Patients suffering an acute ischemic stroke can be treated with intravenous thrombolysis in the absence of contraindications. A known onset time is a prerequisite as treatment, according to guidelines, has to be started within 4.5 hours. In patients awakening with a stroke, the last time they were seen without a neurological deficit is assumed to be the time of onset. Thus, despite of lack of contraindications on initial brain imaging, these patients are largely excluded from therapy. This review discusses the underlying pathophysiological, clinical, and radiological evidence surrounding wake-up stroke and its consequences for making treatment decisions.

**KEYWORDS**

acute ischemic stroke, computed tomography, diffusion, imaging, magnetic resonance imaging, penumbra, perfusion, unknown onset, wake up

**INTRODUCTION**

Stroke is one of the leading causes of disability and mortality worldwide. In 2002, treatment with intravenous recombinant tissue plasminogen activator (rtPA) (intravenous thrombolysis—IVT) was introduced as a therapeutic option, initially within the first three hours of symptom onset and from 2008 expanded to 4.5 hours. Despite the effectiveness of IVT within the first hours of symptom onset, its potency decreases with time. The narrow therapeutic window precludes its use in patients arriving too late at the hospital and additionally makes treatment challenging in patients with unclear onset or in those awakening with neurologic deficits. Symptom onset has, in these patients, often been defined as the last time the patient was seen without any neurological deficit. For this reason, a large number of patients are excluded from IVT therapy, despite the lack of contraindications on brain imaging. Observational studies suggest that as many as 8%-25% may wake up with a neurologic deficit, and thus be ineligible for treatment with IVT.

There have been numerous studies challenging the exclusion of patients with wake-up stroke (WUS) from IVT treatment based solely on symptom onset. WUS is interweaved into the circadian distribution of stroke, and pathophysiological evidence suggests that the time of symptom onset may be close to the time of awakening. It is now believed that neuroradiological imaging, in particular magnetic resonance imaging (MRI), can provide precise information about penumbral tissue and is therefore increasingly used in patient selection for IVT therapy including WUS. However, these criteria are criticized as they likely exclude too many patients from IVT treatment.

We aimed to review the underlying pathophysiological evidence indicating that symptom onset may be close to the time of awakening and provide an overview of the neuroradiological modalities in the selection of WUS patients for IVT therapy.

**SLEEP**

Normal sleep duration is 7 hours+2 of which the first 90 minutes are non-REM sleep. REM sleep occurs late in the night and in the early morning hours. REM sleep is associated with an increase in brain activity in sensory and motor areas, an increased and fluctuating heart rate, up to a 30% increase in blood pressure and increased sympathetic activity. Although some experimental studies indicate that partial sleep deprivation may reduce stroke incidence and severity, most experimental and observational studies report a strong association between shorter/longer sleep durations and higher risk of stroke. Circadian variation of stroke- and sleep-related disorders
such as obstructive sleep apnea (OSA) and atrial fibrillation (AF) play an important role in increasing the stroke risk.\textsuperscript{15,16}

3 | CIRCADIAN VARIATION OF STROKE

The circadian variation of stroke, with a major morning peak and a minor early evening peak, has been long established.\textsuperscript{17} Most studies describing circadian variations are solely ‘time of day’ studies, presuming that the observed stroke patients follow a normal diurnal activity. A comprehensive meta-analysis of 31 studies including 11,816 strokes confirmed the prominent circadian pattern of all stroke subtypes with a peak occurrence between 6:00 and 12:00. Ischemic stroke had a 55% higher probability in this time frame and with significant increase between 04:00 and 08:00.\textsuperscript{18} The authors concluded that their analysis contradicted older conclusions that strokes are more likely to occur during sleep.

