion of tissue that was FLAIR-negative, leading to lower SIR measured in early-stage stroke, and significant correlation of SIR with respect to onset time.

The differences in results may also be due to the more severe strokes involved in Petkova's cohort (which excluded patients with NIHSS less than or equal to 3) compared to Ebinger's cohort (median NIHSS 4 [IQR 1–7]).

Advanced neuroimaging markers—In addition to DWI-positive and FLAIR-negative imaging, investigators have proposed using advanced imaging sequences that may provide better prediction of stroke duration. A study by Siemonsen et al. proposed using quantitative T2 (qT2) mapping for predicting stroke onset time in place of the qualitative assessment currently available with FLAIR imaging and T2WI 35. Indeed, much of the experimental literature supporting T2 as an accurate marker for stroke duration is based on quantitative T2 imaging. Using a triple-echo T2 sequence in 36 patients imaged within 6 hours of stroke onset, the authors found that the predictive accuracy of qT2 for identifying patients imaged within 3 hours of onset was 0.794 compared to 0.676 using FLAIR. This suggests that qT2 may provide a more objective metric for identifying early lesions than afforded by visual assessment of FLAIR lesions.

Sodium MRI has been shown to increase linearly with stroke onset time 2–7 hours post MCA occlusion in rats 36 and 0 to 6 hours post MCA occlusion in non-human primate models 37. For human studies, sodium MRI performed more than 24 hours from stroke onset (N=31) exhibited mean tissue sodium concentrations greater than 70 mmol/L, suspected to be a threshold for identifying infarcted tissue 37. Another study in patients imaged between 4 to 104 hours (N=21) also demonstrated that sodium imaging SI nonlinearly increased with stroke duration 38. Within 7 hours of stroke onset, the increase was noted to be 10% or less, whereas beyond 9 hours from symptom onset the rate more than doubled to 23%, saturating at approximately 48 hours. Analysis of sodium changes in the area of DWI and PWI mismatch in nine patients imaged 4 to 32 hours post-onset showed no changes 39. However, in the DWI lesion for these patients, sodium MRI SI was found to increase with stroke duration, becoming elevated after 17 hours but showing no significant difference for studies within 7 hours. These results have led some to speculate that patients who present with minimal abnormality on sodium imaging could be safely treated with reperfusion therapy.

T1rho ($T_{1\rho}$) has also been shown to correlate with symptom onset time in experimental rat models of stroke imaged up to 7 hours post-onset 40. $T_{1\rho}$ has been shown to correlate with regions of irreversible ischemia in transient stroke models, increasing within minutes post-occlusion 41–42. Because $T_{1\rho}$ is less affected by blood-oxygenation level-dependent effect than T2, $T_{1\rho}$ increases earlier than T2. In comparison, T2 images acquired simultaneously with the $T_{1\rho}$ were shown to first decrease within minutes post-stroke 40, consistent with reports in human stroke patients 43, before increasing. Indeed this very early decrease in T2 may contribute to the specificity of FLAIR-negative scans for identifying early stage stroke.

Image-based markers of tissue salvageability

Beyond serving as a surrogate for stroke duration, many investigators postulate that imaging can be used a marker of tissue salvageability. There have been a few studies investigating this hypothesis. Studies have shown that MRI-based thrombolysis selection improved safety profile irrespective of time window 44–45. ECASS 3 demonstrated that in a carefully selected population, rt-PA could be safely administered to patients treated between 3 and 4.5 hours since last known well 5. Even with this expanded time window, by defining “stroke symptom onset” in the most conservative manner, namely using the time the patient was last known well, many patients whose onsets are unwitnessed are ineligible for IV rt-PA therapy even if their true time of onset (could it somehow be established) would qualify them for treatment. This has led some to propose the use of a “tissue clock”, in place of a “wall

clock” for determining treatment options for patients since “time” is essentially a surrogate for tissue injury. Welch et al. speculated that histopathophysiologic changes in human stroke can be non-invasively tracked by monitoring changes in MRI profiles⁴⁶. His hypothesis was based on imaging findings from experimental animal models of stroke for which stroke onset times were well-defined and histopathology samples were available^{25, 28}. Based on animal experiments described above^{28, 47}, Welch et al. formulated a “tissue signature” model combining MRI changes to predict histopathology after stroke^{46, 48}. The authors describe six MRI signatures that can be used to characterize degree of tissue injury and chance of recovery (Table 3). As one notes from the table, the DWI-positive and FLAIR-negative pattern proposed as a surrogate for early stroke onset is consistent with Signature B, which is representative of not only early stage stroke, but tissue with the greatest likelihood of recovery with reperfusion. Figure 4 shows an example of these temporal changes on DWI, ADC and FLAIR images from a 54 year-old patient imaged within 2.9 hours since last known well. FLAIR is a T2-WI with signal from cerebrospinal fluid suppressed, thereby improving lesion conspicuity⁴⁹. Also shown is the admission non-contrast CT (NCCT) for comparison. For the acute scans, DWI and ADC are clearly abnormal, while NCCT appears negative and the FLAIR shows a subtle lesion. Over time, the lesion becomes more conspicuous on FLAIR, while pseudonormalizing on ADC. ADC values for human stroke have been observed to pseudo-normalize approximately 1 to 2 weeks post-onset for patients not given reperfusion therapy⁵⁰ with maximal T2-WI lesion volumes observed at approximately 1 week, before stabilizing at approximately 30 days⁵¹. The observed differences in ADC and T2-WI lesion evolutions between human stroke and animal stroke models are likely due to animal models being imprecise replicas of human stroke⁵², where ADC and T2-WI changes depend upon often unmodeled clinical factors such as age, gender, and stroke-subtype⁵³. Furthermore, as both ADC and T2-WI temporal changes have been shown to differ with severity of ischemic insult, variations in collateral blood flow can contribute to these discrepancies²⁸. In our example (Figure 4) ADC appears pseudonormal by Day 2 (though of course, T2 is clearly abnormal as seen on FLAIR images).

Apparent diffusion coefficient values—Studies have investigated imaging parameters other than DWI-positive and FLAIR-negative mismatch to provide insight into severity of ischemic injury. Indeed some have demonstrated that patients with known onset times were safely treated with rt-PA despite presenting with FLAIR-positive patterns, with similar clinical and radiological outcomes as the FLAIR-negative group⁵⁴. Thus, excluding those wake-up stroke or unclear onset stroke patients who are FLAIR positive, may be overly restrictive, and other more sensitive, but just as specific, criteria should perhaps be used, such as degree of ADC reduction. Although Petkova et al. showed a significant positive association in relative ADC values with respect to stroke onset time ($R=0.47$, $P<0.001$)³², these results may be confounded by the bi-phasic nature of ADC. ADC values dramatically decrease within the first minutes-to-hours post-stroke onset, followed by pseudonormalization, eventually becoming elevated in chronic stages of stroke^{46, 50}. Some have speculated that the rates of these transitions across patients depend on stroke etiology, severity of ischemic insult and extent of collateral flow. As a result, some have focused on identifying thresholds for predicting when tissue has become irreversibly injured and no longer suited for reperfusion therapy. Some studies suggest that there may be a threshold of severe ADC reduction for which thrombolytic therapy may be unsuitable^{55, 56}, though other reports have suggested that this may not be the case^{57, 58}, the discrepancies potentially due to the heterogeneity of values found in the ADC lesion⁵⁹. An ADC threshold ($0.65 \times 10^{-3} \text{ mm}^2/\text{s}$) was found to be an excellent predictor of tissue infarction measured on histology⁶⁰. Consistent with the hypotheses that the amount of salvageable tissue after ischemia is a function of degree and duration of flow deficit⁶¹, the correlation

between the ADC threshold and CBF values varied with stroke duration. At 30 minutes, this ADC threshold corresponded with severe flow deficit (15 ml/100 g/min) while at 60 min, the threshold reflected moderate deficits (40 ml/100 g/min) 60. Tissue demonstrating severe initial ADC reductions was also found likely to infarct even with reperfusion in human stroke. The threshold for irreversible injury also varied by mechanism for reperfusion intervention, being 50% for intravenous rt-PA therapy⁶² and $0.55 \times 10^{-3} \text{ mm}^2/\text{s}$ for intra-arterial therapy⁶³. Tissue with ADC values less than $0.55 \times 10^{-3} \text{ mm}^2/\text{s}$ was also found more frequently in regions that eventually experienced hemorrhagic transformation secondary to infarction⁵⁵. The use of a threshold for predicting infarction assumes that tissue with ADC values above this cutoff, albeit reduced, can potentially be saved. Although tissue demonstrating increased ADC restriction have been shown to reverse after restoration of CBF, histological evidence from experimental stroke studies have shown persistent neuronal injury despite normal appearing ADC 64. In addition, for both experimental and human studies, secondary injury has been noted in tissue where the ADC apparently recovered, only to be discovered infarcted by later imaging 65, 66 or histologic studies 64, 67–70.