Rigorous investigations have been conducted to explain this circadian pattern of stroke which is independent of stroke subtype, patient characteristics, and the presence of other predisposing risk factors.\textsuperscript{19} Interestingly, this pattern is similar to that of myocardial infarction and sudden cardiac death.\textsuperscript{20-22} Several endogenous factors may contribute to this circadian variability: Sympathetic activity exhibits a similar circadian variability with peaks in the morning\textsuperscript{23} causing, in combination with the renin-angiotensin-aldosterone axis, an early morning rise in blood pressure (BP) and heart rate.\textsuperscript{24,25} Pathological, non-dipping, nighttime BP (BP normally dips during the night by 10%-20%) is seen as independent risk factor for stroke.\textsuperscript{26} Additionally there is an increase in platelet aggregation and a reduction in fibrinolytic activity, peaking during the morning hours, promoting thromboembolic events and consequently stroke.\textsuperscript{27}

4 | CIRCADIAN VARIATION OF ATRIAL FIBRILLATION

Atrial fibrillation has also been shown to have a circadian variability. In a study analyzing 25,500 consecutive Holter recordings, 150 patients with paroxysmal AF were found.\textsuperscript{15} A prominent circadian rhythm of the total duration of AF was detected with two peaks: one at midnight and the other at 13:00. Interestingly, the termination of AF had a morning peak around 6:00. Termination of AF and spontaneous conversion to sinus rhythm is known risk factor for ischemic stroke.\textsuperscript{28} Thus, confirming the implication of the above finding in a population of patients with ischemic stroke or TIA, there was found to be an independent association between recently diagnosed atrial fibrillation and WUS.\textsuperscript{29} Twenty-seven of 272 patients with cerebral infarction (9.9%) were recently diagnosed with AF (OR 3.6, 95% CI 1.2-7.7, \(P=0.019\)).

5 | OBSTRUCTIVE SLEEP APNEA

Obstructive Sleep Apnea affects over 15 million people and up to 25% of all middle-aged adults.\textsuperscript{30,31} OSA is strongly associated with being overweight and obesity. About 60%-90% of patients have a body mass index (BMI)≥28 kg/m\textsuperscript{2}, and this BMI has a sensitivity of 93% and a specificity of 74% for the presence of OSA.\textsuperscript{32} Several epidemiologic studies have established a link between OSA and cardiovascular disease.\textsuperscript{33,34} In a recent study including 1022 consecutive patients who underwent polysomnography, 697 (68%) had OSA. The study showed that OSA was independently associated with stroke or death of any cause (HR 2.24; 95% CI, 1.30-3.86; \(P=0.004\)).\textsuperscript{16} OSA was confirmed to be an independent risk factor for stroke in several other studies, showing a twofold increased risk for stroke, with the risk increasing to three- to fourfold in patients with severe OSA.\textsuperscript{35,36}

Hypertension often coexists with OSA: About 50% of patients with OSA are diagnosed with hypertension, and OSA is often underdiagnosed in patients with hypertension. About 30% of patients with hypertension have concomitant OSA.\textsuperscript{37-39} Both hypertension and being overweight are well recognized risk factors for stroke.\textsuperscript{40} Other mechanisms linking OSA and stroke are varying: Vascular and endothelial factors with increased platelet activation and blood flow velocities, atherosclerosis, paradoxical embolism via a patent foramen ovale and disturbed cerebrovascular reactivity have all been associated with OSA.\textsuperscript{41-43} The repetitive hypcapnia in OSA leads to chemoreceptor activation, peripheral vasoconstriction, and sympathetic hyperactivity\textsuperscript{44} to which inflammatory activation and metabolic effects contribute.\textsuperscript{45-47}

Again, AF may play an important role in OSA-related stroke; the incidence of AF is observed to be threefold higher in patients with OSA as compared to the general population.\textsuperscript{31,48} Nonetheless, OSA is identified as independent risk factor for stroke and this link to AF may contribute to WUS in these patients.

6 | RADIOLOGICAL EVIDENCE

6.1 | Computed tomography

In a prospective study, computed tomography (CT) imaging including CT angiography (CTA) and CT perfusion (CTP) was performed on 676 acute stroke patients with symptom onset within 24 hours. Patients were divided into known onset time (n=420), WUS (n=131), and patients with un witnessed symptom onset (n=125). Patients with WUS and known onset time did not differ in patient characteristics. Large vessel occlusions (LVO) treatable using intra-arterial neurointerventional approaches were similar in all groups, representing 38.6% and 35.1% of all occlusions in patients with known onset and WUS patients, respectively. On initial CT, there were no differences in ischemic lesion volumes between patients with known onset and WUS. On CTP, the frequency of cerebral blood flow (CBF) and cerebral blood volume (CBV) mismatch was not significantly different. After adjustment for age, sex, prestroke modified Rankin Scale (mRS), National Institutes of Health Stroke Scale (NIHSS) at admission, the volume of the ischemic lesion, and thrombolytic therapy, the circumstance of stroke symptom identification was no independent predictor of outcome.\textsuperscript{5} In another study, patients were
KURZ et al. classified into known onset time (n=46), WUS (n=17), and stroke of unknown onset due to lack of a witness (n=18). There were no significant difference in CT findings between patients with known onset time and WUS. Likewise, in a recent study by Cortijo, there was no difference in radiological presentation or clinical response to IVT comparing patients with unclear onset time presenting >4.5 hours from last seen normal and stroke patients presenting >4.5 hours were stroke onset was witnessed. Similarly, patients selected from a prospective stroke database were divided into stroke with known onset time treated with rtPA within three hours and WUS presenting within three hours of symptom recognition. Demographic factors, risk factors, stroke severity, and baseline CT findings including Alberta Stroke Program Early CT Score (ASPECTS 7.0 vs 7.5, respectively; P=.2) were the same between the groups. After adjusting for other factors, only rtPA treatment and National Institutes of Health Stroke Scale (NIHSS) scores remained significant predictors for patient outcome. Based on these CT findings and similar results in other studies, WUS seems to occur shortly before awakening in a large subset of patients, making them potential candidates for acute stroke therapies. Case series reports of rtPA treatment in WUS based on CT selection criteria suggest that IVT treatment may be safe and feasible in WUS based on these selection criteria alone.

6.2 Magnetic resonance imaging

In principle, two mismatch concepts are used to identify penumbra using magnetic resonance imaging (MRI): perfusion imaging (PI)—diffusion weighted imaging (DWI) mismatch and DWI—fluid attenuated inversion recovery (FLAIR) mismatch.

6.3 PI-DWI mismatch

PI-DWI mismatch is believed to distinguish between irreversibly damaged and critically damaged, but potentially salvageable tissue. It has been mainly used to select patients eligible for IVT treatment beyond 4.5 hours of symptom onset, but it also gives us an opportunity to treat patients with unknown symptom onset or WUS. Already in 1999, PI-DWI mismatch was used to monitor and triage acute stroke patients for therapy within six hours of symptom onset. The effect of the PI-DWI mismatch on patients’ outcome was prospectively investigated in 19 patients using serial DWI and PI imaging before IVT treatment, after treatment, and at outcome. The control group was a group of stroke patients (n=21) well matched for baseline NIHSS and MRI parameters. PI-DWI mismatch was present in 16 of 19 patients treated with IVT and in 16 of 21 controls. Patients with a mismatch treated with IVT had higher recanalization rates and enhanced

![FIGURE 1](image-url) Fifty-eight-year old male patient awakening with right-sided hemiparesis and aphasia. Magnetic resonance imaging was performed three hours and 20 min after awakening. (A) Diffusion weighted imaging (DWI), (B) ADC, (C) fluid attenuated inversion recovery (FLAIR), (D) CT perfusion (CTP) (CT perfusion). (A) On DWI, restricted diffusion is visible in the left frontal lobe with (B) decreased ADC values. (C) The FLAIR image shows high signal intensity in the same area (DWI-FLAIR match). However, CTP shows a perfusion deficit that is larger than the DWI lesion (DWI-PI mismatch); thus, the patient was successfully treated with IVT.
reperfusion at day 3 (81% vs 47% in controls) as well as a greater proportion of severely hypoperfused acute mismatch tissue not progressing to infarction (82% vs 25% in controls). Infarct expansion was smaller in the IVT group being associated with a better clinical outcome. The DEFUSE study evaluated whether a prespecified MRI profile can identify stroke patients who are potential IVT responders within three to six hours of symptom onset. Seventy-four consecutive stroke patients were investigated prospectively using MRI, immediately before, and between three to six hours after treatment. Patients with a PI/DWI mismatch had significantly greater odds for achieving a favorable clinical response (odds ratio, 5.4; P=.039), and an even more favorable response was seen in patients with a prespecified target mismatch profile (odds ratio, 8.7; P=.011). Patients with no mismatch did not benefit from treatment. Thus, the study concluded that the PW/DWI mismatch concept can identify stroke patients likely to benefit from IVT between three and six hours after symptom onset.