Diffusion-weighted and perfusion-weighted MRI mismatches—Although DWI is extremely sensitive to ischemic injury, detecting changes as early as 3 minutes post-onset 71, by definition, perfusion-weighted imaging (PWI), by either bolus-tracking⁷² or arterial spin labeling⁷³, is the most sensitive technique for detecting ischemia-induced alterations, reflecting areas that are at risk of infarction without reperfusion. Details on PWI is provided in another chapter 74. DWI and PWI have been shown to be highly sensitive and specific in diagnosing acute human cerebral ischemia 75–78. Examples of mismatch patterns are shown in Figure 5. The patient without a mismatch (Figure 5A) is the same case shown in Figure 4, with admission MRI obtained within 3 hours of last known well. There are signs of spontaneous reperfusion (hypointense MTT) and the lesion did not expand. The patient with mismatch (Figure 5B) woke-up with symptoms and was last known well before he went to bed. He was found by his wife with symptoms in the morning. MRI was performed 14.4 hours from last known well and 4.6 hours from symptom discovery; subtle signs of FLAIR hyperintensity can be noted that match the DWI lesion. However, there is a much larger perfusion deficit noted on CBF, MTT and Tmax (the timepoint for which the deconvolved residue function reaches maximum value⁷⁹) maps, into which the infarct expanded by 5 days. Extensive tissue loss and cavitation is noted at 115 days. Patients presenting with patterns similar to those shown in our examples have led to the proposed use of DWI and PWI mismatches for triaging patients for thrombolytic therapy, even those whose onset time is known to be beyond the therapeutic time window of 3 to 4.5 hours, such as Fig 5B. The Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE; N=74) trial 80 and Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET; N=101) were observational studies where the investigators sought to find patterns of DWI and PWI mismatch that predict good outcome after late thrombolytic therapy 81. Both studies used Tmax as the perfusion metric and a threshold of greater than or equal to 2 seconds for lesion segmentation. Patients were classified as having a mismatch if $(\text{PWI} - \text{DWI}) \geq 10 \text{ cm}^3$ AND $(\text{PWI} \div \text{DWI} \times 100)$ was 120% or greater. DEFUSE found that early reperfusion was associated ($P=0.039$) with a favorable outcome in patients with DWI and PWI mismatch, whereas patients without mismatch did not benefit from early reperfusion 80. DEFUSE identified a “malignant pattern” associated with severe ICH and poor outcome after reperfusion characterized by either a large DWI lesion volume ($> 100 \text{ cm}^3$) or large PWI lesion volume using a threshold of 8 seconds or more ($> 100 \text{ cm}^3$). EPITHET found that for patients who demonstrated mismatches (N=80), subjects treated with rt-PA tended to have lower infarct growth and increased reperfusion than those given placebo 81. Trials which used DWI and PWI mismatches for inclusion criteria with varying degrees of success and failure in terms of favorable clinical outcome include Desmoteplase in Acute Ischemic

Stroke Trial (DIAS, N=57, time-window, 3 to 9 hour window) 82, Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS, N=37, 3 to 9 hour window) 83, DIAS II (N=186 treated, 3 to 9 hour window) 84, pilot trial of normobaric hyperoxia (N=16, 0 to 12 hour window) 85, and Flo24 (N=26, 8–24h time window) 86. On-going studies which use admission PWI for patient triage or randomization include Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND, expected enrollment N=400, 3 to 9 hours) 87, and Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE, N=120, 0–8 h) 88. EXTEND is a Phase III trial that builds upon the results of EPITHET; however, unlike EPITHET, patients will be given rt-PA based on PWI and DWI mismatch, using a Tmax threshold greater than 6 seconds for lesion identification. For MR RESCUE, PWI and DWI mismatch will be used for patient randomization based on a computer algorithm, but a mismatch does not need to be present for enrollment. DEFUSE 2 plans to validate the profiles identified by DEFUSE in 100 patients treated 3 to 8 hours 89. DIAS3/DIAS4 (N=400, 3 to 9 hours) 90 and MR RESCUE 88 use angiographic information requiring the presence of a large vessel occlusion or high grade stenosis on CTA or MRA for patient enrollment.

Clinical trials involving patients with unwitnessed stroke onset

With the prevalence of imaging techniques that are sensitive and specific to identifying early stroke duration and potential tissue salvage, several interventional trials in stroke patients with unknown onset time have been proposed. The designs of the trials vary. One study involving patients who awaken with deficit who can be treated within 2.5 hours of awakening, AWOKE 91, requires a 20% lesion mismatch based either on CT perfusion (CBV and MTT) or MR PWI (DWI and Time-to-Peak). Expected number of patients to be enrolled is 20. Inclusion criteria involve patients age 22 years or older, with an ASPECTS score 7 or higher on DWI or CT-CBV or CTA-SI. Another study involving wake-up stroke patients is the Wake Stroke Study 92 which plans to enroll 40 subjects who can be treated within 3 hours of awakening, age 18 to 80 years, admission NIHSS 25 or less. Imaging criteria excludes subjects presenting with hypodensity greater than one-third MCA territory. MR WITNESS, a phase II safety study, involving 80 wake-up and unclear stroke onset patients, 18–80 years of age, admission NIHSS 25 or less, presenting with a DWI-positive and FLAIR-negative mismatch who are imaged within 3 h of symptom discovery (and within 24 h of last seen well) and who could be treated within 4.5 h of symptom discovery has been proposed. 93–94. In addition, FLAIR-positive patients who have a SIR less than 1.15 may also be enrolled if meeting other inclusion and exclusion criteria. All three trials are open-label, single-arm studies where the primary outcome is safety, as measured by the frequency of sICH. Secondary outcomes for all 3 studies include modified Rankin Scale at 3 months. Unlike the other three studies, a planned trial by Thomalla et al., Wake-UP, is a randomized, double-blind, placebo-controlled trial in 800 wake-up stroke patients, where the primary outcome will be favorable outcome at 3 months (Götz Thomalla, MD, Hamburg, Germany, personal communication, January 2011). Imaging enrollment criteria are expected to be similar to that of MR WITNESS.

Summary

With further refinement and large confirmatory studies, imaging techniques individually or in combination may provide additional insight into tissue injury and salvageability and be used to extend rt-PA to more wake-up stroke patients and patients with unclear onset who will benefit from therapy.

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Fig 1. Depiction of 3 different scenarios for assessing rt-PA eligibility based on time of stroke onset

Case Example: A 68 year old right handed man, Patient X, who was last seen well by his daughter at 8 AM was later discovered by her at 4:00 PM to be aphasic with a right hemiparesis, and rushed to the emergency department (ED) by 4:30 PM. He has no contraindications to IV rt-PA except for time of stroke onset. The following scenarios review the current guideline-based care (A, B) and the rationale for image-based “witnesses” (C).

SCENARIO A) Guideline-Based Care: Not Eligible for rt-PA Treatment

Under AHA guidelines and FDA indications, Patient X’s stroke onset is *defined* as 8 am (i.e., last known well time was 8 AM) and stroke duration is 8.5 hours. He is considered ineligible for guideline-based thrombolysis.

SCENARIO B) Guideline-Based Care: Eligible for rt-PA Treatment

At 4:40 PM, the son (who is a reliable human witness) of Patient X and who lives at home with him is called by the ED physician and states that he was with his father at 3 PM and that his father was normal at that time (i.e., last known well time is 3 PM); therefore the stroke onset time is then *defined* as 3 PM, and stroke duration is calculated to be 1.5 hours. He is eligible for thrombolysis and receives IV rt-PA at 5:30 PM, which is 60 min after ED arrival.

SCENARIO C) Image-based witness: Eligible for rt-PA Treatment

No human witness besides the daughter has seen Patient X since 8 am. However, a clinically obtained MRI performed at 5:00 PM produces an MRI pattern that suggests the patient’s stroke occurred less than 3.5 hours ago. Because he has no other contraindications to rt-PA, he is now eligible for off-label thrombolytic therapy. His daughter provides written informed consent and he receives study drug (IV rt-PA) at 5:30 PM. Based on the imaging hypothesis, he received rt-PA sometime between 1.5 and 4.0 hours since “true” stroke onset.