Secondary analyses of randomized controlled trials with PI/DWI selection including the EPITHET trial and the DIAS-2 trial demonstrated reduction of infarct growth and better patient outcome in patients with PI/DWI mismatch. In DIAS-2, the odds ratio for good clinical response based on the mismatch concept was 2.83 (desmoteplase vs placebo; 95% CI, 1.16-6.94; P=.023). The PI-DWI mismatch concept has been used in a few case reports and series to treat WUS patients or stroke patients with unknown symptom onset. However, the challenges of the PI-DWI mismatch definition and definition of a perfusion lesion in the mismatch trials led to a more restrictive definition used in the ongoing Extending the time for Thrombolysis in Emergency Neurological Deficits (EXTEND) trial where patients with WUS are also included.

#### 6.4 DWI-FLAIR mismatch

Already within the first minutes of a stroke, cytotoxic edema can be detected on DWI series—while changes on T2-weighted and FLAIR series become first evident after some hours. These characteristic findings are used in determining which WUS patients are eligible for IVT therapy. The DWI-FLAIR mismatch concept for stroke patients was initially established in 2009, where IVT treatment could be administered within three hours after symptom onset. The DWI-FLAIR mismatch concept had a high specificity (0.93) and a high positive predictive value (0.94), whereas sensitivity (0.48) and negative predictive value (0.43) were relatively low. The mismatch concept was also evaluated in a number of other studies showing the time dependency of the hyperintense FLAIR signal. In 2011, a multicenter observational study investigated the feasibility of the DWI-FLAIR mismatch concept within 4.5 hours after stroke onset in 543 patients. The DWI-FLAIR...
mismatch categorized stroke patients within 4.5 hours of symptom onset with a sensitivity of 62% (95% Cl: 57-67) and a 78% specificity (95% Cl: 72-84) (83% positive predictive value, 54% negative predictive value). The authors conclude that patients with an ischemic lesion on DWI series without an abnormal signal on FLAIR imaging are likely to be within a 4.5-hour time window; however, many patients within the same time window exhibit a FLAIR lesion and can therefore be incorrectly categorized in the group ineligible for reperfusion therapy (Figures 1 and 2). Currently the safety and efficacy of MRI-based thrombolysis is being tested in a randomized, double-blind, placebo-controlled trial. Although this trial will undoubtedly gather important information about the safety and feasibility of IVT in WUS patients selected by DWI-FLAIR mismatch, it will not provide evidence on how many patients potentially could have been treated if selected using other imaging modalities. However, more information about this clinically relevant limitation will be provided by the ongoing EXTEND trial in Australia, where patient selection is based on both MRI criteria (MR perfusion and diffusion) and CT criteria (including CT perfusion). EXTEND aims to have a European substudy using only MRI selection criteria for patient inclusion (ECASS 4-EXTEND-Europe).

There is still need for research on penumbral imaging; however, several trials reporting on rtPA treatment in WUS based on MRI selection criteria suggest that IVT treatment may be safe and feasible in this patient group.

7 | CONCLUSIONS

With a strict time frame for reperfusion therapy and the ongoing neural loss during an acute stroke, patients with WUS are challenging for both the stroke clinician and the neuroradiologist. Several risk factors for ischemic stroke tend to follow a circadian rhythm consequently leading to an increased risk for stroke in the early morning hours. When comparing clinical characteristics and initial CT findings in patients with WUS and patients with known onset, no differences have been found, indicating that stroke onset occurs close to wake-up and not during earlier sleep phases. The use of MRI to select patients whom would benefit from reperfusion therapy is clinically useful, but there are still questions to be answered regarding the imaging criteria for therapy selection. Based on existing evidence, WUS should not be considered a contraindication for reperfusion therapy, but treatment options should be tailored individually based on clinical and neuroradiological criteria.

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CONFLICT OF INTERESTS

All authors state that they have nothing to disclose and no conflict of interests.

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