Figure 2.

Examples of (A) DWI-positive and FLAIR-negative image for an 80-year-old female imaged 1.5 hours from last known well with admission NIHSS of 20, (B) DWI-positive, FLAIR-positive image for an 48-year-old male imaged 6.2 hours of last known well with admission NIHSS of 3 and (C) DWI-positive, subtle FLAIR lesion abnormality (arrowhead) for an 85-year old male imaged 2.5 hours from last known well and admission NIHSS of 6 who would be classified as FLAIR-negative using the algorithm described by Petkova et al 32.

Figure 3.

Example of the effect of image contrast on FLAIR lesion conspicuity for an 89-year-old woman imaged 6 hours from witnessed onset. Using default contrast, the FLAIR appears normal and would be classified FLAIR negative. However, by changing the contrast, the lesion becomes more evident (arrow), changing the classification to FLAIR-positive.

Figure 4.

Example of temporal changes in DWI, ADC, FLAIR images along with admission NCCT for a 54-year-old male patient imaged serially with MRI at 2.9 hours, 2.4 days, 42 days and 111 days post-onset. Admission NIHSS was 1, 3 month mRS was 2. Both DWI and ADC are readily abnormal by admission, while the FLAIR shows subtle signs of abnormality (arrowhead). NCCT appears normal. Regions of ADC appear pseudonormal on the subacute scan, becoming elevated by 1 month (arrows). DWI appears hyperintense across all time-points. FLAIR lesion volume appears largest at Day 2 as a result of edema, before stabilizing its infarct size at 42 days.

Figure 5.

Examples of (A) DWI and PWI without mismatch for the same patient imaged serially in Figure 4 and (B) DWI and PWI lesion mismatch for a 59 year old male with unknown onset who awakened with symptoms. Admission MRI was performed 14.4 hours from last known well with an NIHSS of 9. For the case with mismatch (B), the patient's lesion expanded into the perfusion deficit, while for the case without mismatch (A), no lesion expansion, besides edema, is noted. Also shown for (B) are serial FLAIR data where edema is evident at Day 5, while the 115-day study shows extensive cavitation and tissue loss.

Summary of DWI-positive and FLAIR-negative studies identifying patients within 3 h of stroke onset

Table 1

Author Year	Admission NIHSS (IQR)	Time Range	MRI scans	Studies within 3 h (%)	Sensitivity	Specificity	κ (readers)	Field Strength (Manufacturer)
Thomalla 2009	14 (8–17) [†]	0–6h	101	71 (70)	48%	93%	0.29 (4)	1.5 T (Siemens)
Elbinger 2010 [*]	4 (1–7) [†]	0–12h	71	41 (58)	51%	80%	NA	3 T (Siemens)
Aoki 2010	5 (2–11)	0–24h	361	140 (39)	83%	71%	0.65 [‡] (2)	1.5 T (General Electric)
Petkova 2010	11 [§]	0–12h	130	63 (48)	82%	97%	0.97 (2)	1.5 T (General Electric)

^{*} Patients with DWI lesions > 0.5 cm³

[†] All patients including DWI-negative studies

[§] Mean NIHSS calculated from Table 1 in Petkova et al 32

Table 2

Summary of DWI-positive and FLAIR-negative studies identifying patients within 4.5 h of stroke onset

Author Year	MRI scans	Studies within 4.5 h (%)	Sensitivity	Specificity
Thomalla 2009	101	92 (91)	38%	89%
Ebinger 2010*	71	51 (72)	49%	90%
Aoki 2010	361	212 (59)	74%	85%

* Patients with DWI lesions > 0.5 cm³

Table 3

MR Tissue Signatures 46-48

Signature	ADC	T2-WI	Interpretation	Prediction
A	Normal	Normal	Normal	Normal
B	Low	Normal	Compromised Tissue	May or May Not Recover
C	Low	High	Transition to cellular necrosis	Less likelihood of recovery
D	Normal	High	Transition to pan-necrosis.	Not likely
E	Normal	High	Necrosis	Unlikely
F	High	Normal	Necrosis	Unlikely